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Advanced Treatment Planning

23-27 September – Athens, Greece

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Faculty

Course Director

- Gert Meijer, Medical Physicist, Utrecht (NL)

Co-chair

- Neil Burnet, Radiation Oncologist, Cambridge (UK)

Teachers

- Nicola Dinapoli, Radiation Oncologist, Rome (IT)
- Ursula Nestle, Radiation Oncologist, Freiburg (DE)
- Markus Stock, Medical Physicist, Vienna (AT)
- Desirée van den Bongard, Utrecht (NL)
- Marcel van Herk, Radiotherpay Physicist, Manchester (UK)

Local organiser

- Efi Koutsoveli

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Hands-on sessions

Treatment planning systems thanks to

- Eclipse by Varian Medical Systems
- Monaco by Elekta
- Pinnacle by Philips Healthcare
- RayStation by RaySearch
- TomoTherapy by Accuray

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Broadening the therapeutic band width

Neil Burnet

Manchester Cancer Research Centre,
University of Manchester and Christie Hospital,
Manchester, UK

ATP
Athens 2018

Radiotherapy technology is advancing rapidly

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

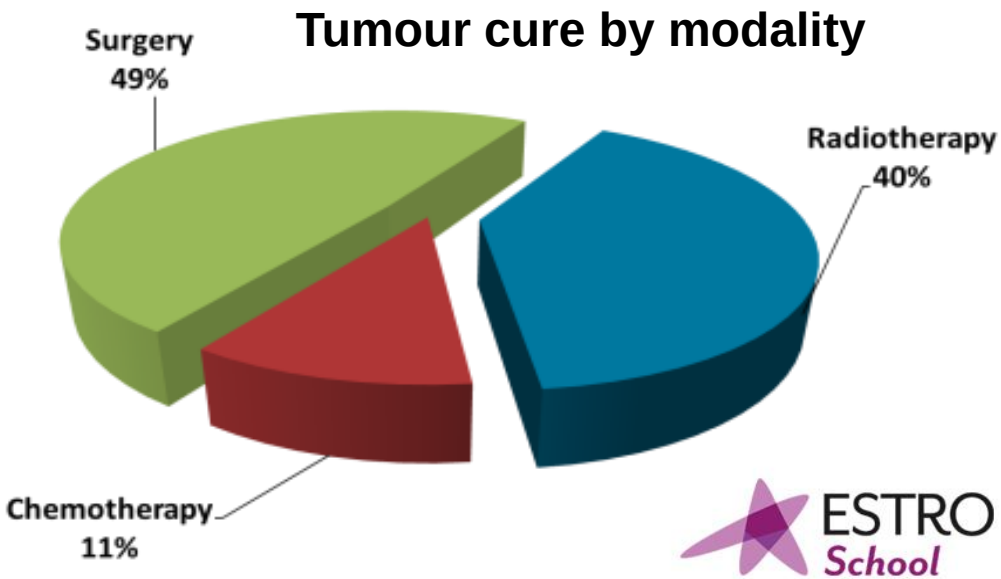
Introduction

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

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Quality of RT affects outcome

Quality of RT affects outcome

VOLUME 28 · NUMBER 18 · JUNE 20 2010

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

JOURNAL OF CLINICAL ONCOLOGY

ORIGINAL REPORT

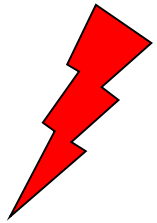
Critical Impact of Radiotherapy Protocol Compliance and Quality in the Treatment of Advanced Head and Neck Cancer: Results From TROG 02.02

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

- Very scary results
- Poor radiotherapy

20% ↓ in OS

24% ↓ in DFS



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Quality of RT affects outcome

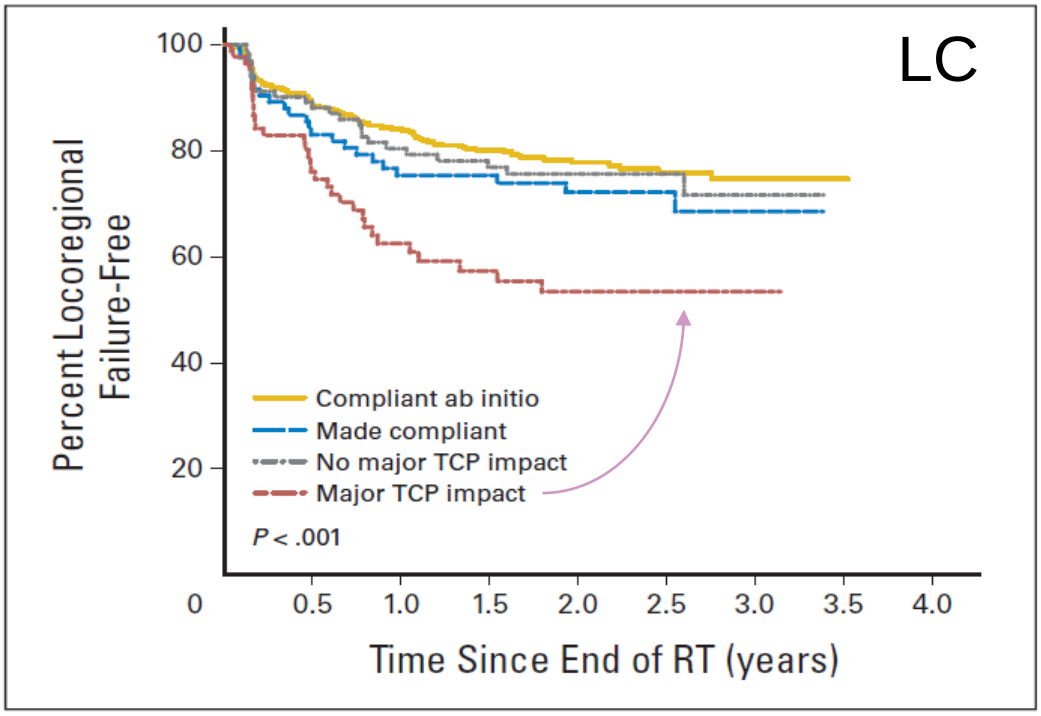

Fig 3. Time to locoregional failure by deviation status

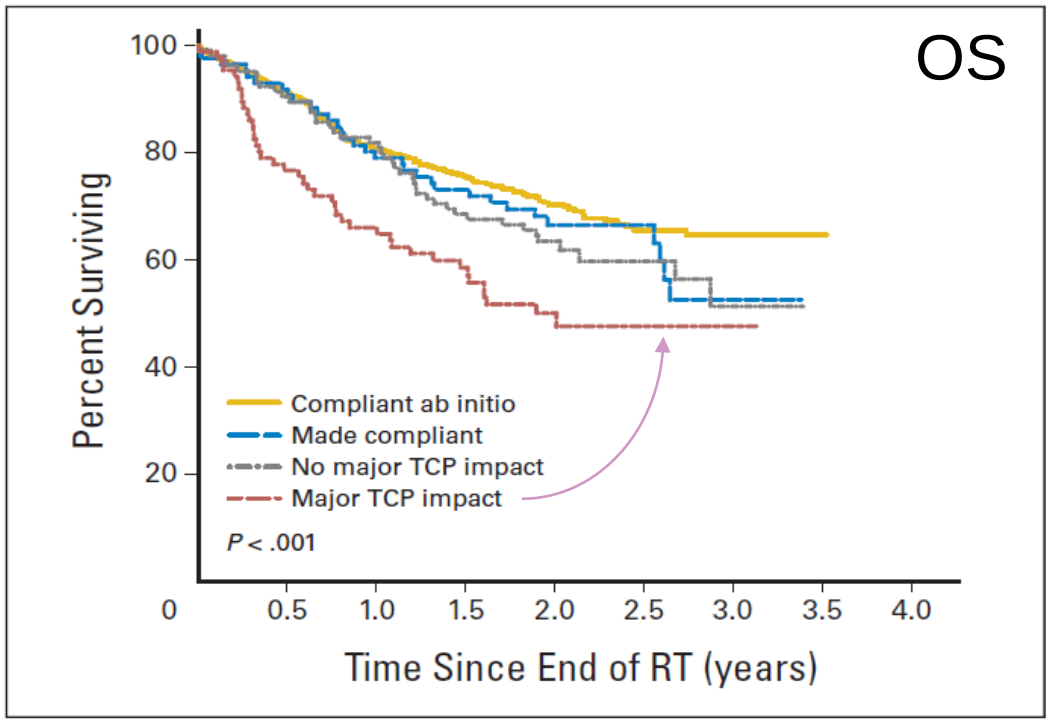

Fig 2. Overall survival by deviation status:

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

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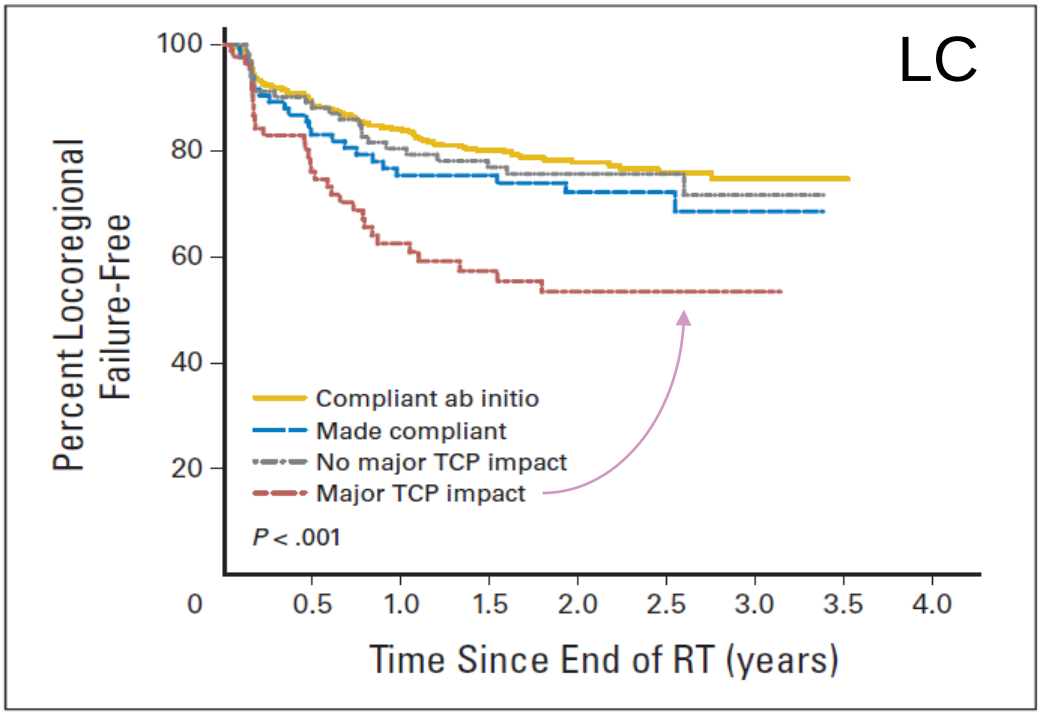
Quality of RT affects outcome



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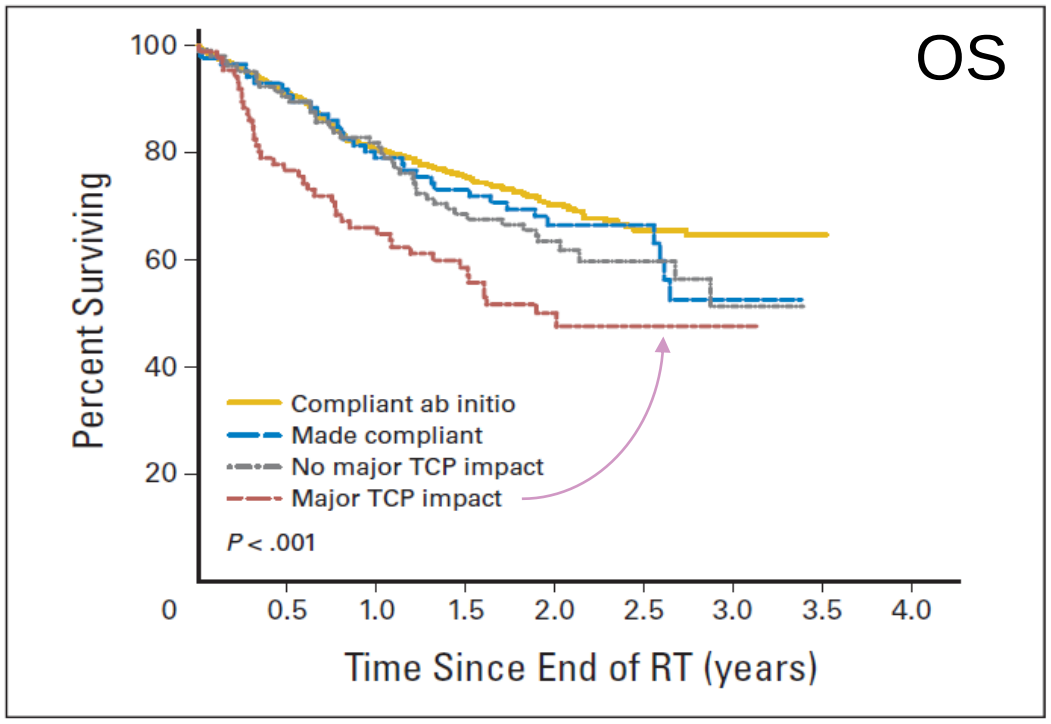

Fig 2. Overall survival by deviation status:

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

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Broadening RT band width

Broadening RT band width

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

- Biological strategies
  - Fractionation
  - Exploiting individual variation in normal tissue toxicity
  - Drugs – sensitise tumours & protect normal tissues
  - Immune response modifiers
  - Synergy from conventional chemotherapy

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

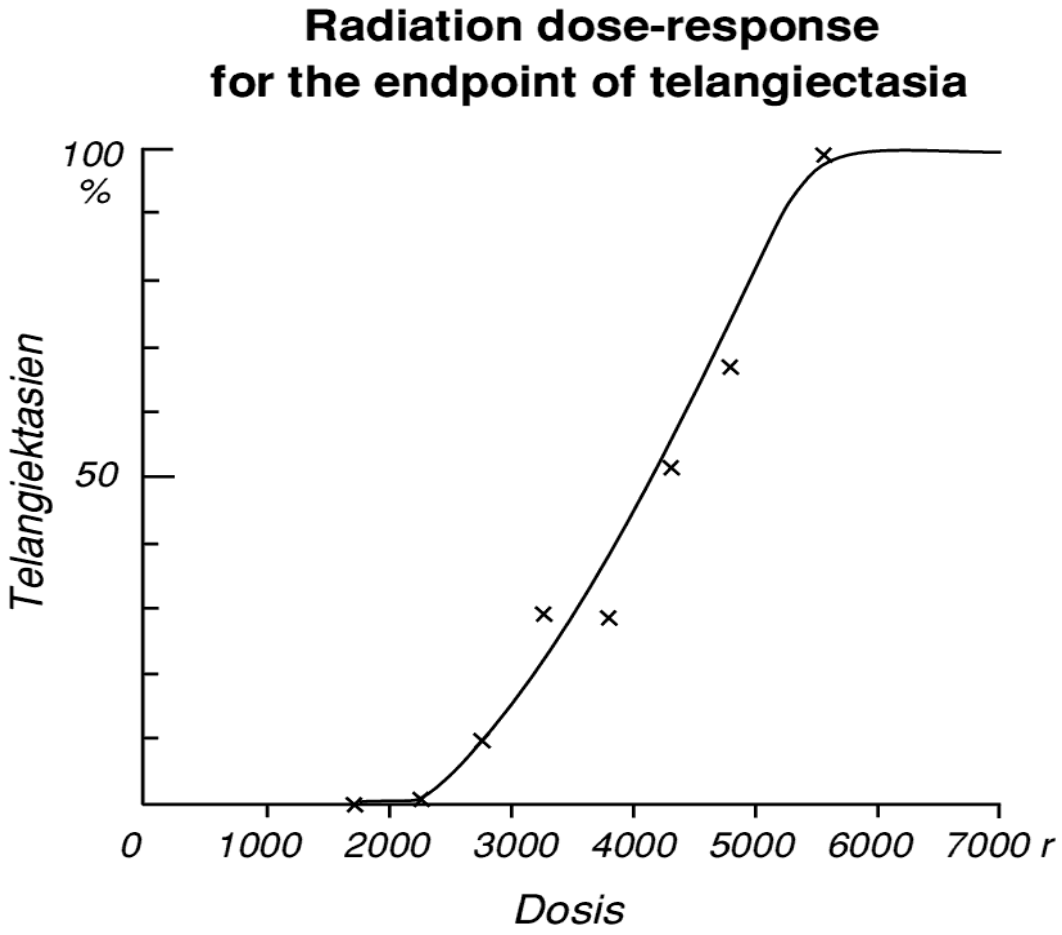
- Local control will translate into overall cure in many patients
  - For breast –1 life saved for every 4 recurrences prevented

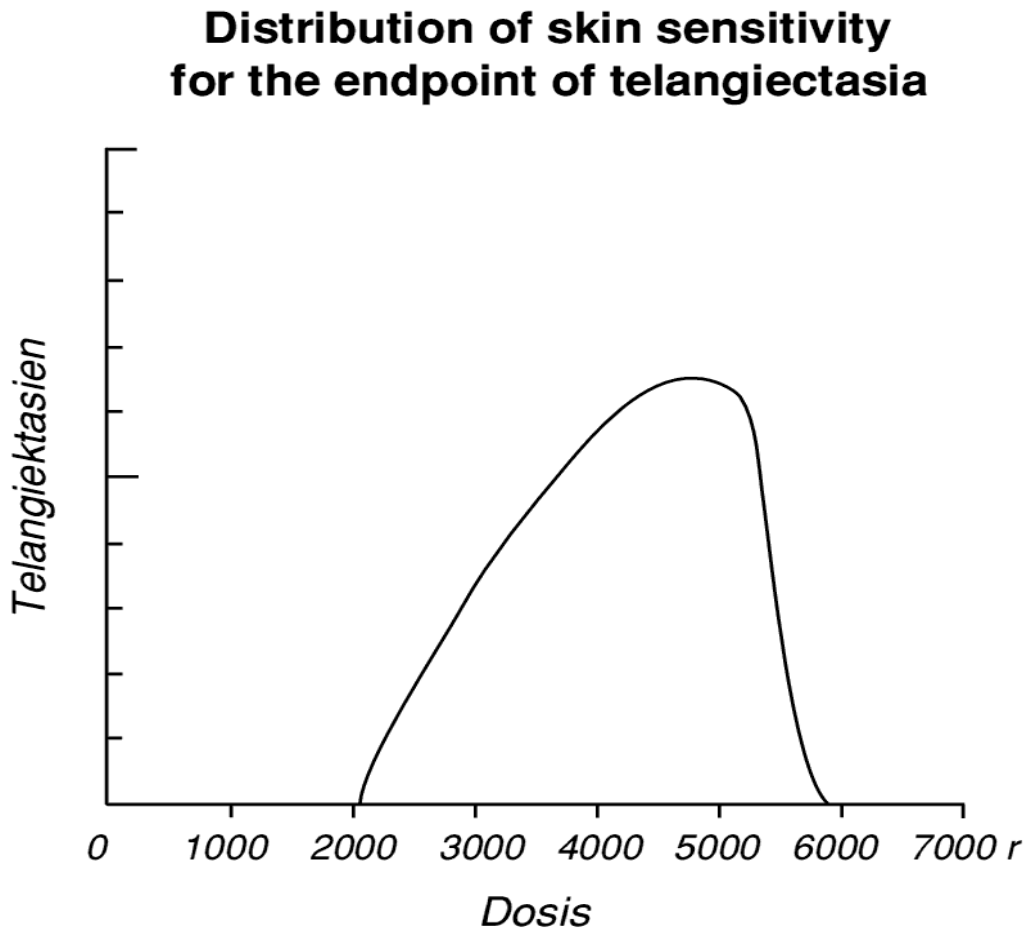
- Three variations on improved therapeutic ratio
  - Same cure, lower toxicity
  - Higher cure, same toxicity
  - Higher cure, lower toxicity (if we can !)

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

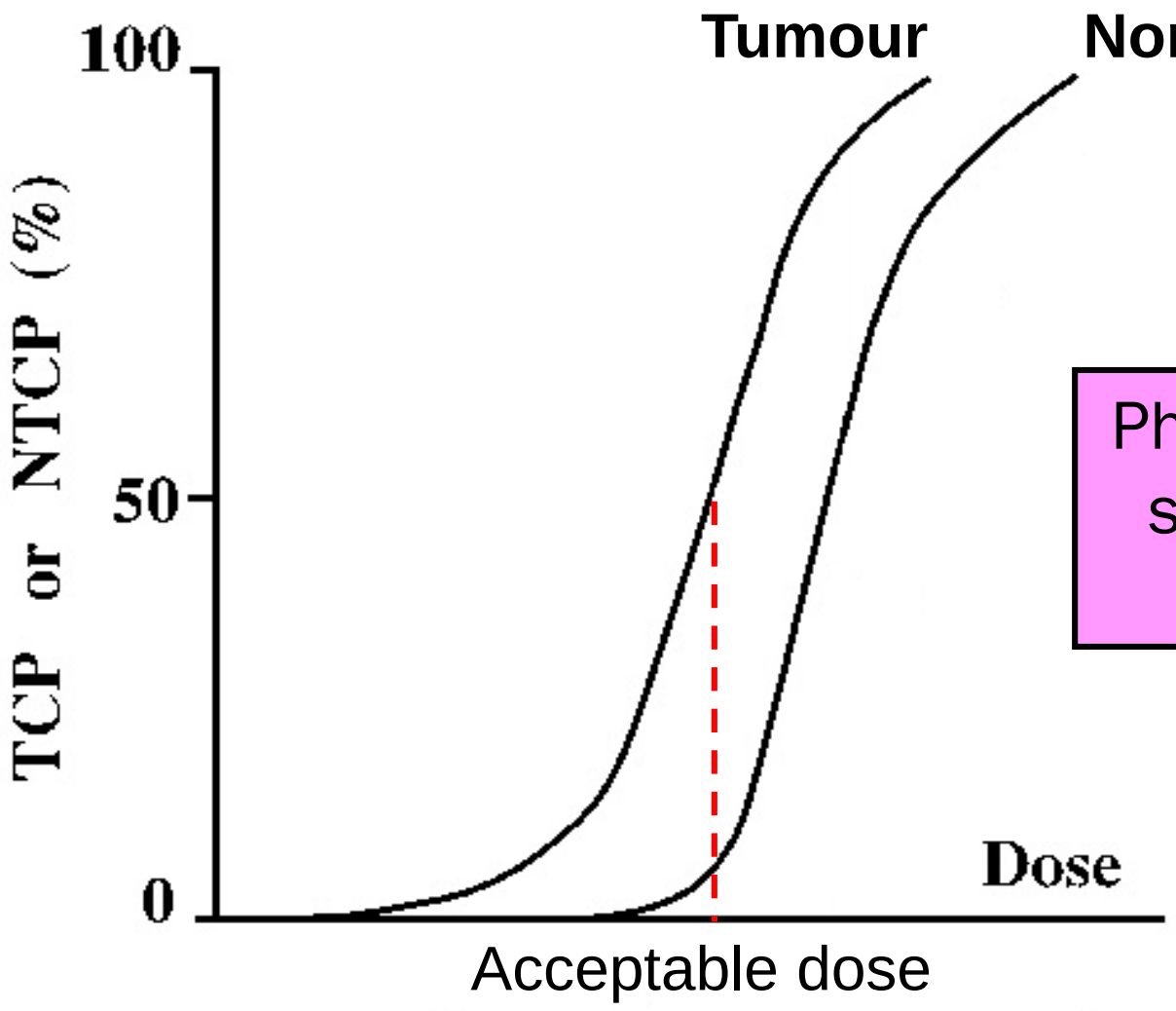
The first normal tissue dose response curve

Holthusen - Strahlentherapie 1936



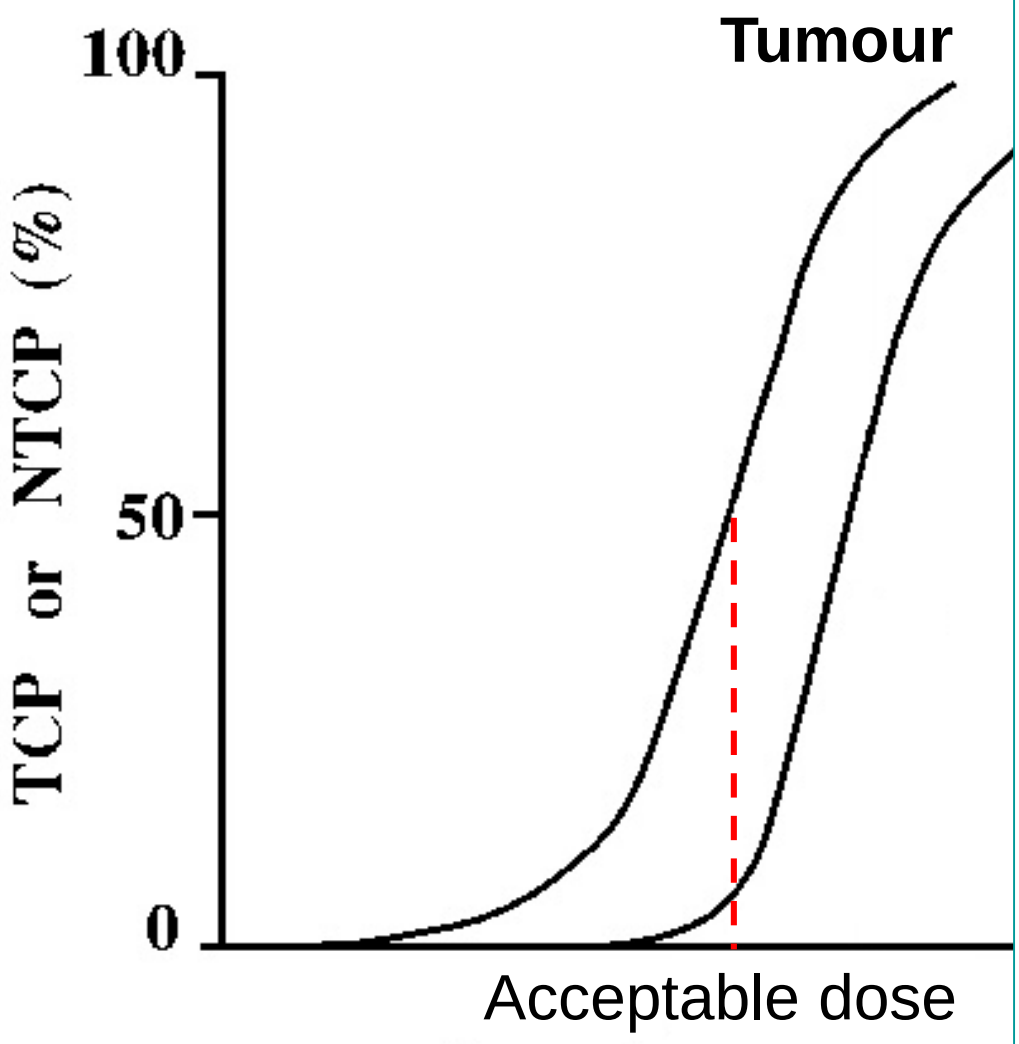


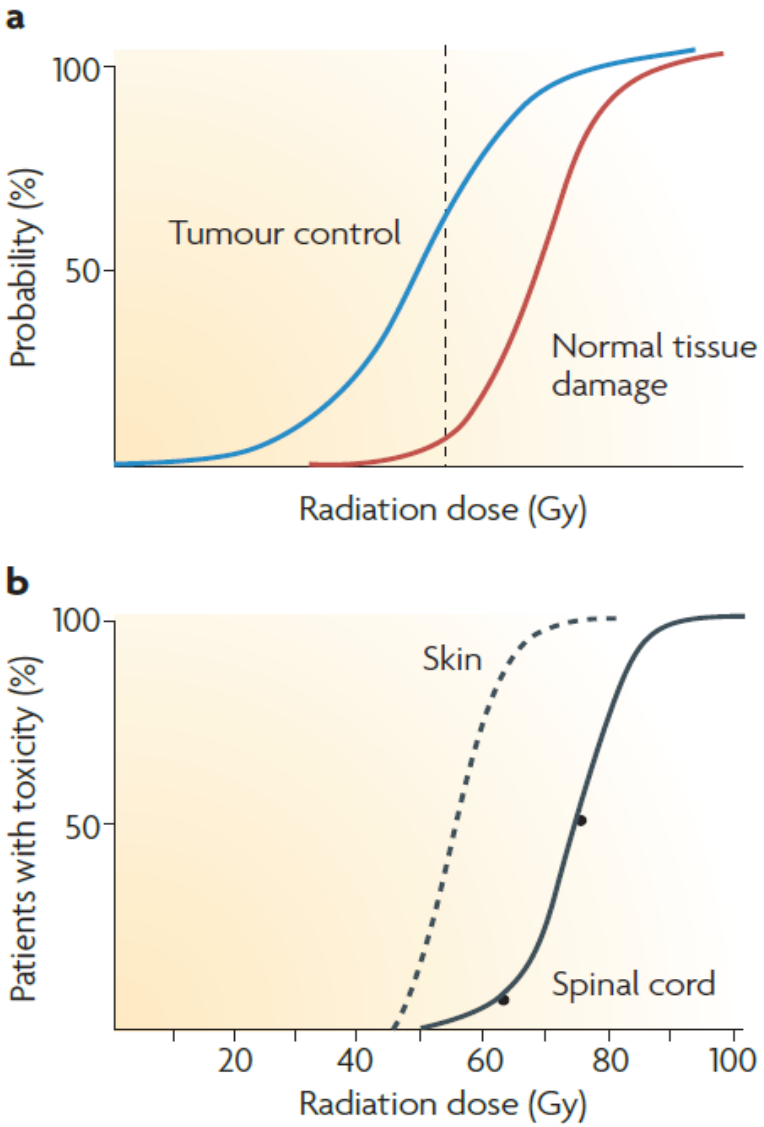
Increase the therapeutic ratio



Physical *and* biological strategies can move the curves apart

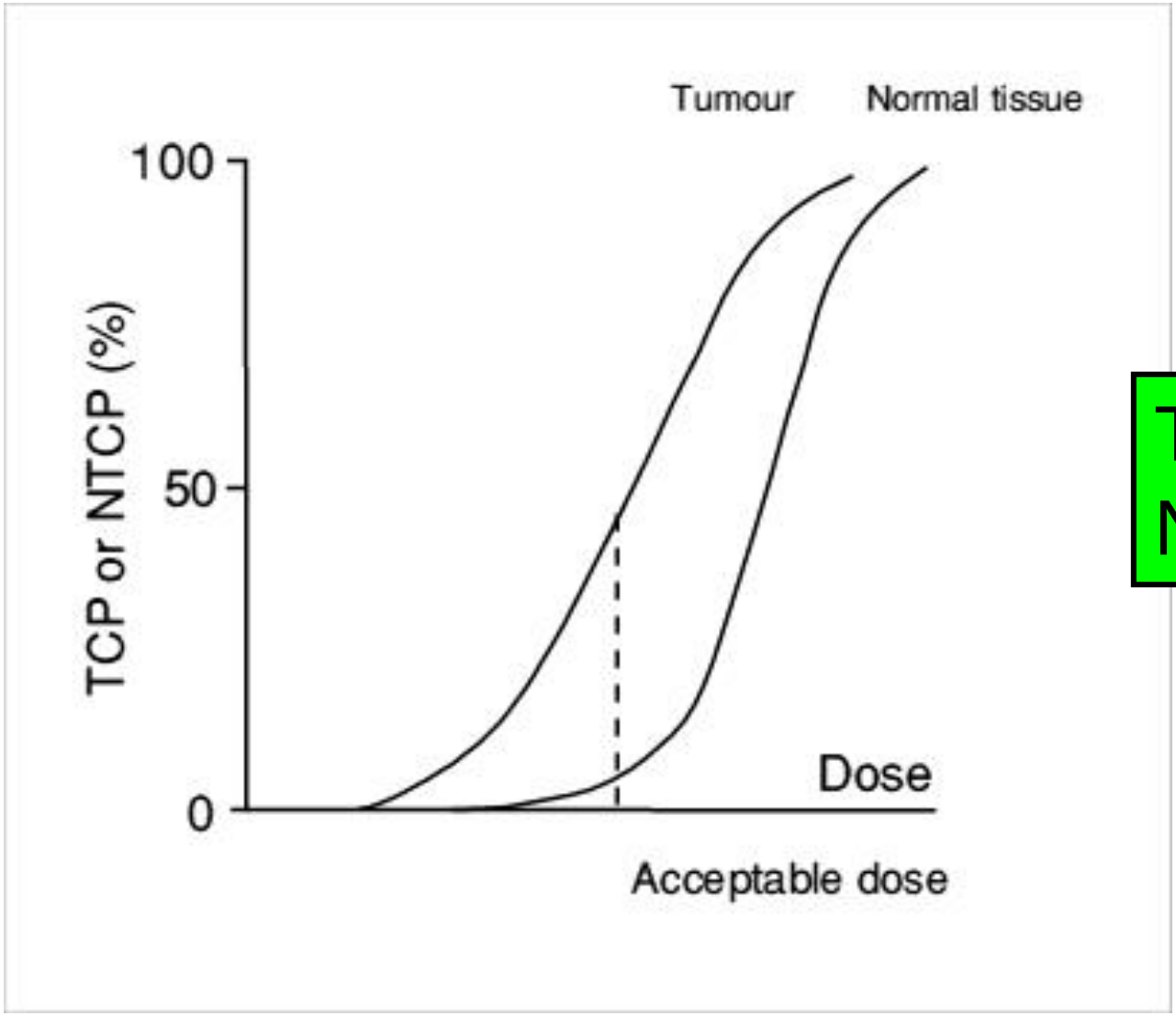
Increase the therapeutic ratio





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

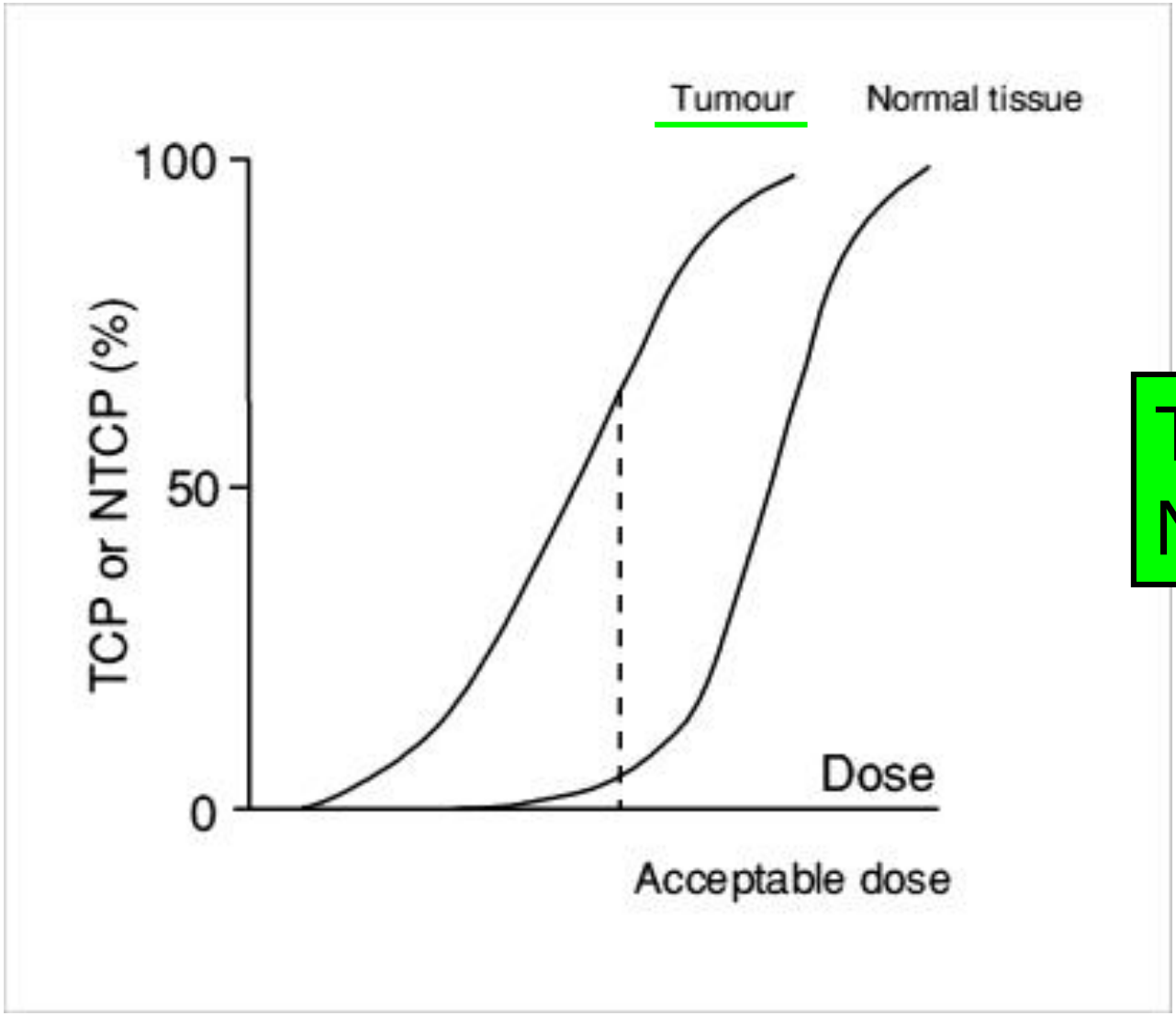
Increase the therapeutic ratio



TCP 50%
NTCP 5%

(a)

Increase the therapeutic ratio



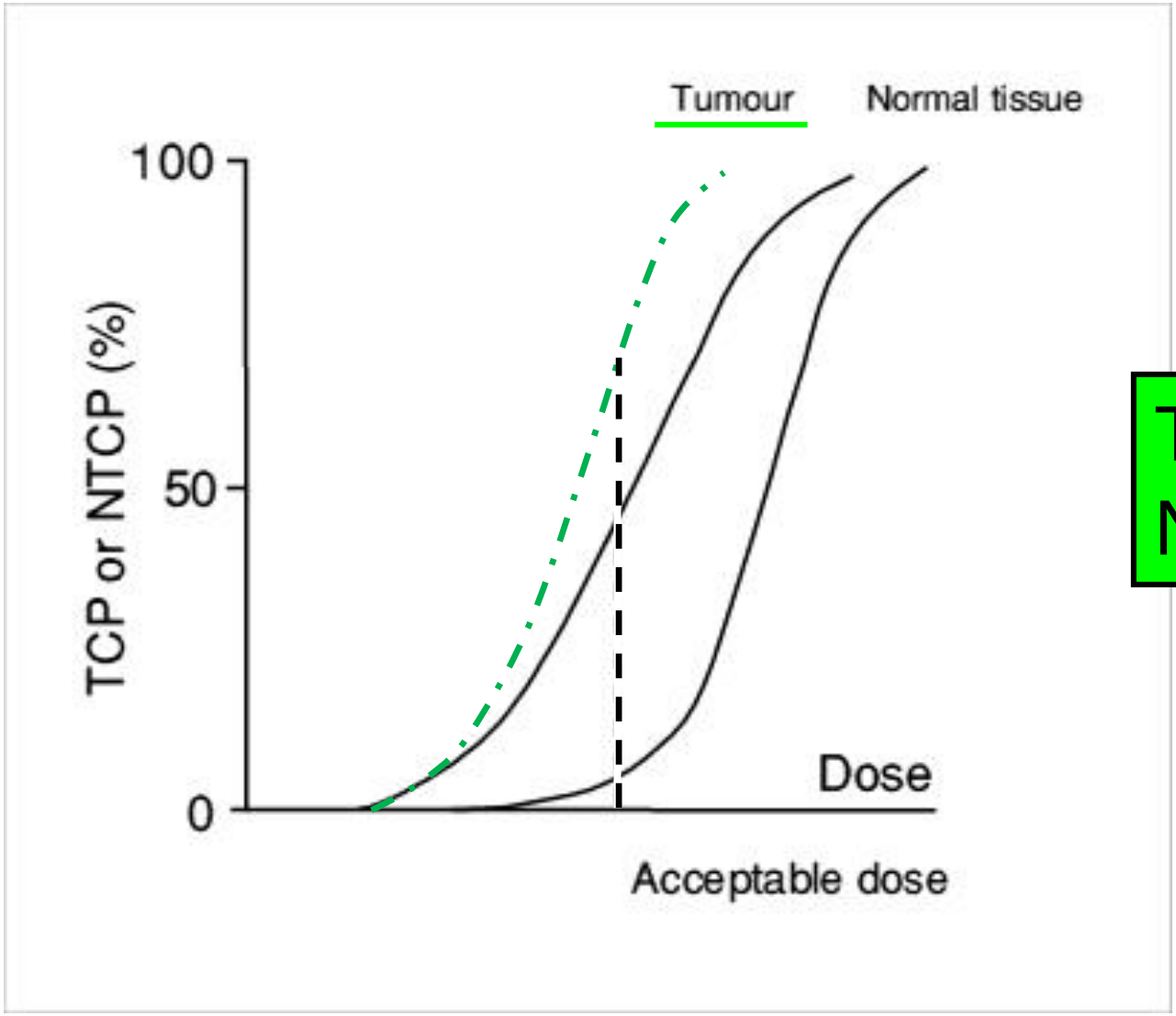
TCP 70%
NTCP 5%

(b)

Increase the therapeutic ratio

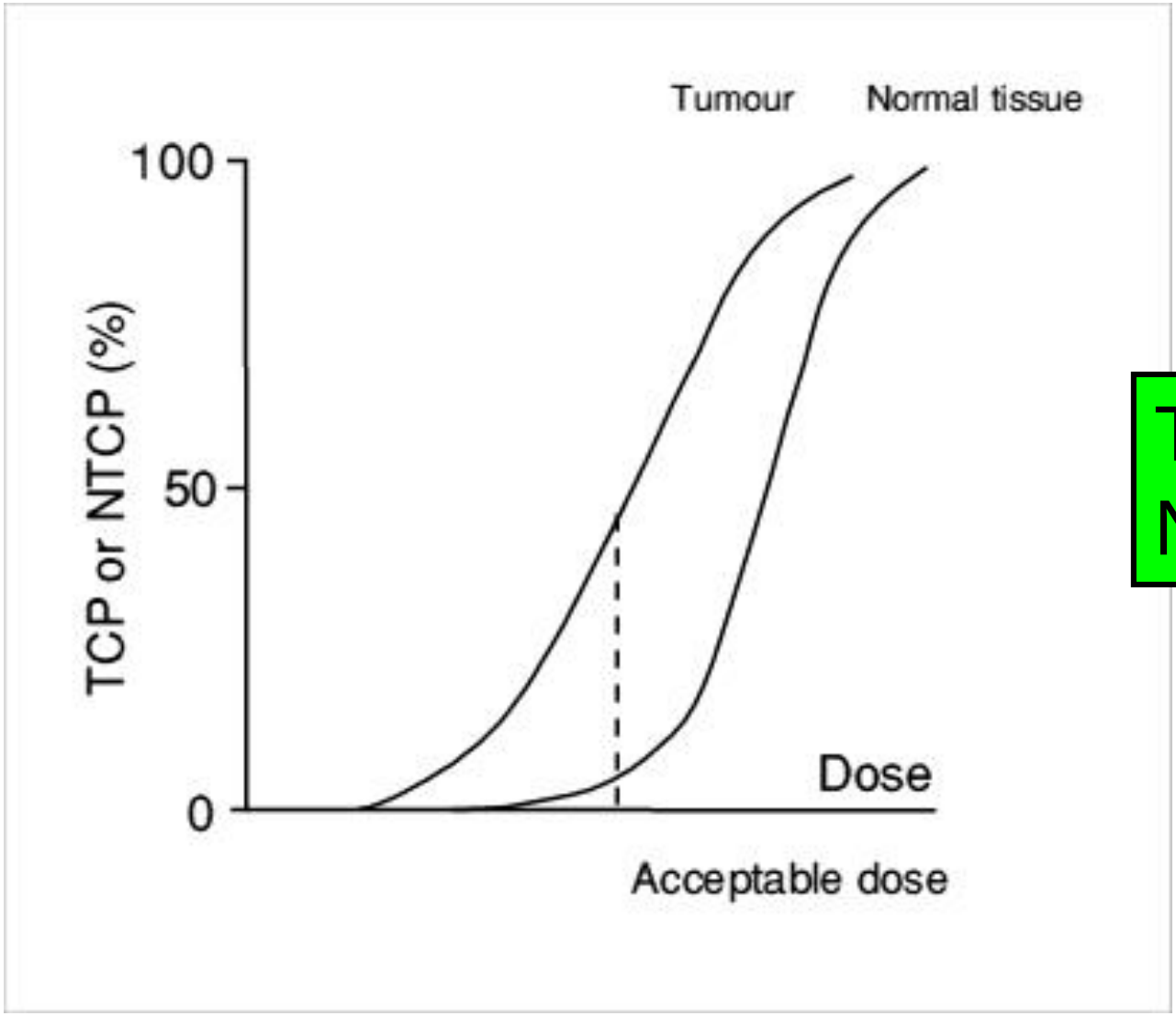
Most approaches steepen the TCP curve

(b)



TCP 70%
NTCP 5%

Increase the therapeutic ratio



TCP 50%
NTCP 5%

(a)

Back to the beginning

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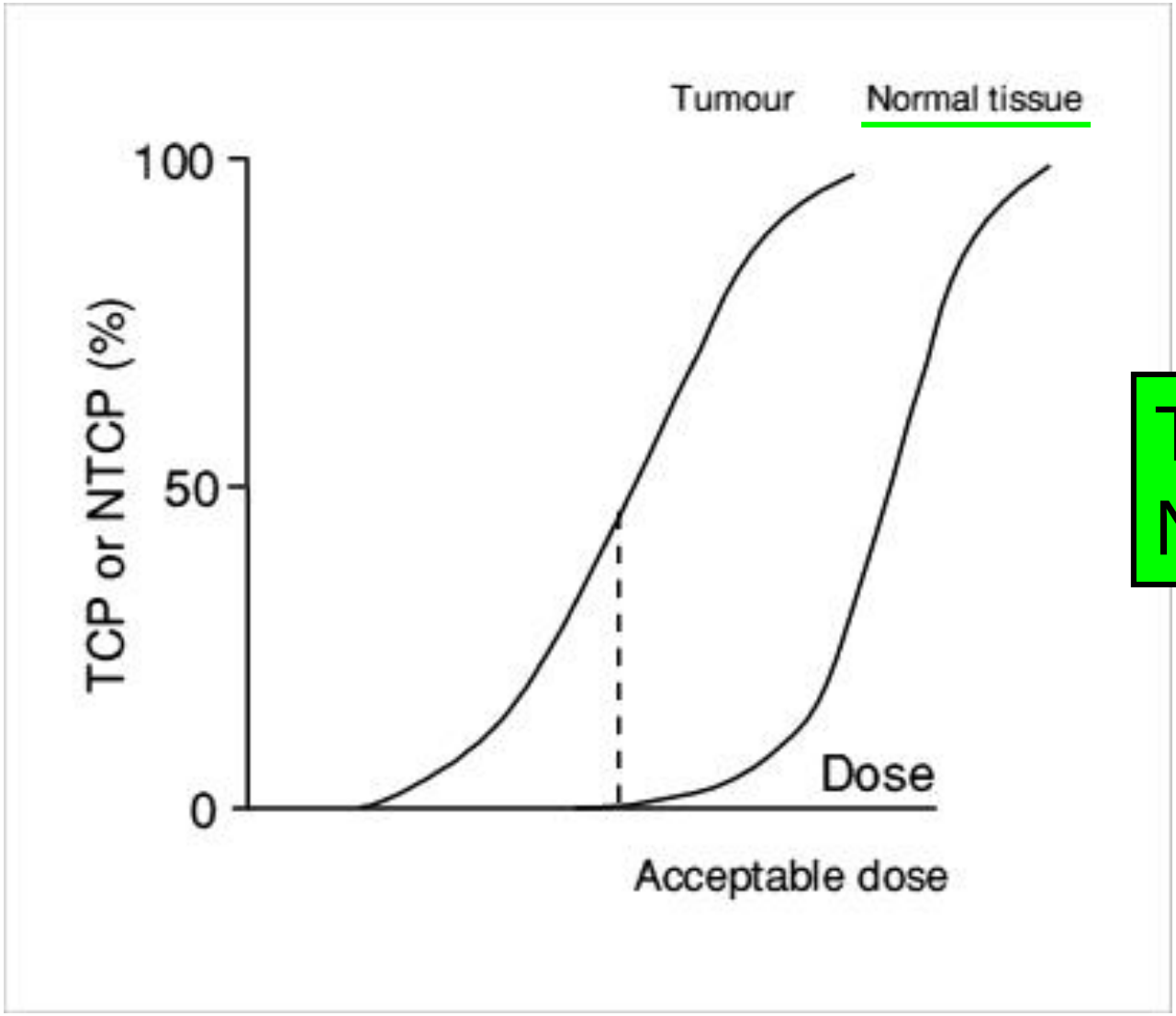
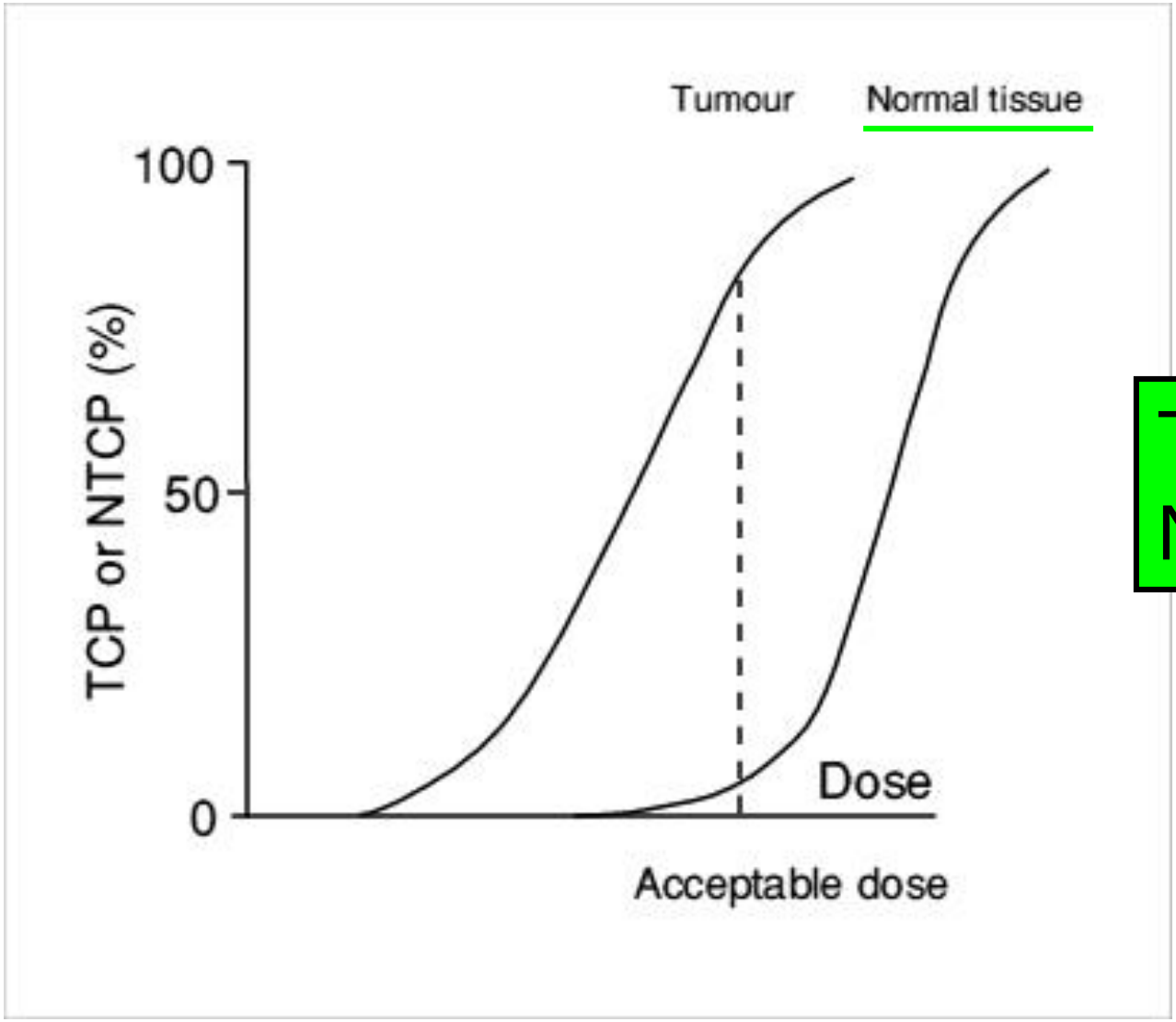
Increase the therapeutic ratio



TCP 50%
NTCP ~0%

(c)

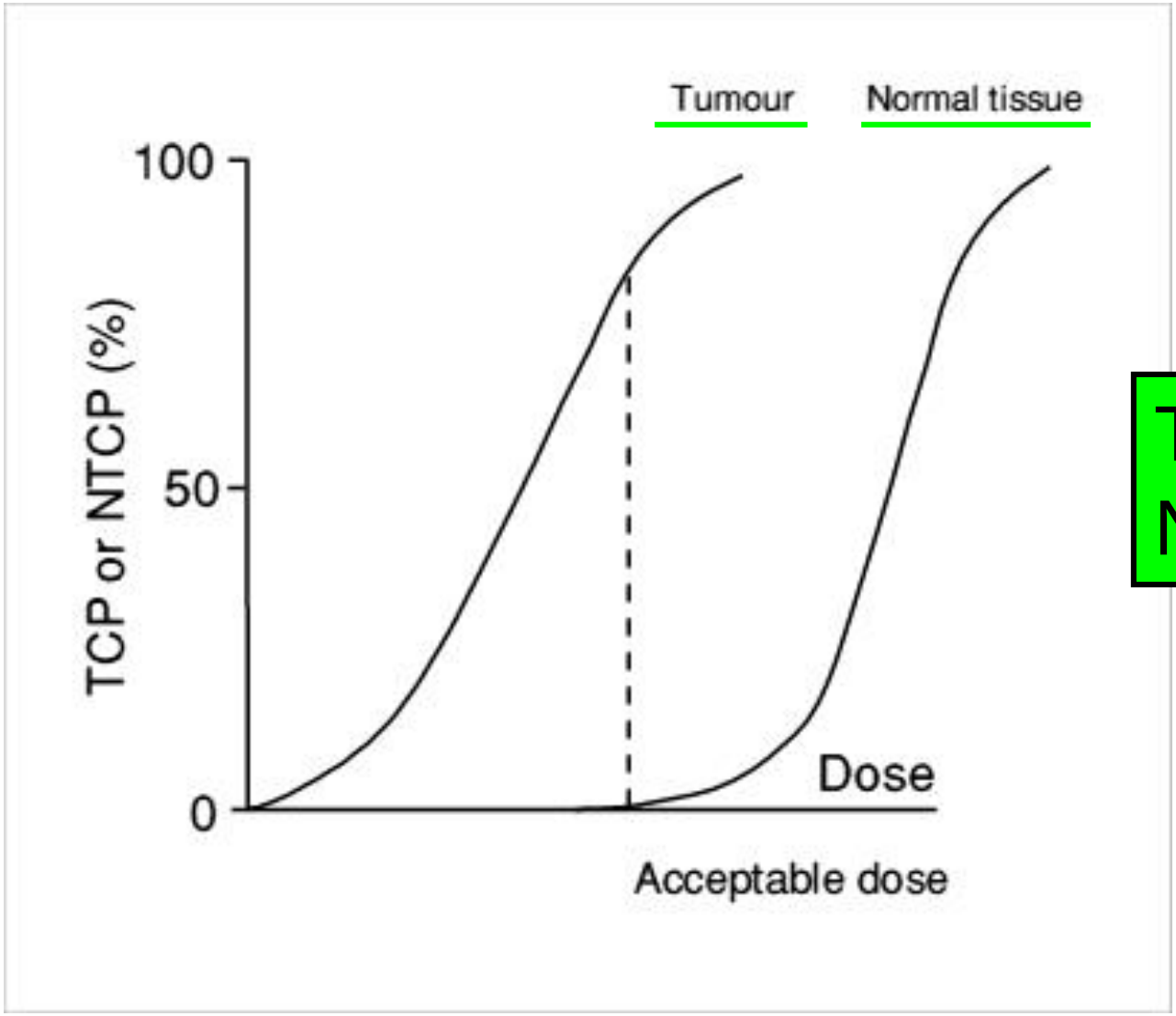
Increase the therapeutic ratio



TCP 80%
NTCP 5%

(d)

Increase the therapeutic ratio



TCP 80%
NTCP ~0%

(e)

Normal tissue toxicities

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

Normal tissue toxicities

- A balance in time

- Balance risks of:
  - **late** normal tissue/organ damage against
  - **very late** second malignancy

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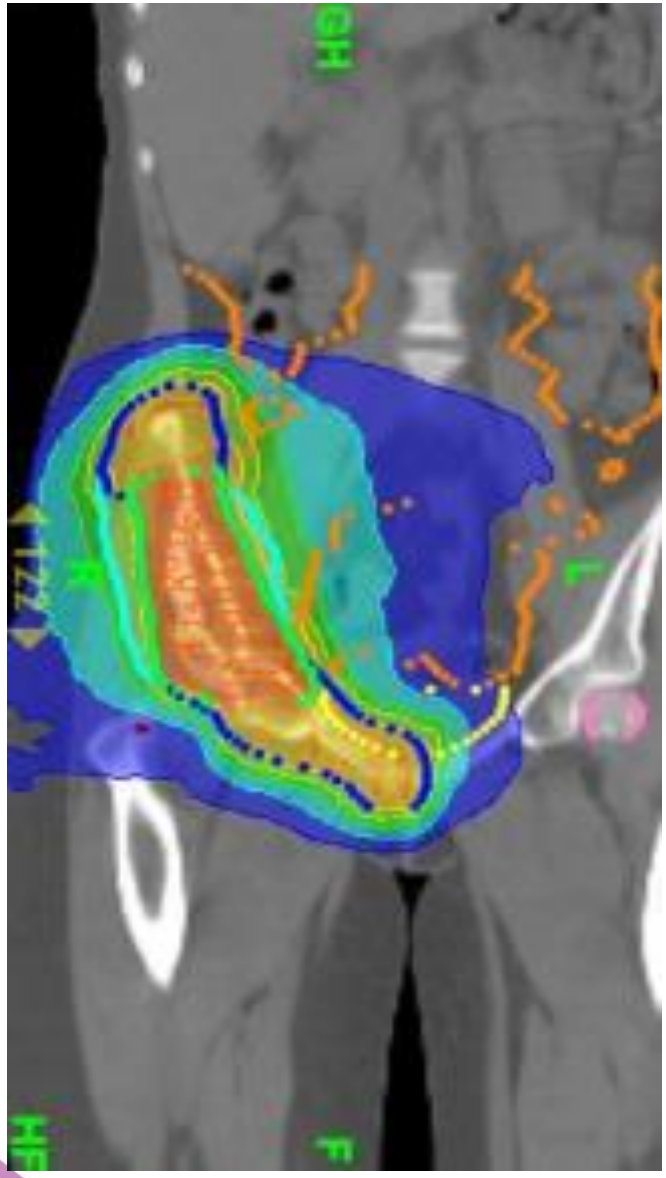
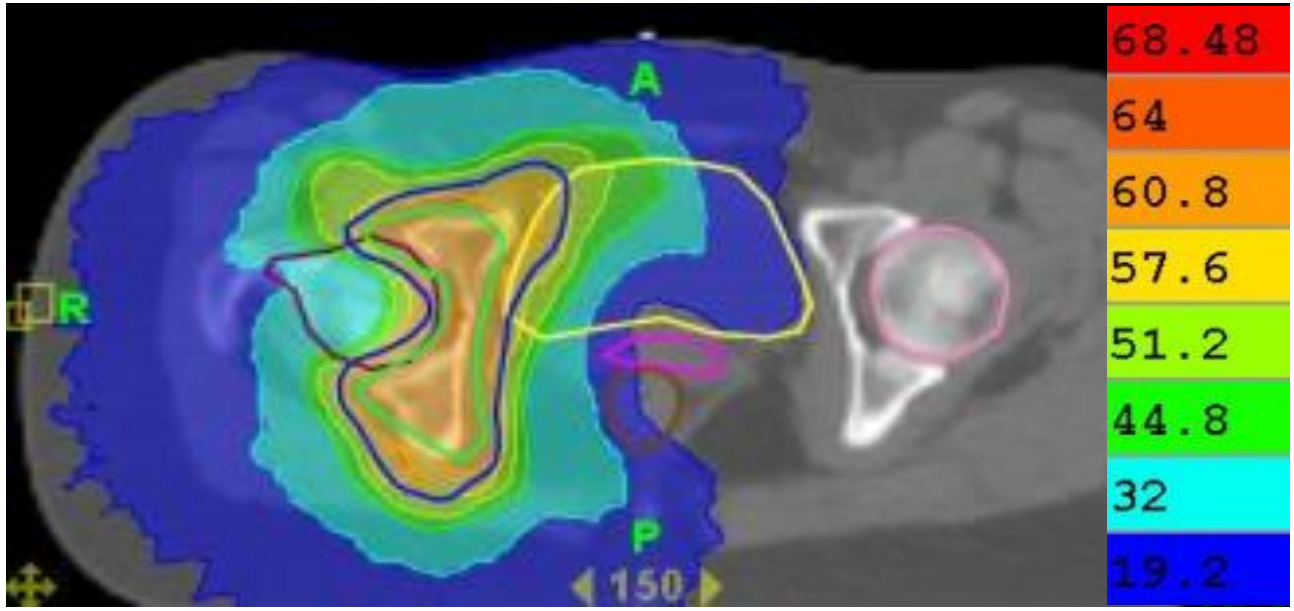
Pelvic Ewing's sarcoma



- 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

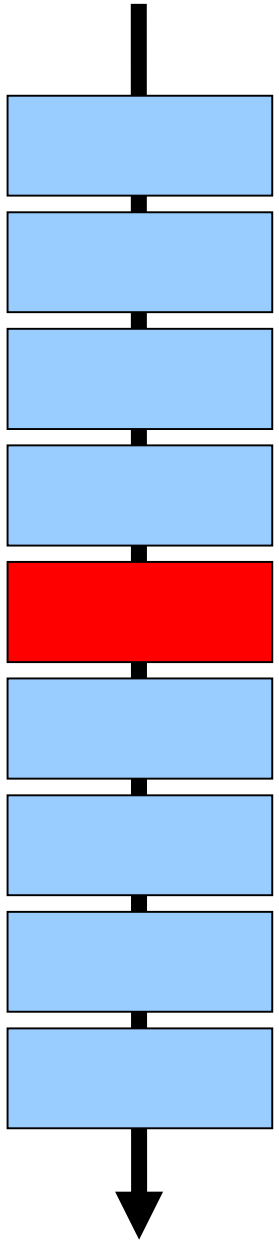
- Damage to 1 part causes failure
- Serious clinical consequence

- High dose most important

- For example …

… spinal cord,
brainstem,
optic nerves

… ? oesophagus



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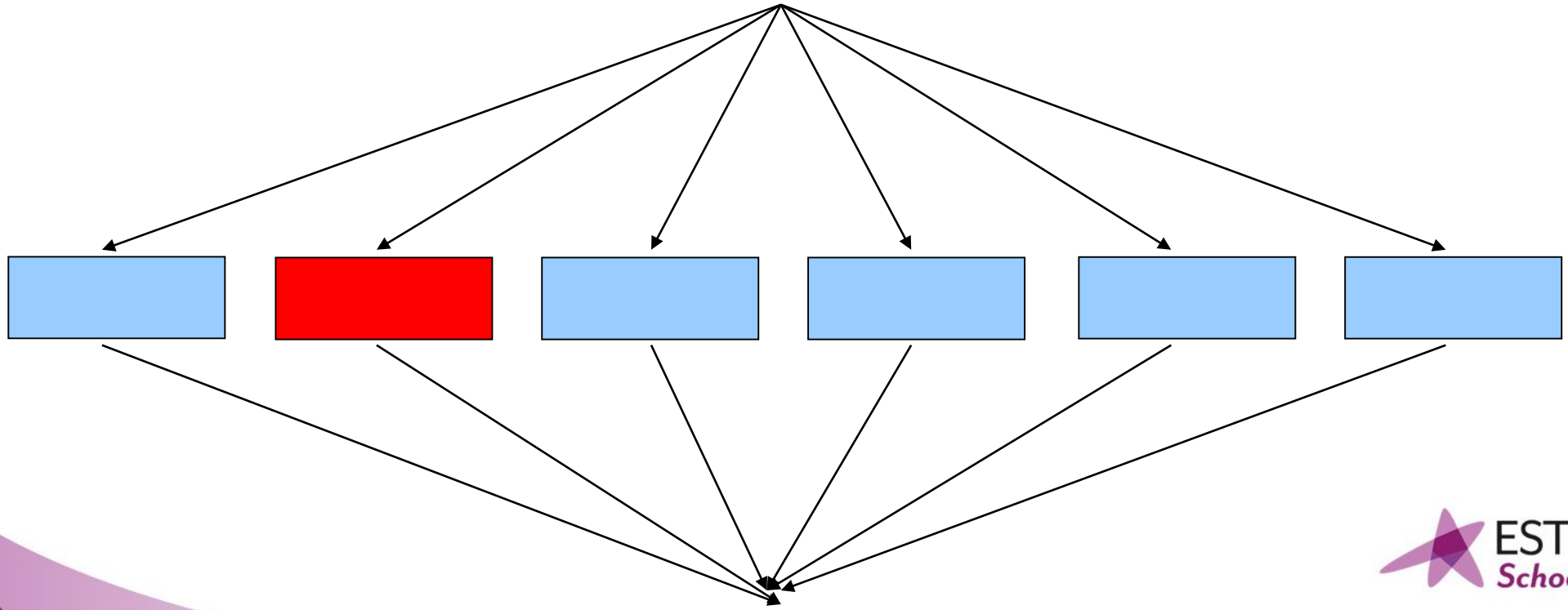
Normal tissue response

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

… lung, liver, salivary glands, skin …



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Normal tissue response

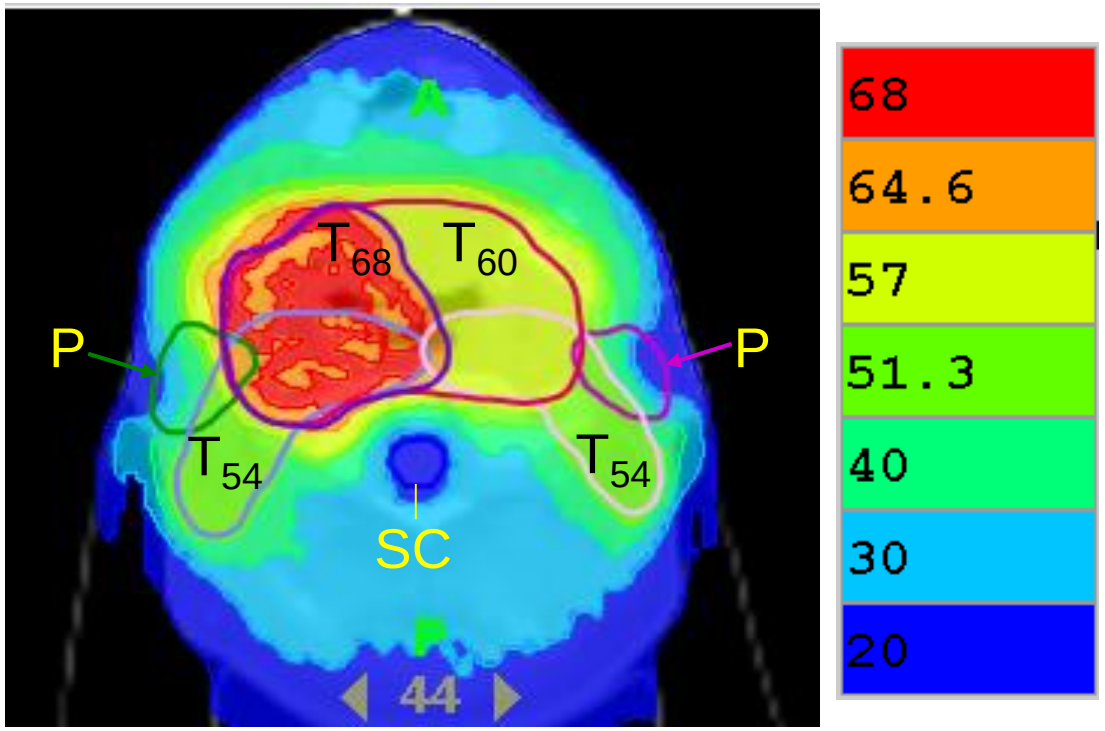
- Volume and architecture important

- 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

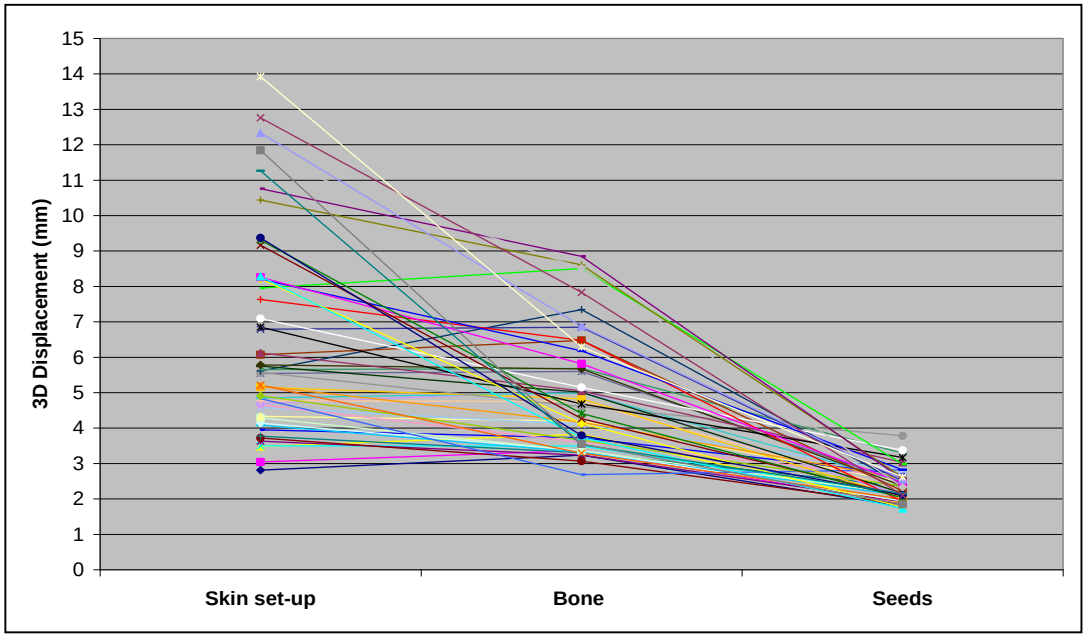
- IMRT for Head and neck cancer
- Sparing parotids reduces toxicity ¶
- Restricting dose to spinal cord allows high dose



¶ 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)
    - ➢ *Reduces* total patient dose (integral dose)
  - ➢ Delivers dose more precisely to target and normal tissue
  - ➢ Especially important with steep dose gradients



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

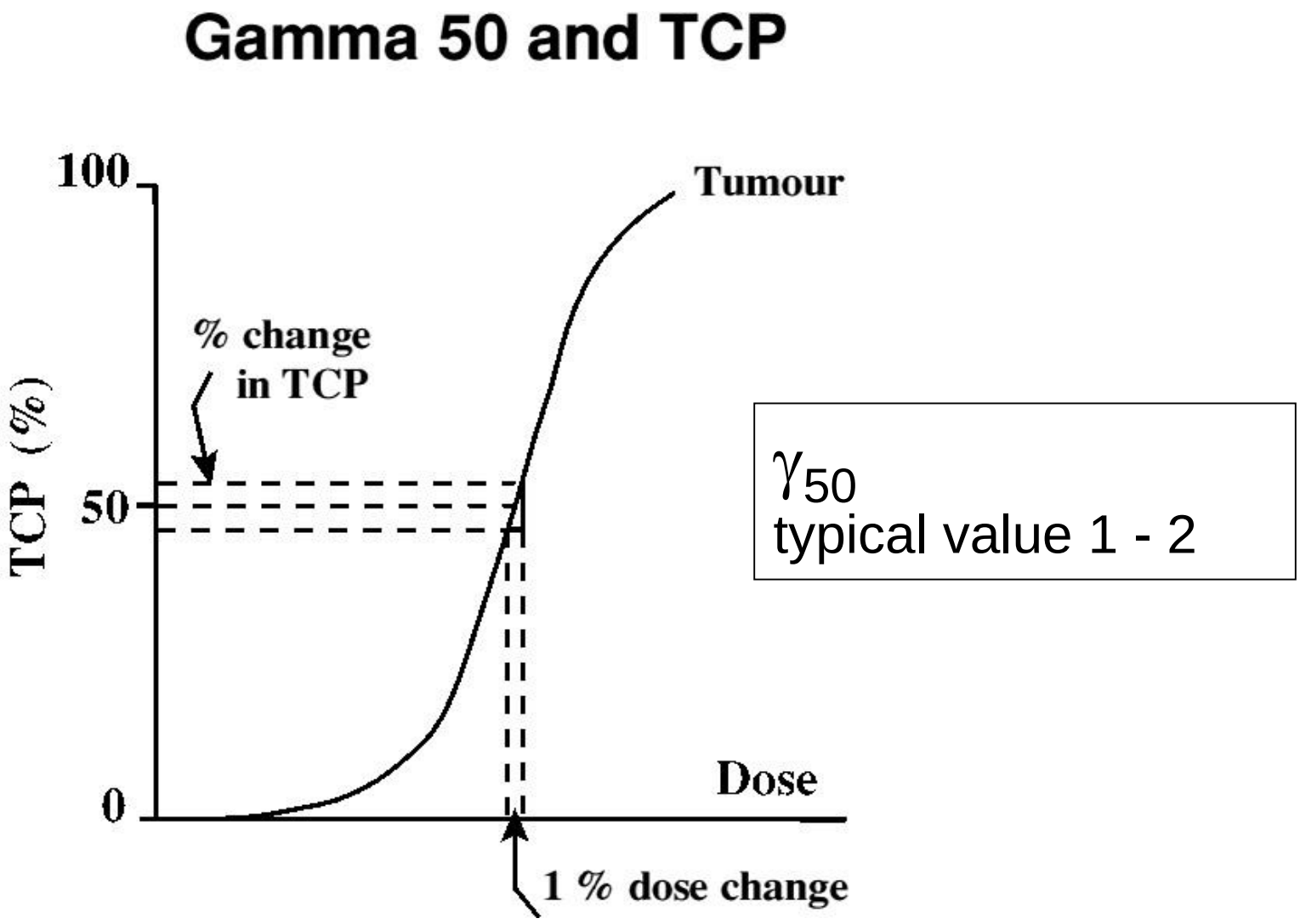
Broadening the band width

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

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

- This applies to
  - individual patients
  - populations

Broadening the band width



γ_{50}
typical value 1 - 2

Broadening the band width

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

Broadening the band width

- 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

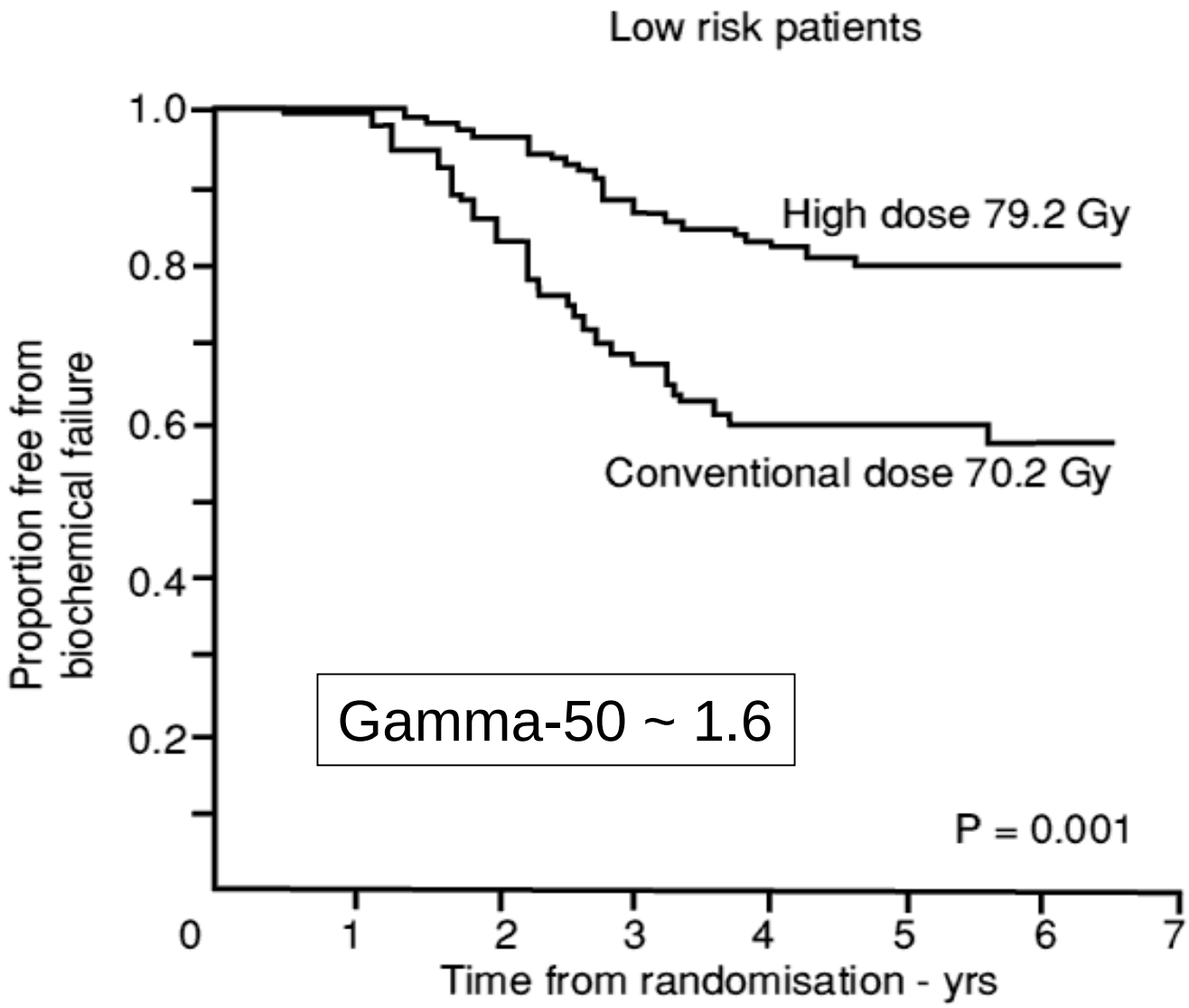
Mike Sharpe
‘Mike on his bike’

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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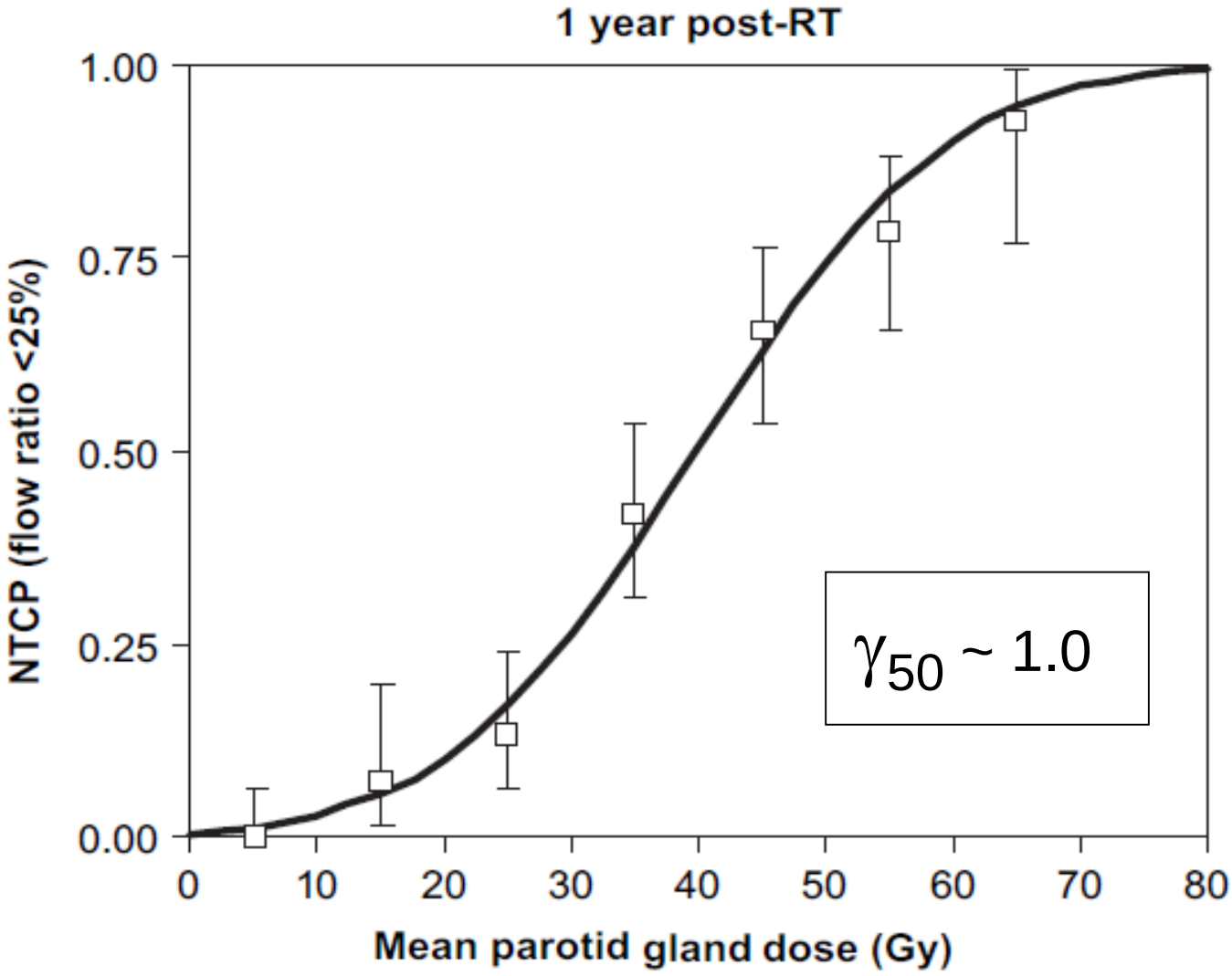
Broadening the band width

Parotid toxicity



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

Combined Michigan & Utrecht data

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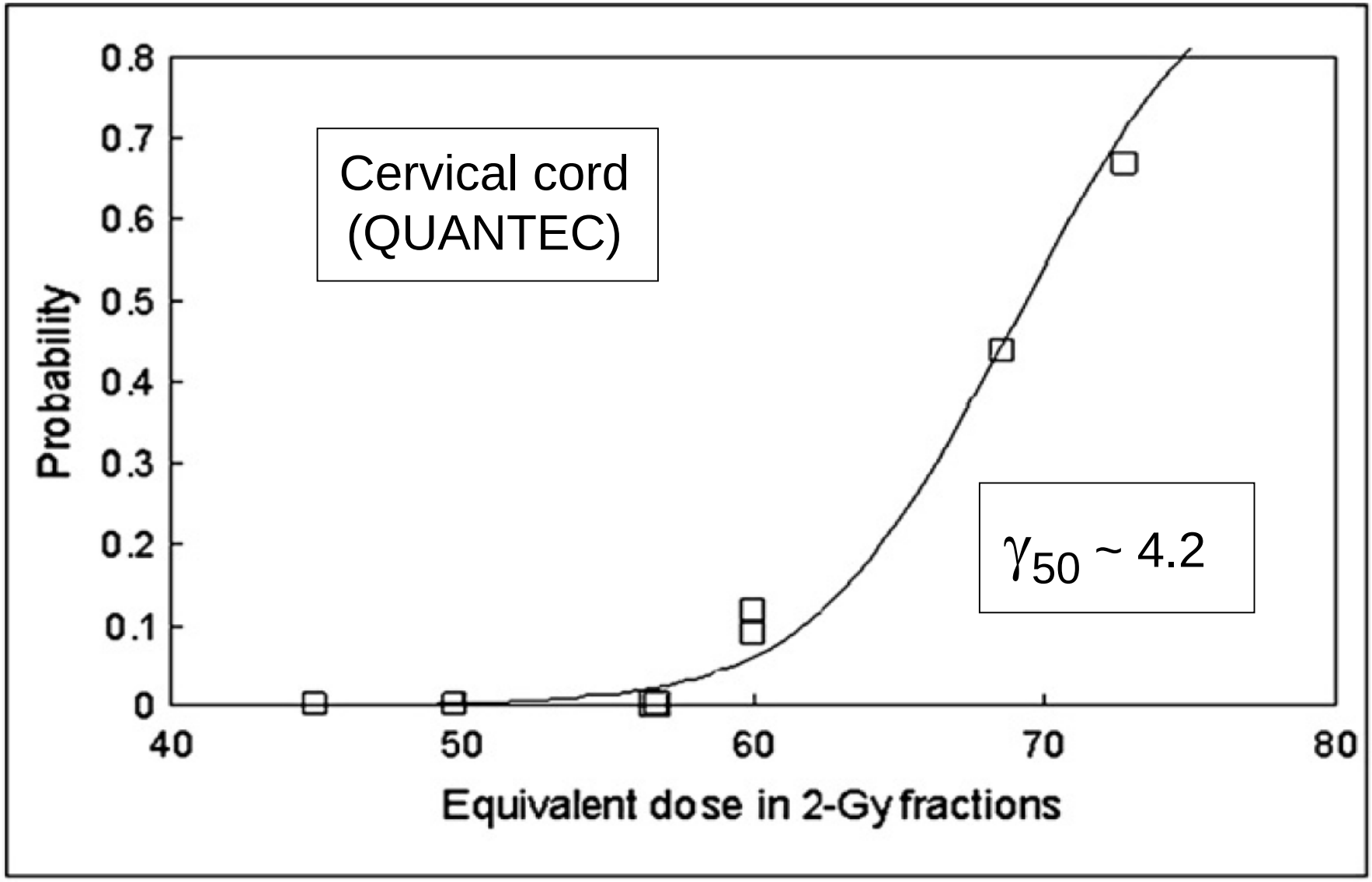
Broadening the band width



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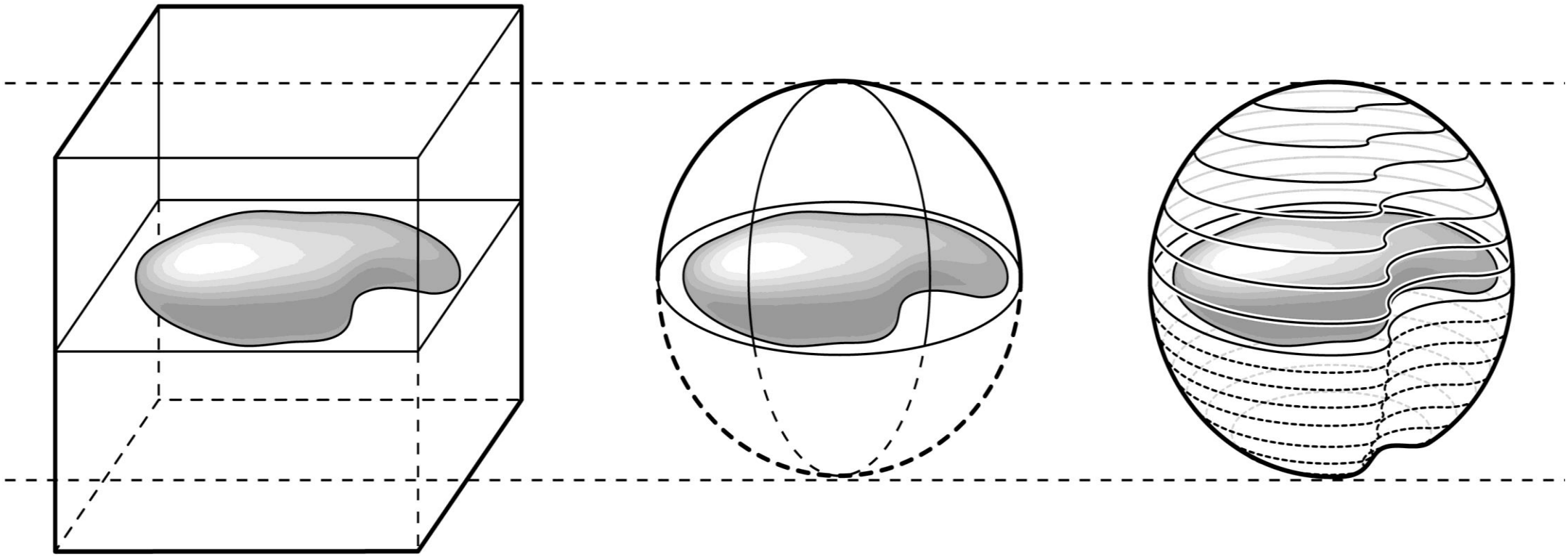
Treatment volumes compared



Conventional ‘square’ plan

3D CRT plan

IMRT plan

Use the best equipment you can!

- Old equipment
- Poor maintenance
- Bad choice!

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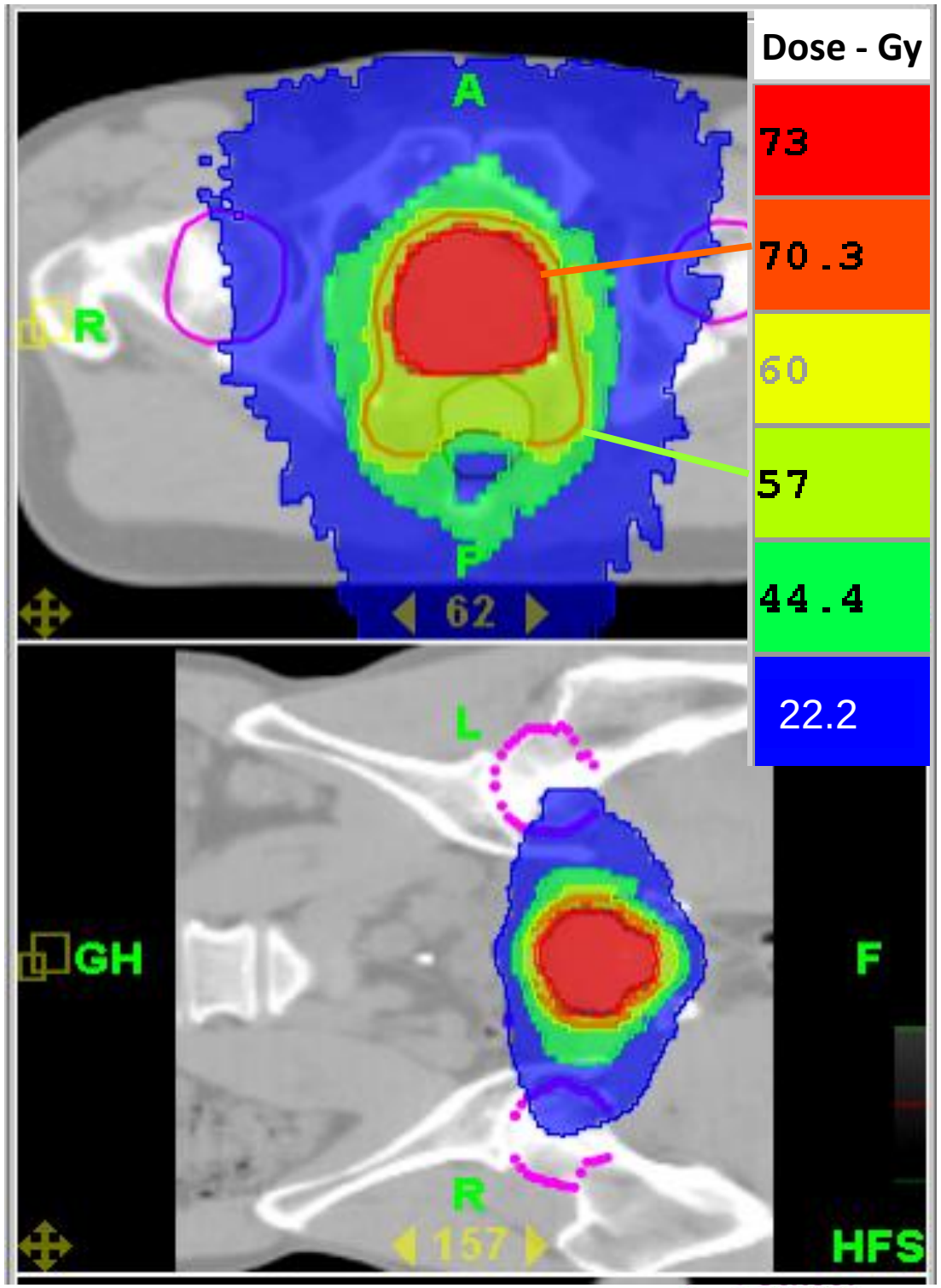
Ca prostate

- Ca prostate

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

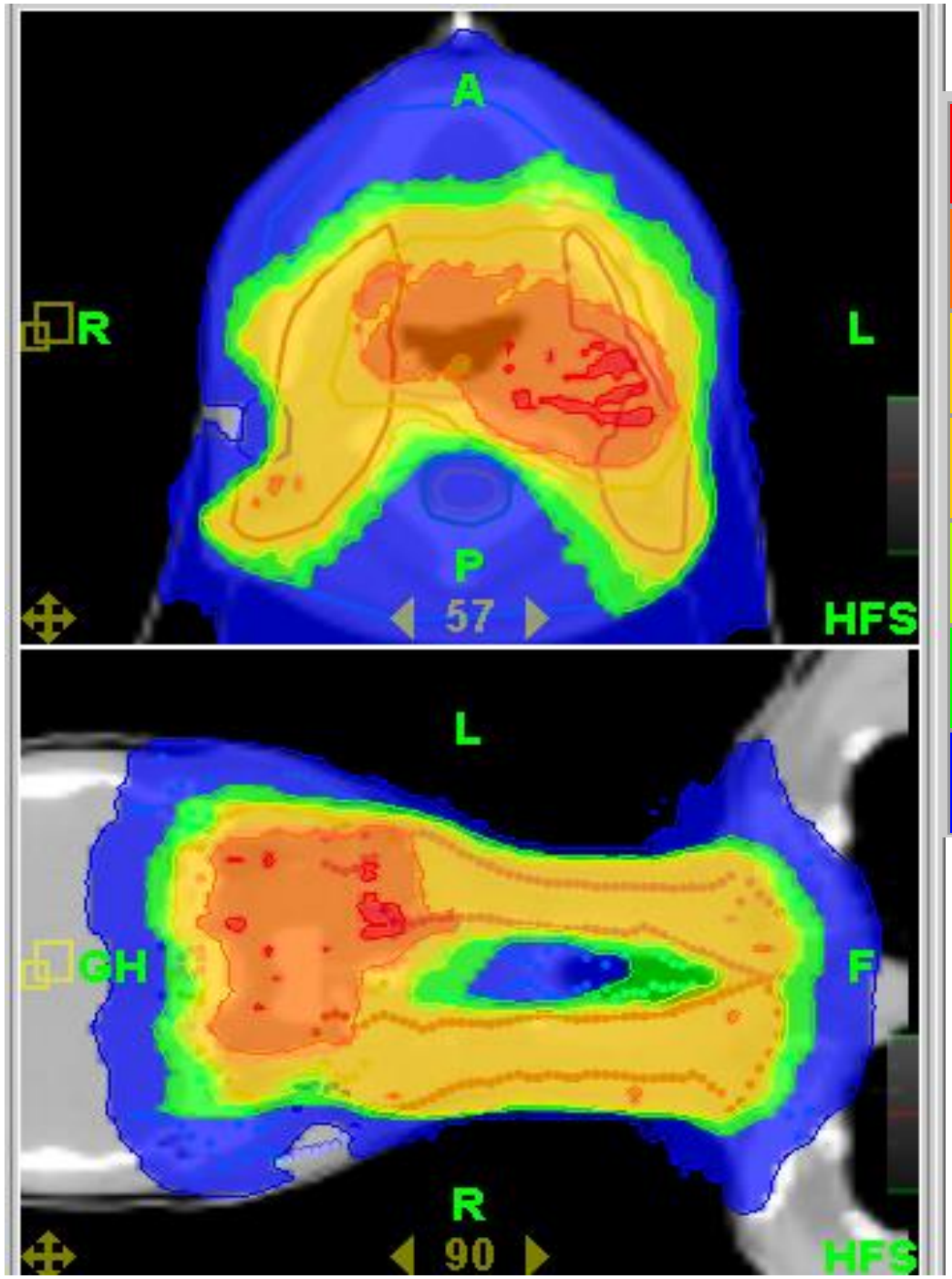
- Rectal sparing behind PTV



Ca nasopharynx

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

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



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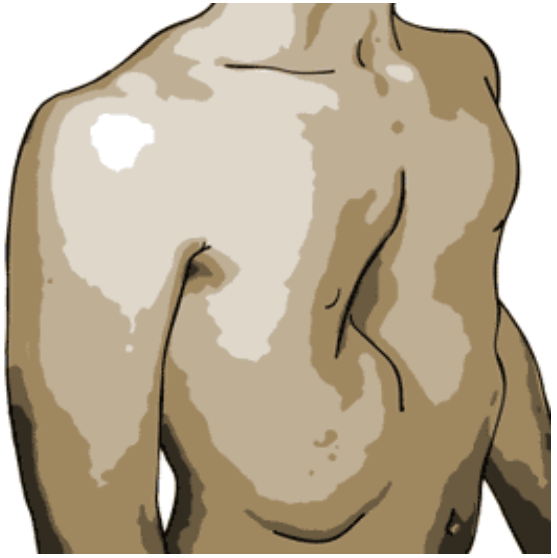
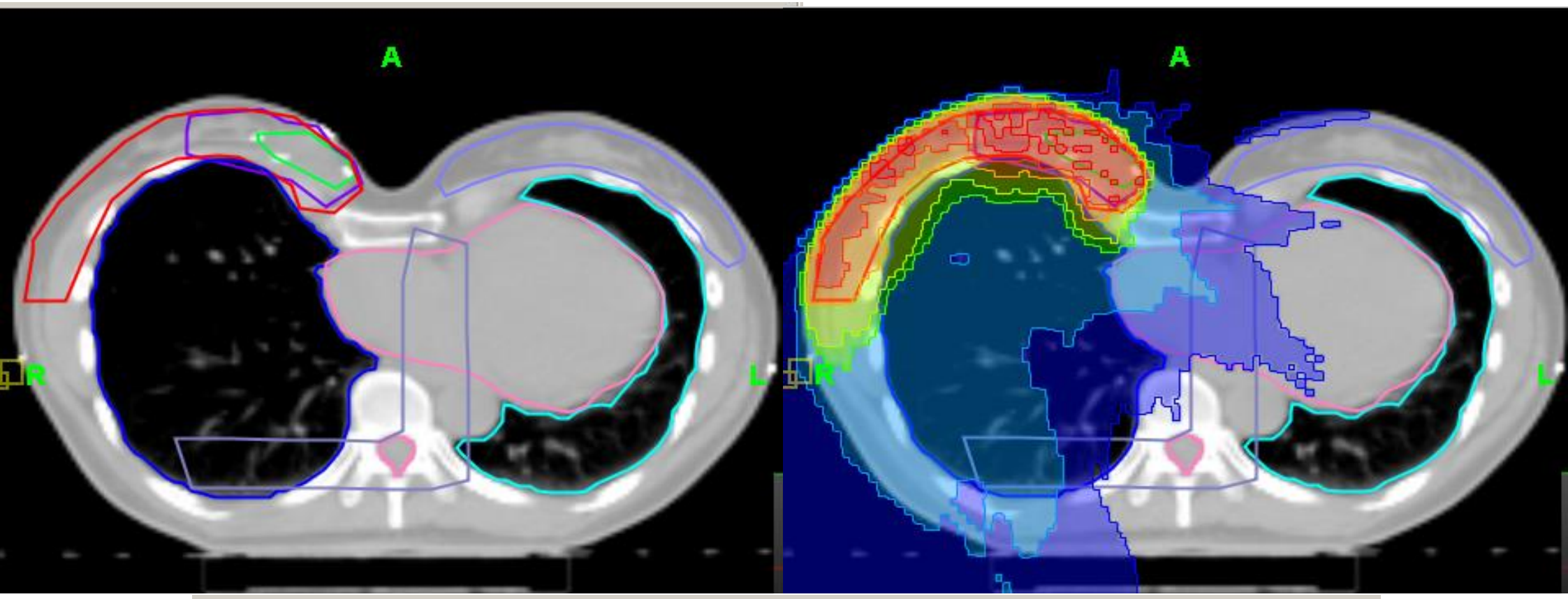
Ca breast

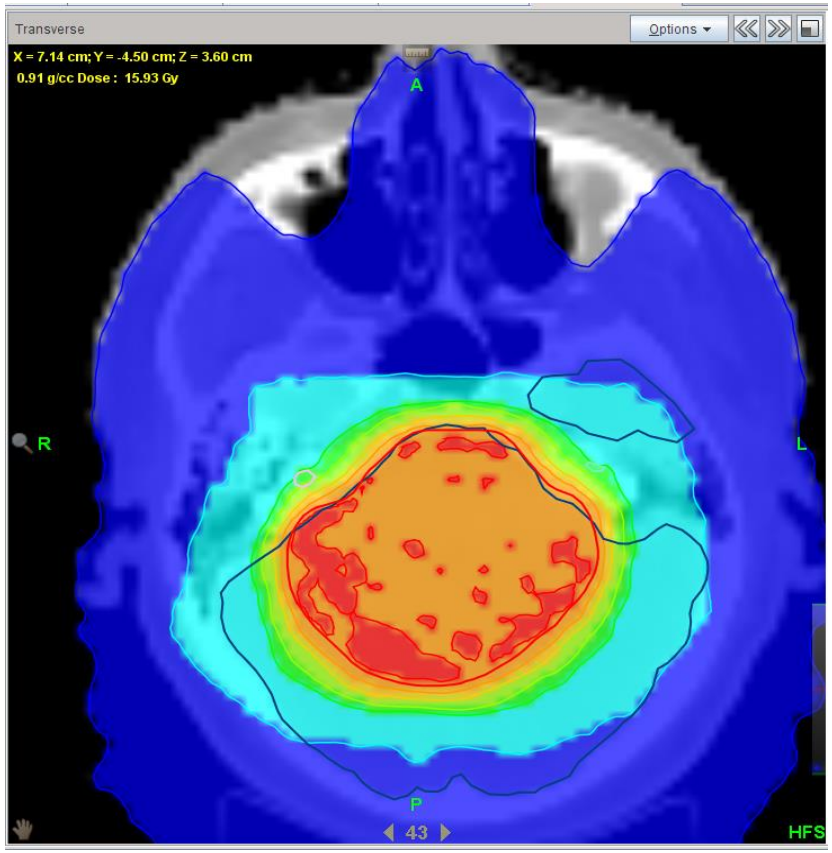
- Ca breast
- Pectus excavatum
- 40 Gy / 15 #

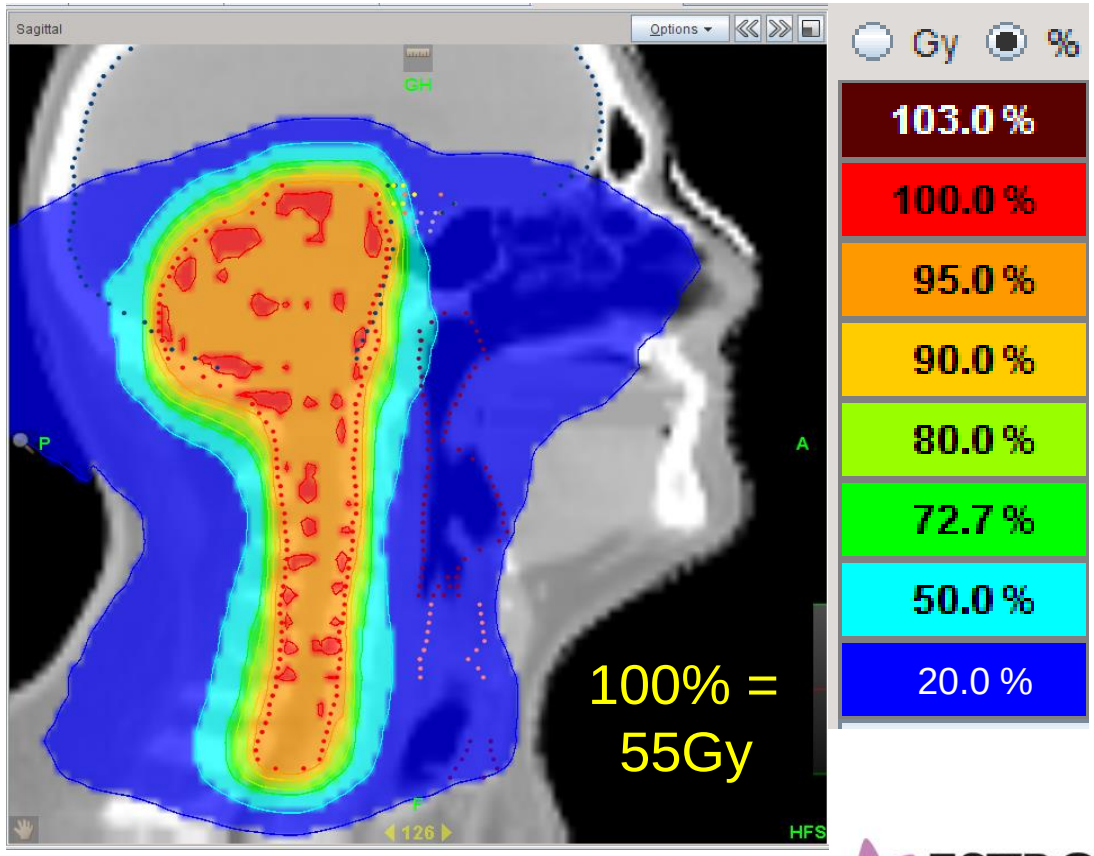




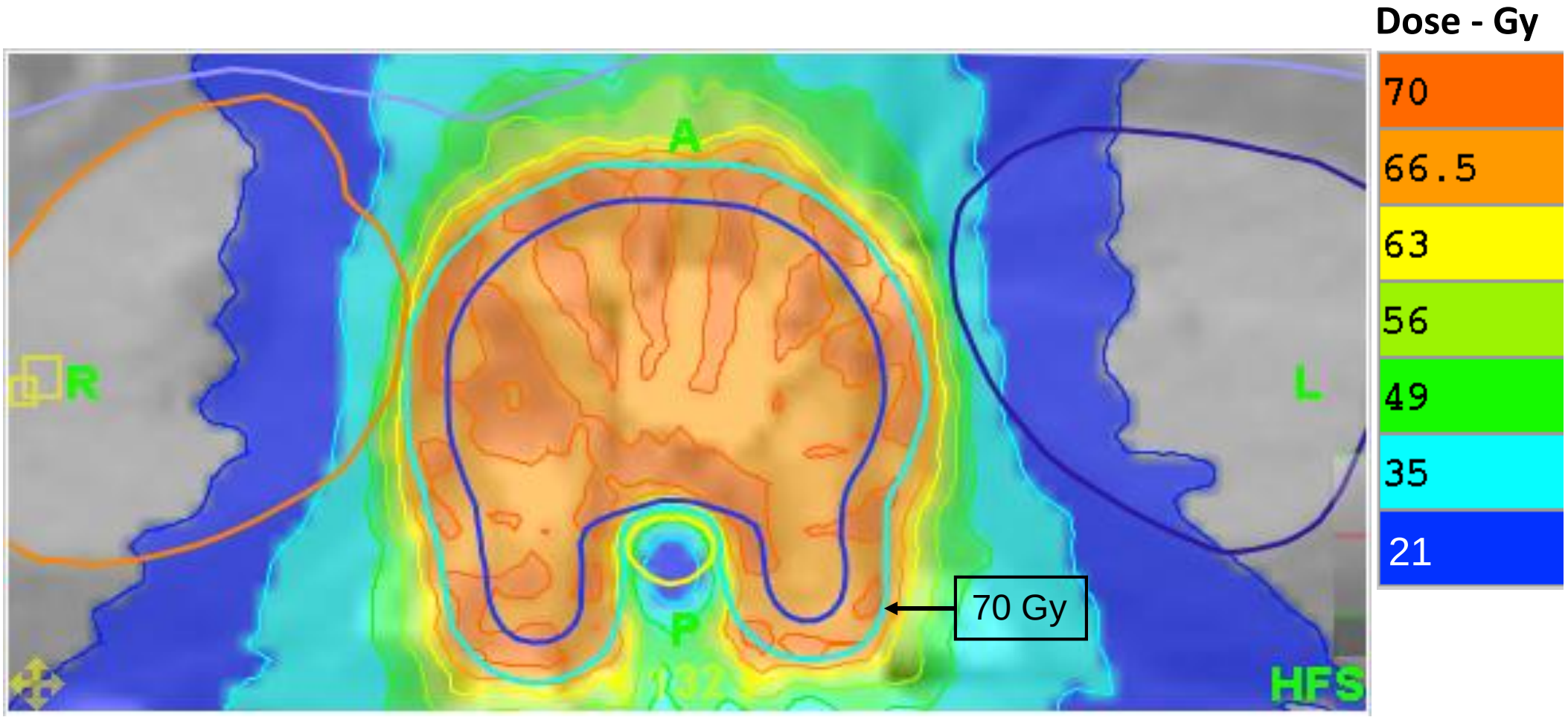
Brainstem + upper cord glioma

- 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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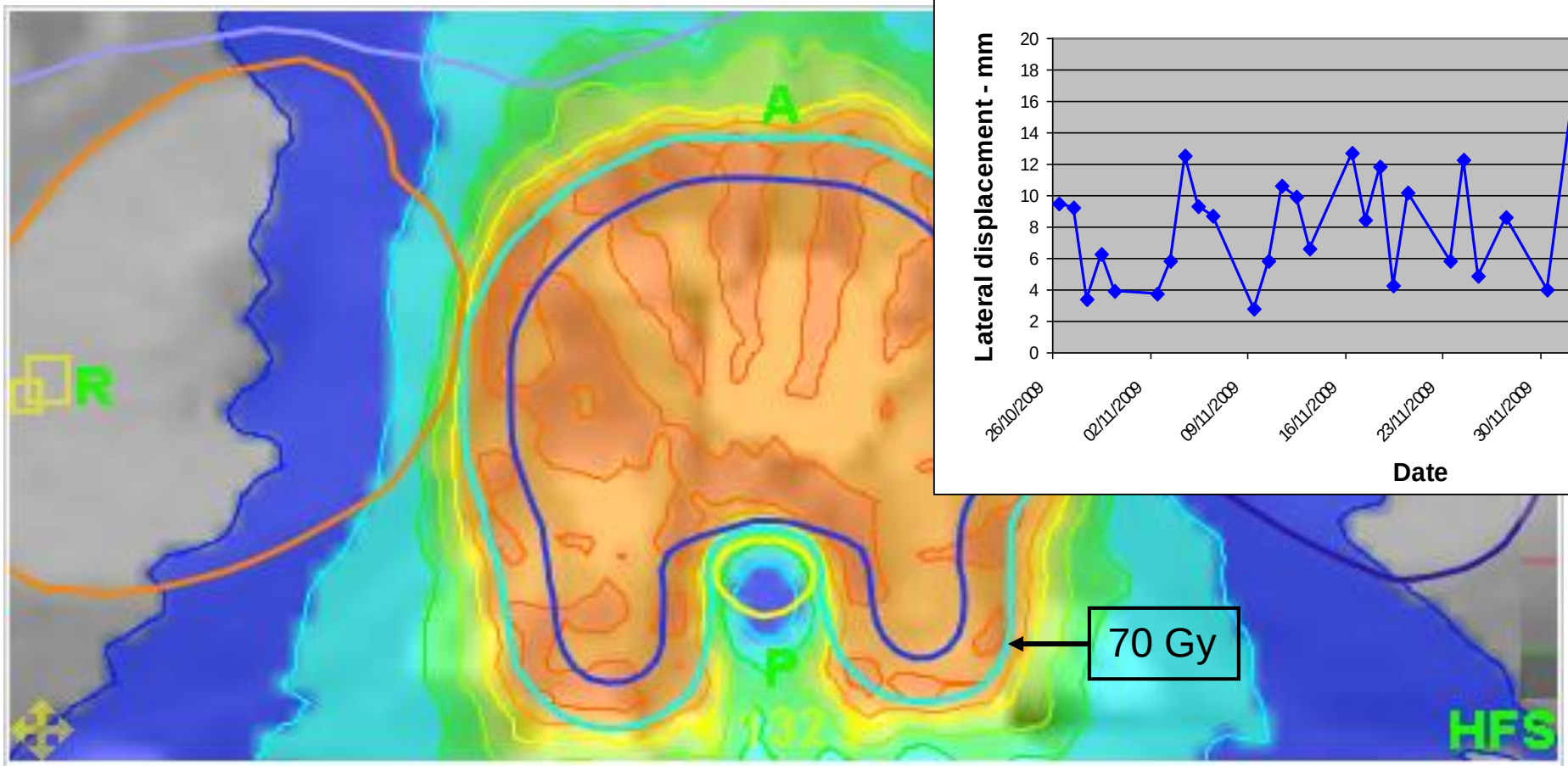
IMRT for chordoma



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

Photo of patient in the treatment room having just completed course of high dose RT to para-aortic nodes

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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Thank you

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Dose calculation algorithms & their differrences in clinical impact

Advanced Treatment Planning Course
23-27 September 2018 – Athens, Greece

Markus Stock

MedAustron
Ion Therapy Center

Content

- Motivation
- Physics of dose deposition
- Dose calculation for photons
  - Model based methods (PBK)
  - Analytical Anisotropic Algorithm and Point Kernel
  - Linear Boltzmann Transport Equation and Monte Carlo Algorithm
  - Comparison of algorithms
- Calculation algorithm and the clinical impact – things to consider when switching
- Dose calculation for protons

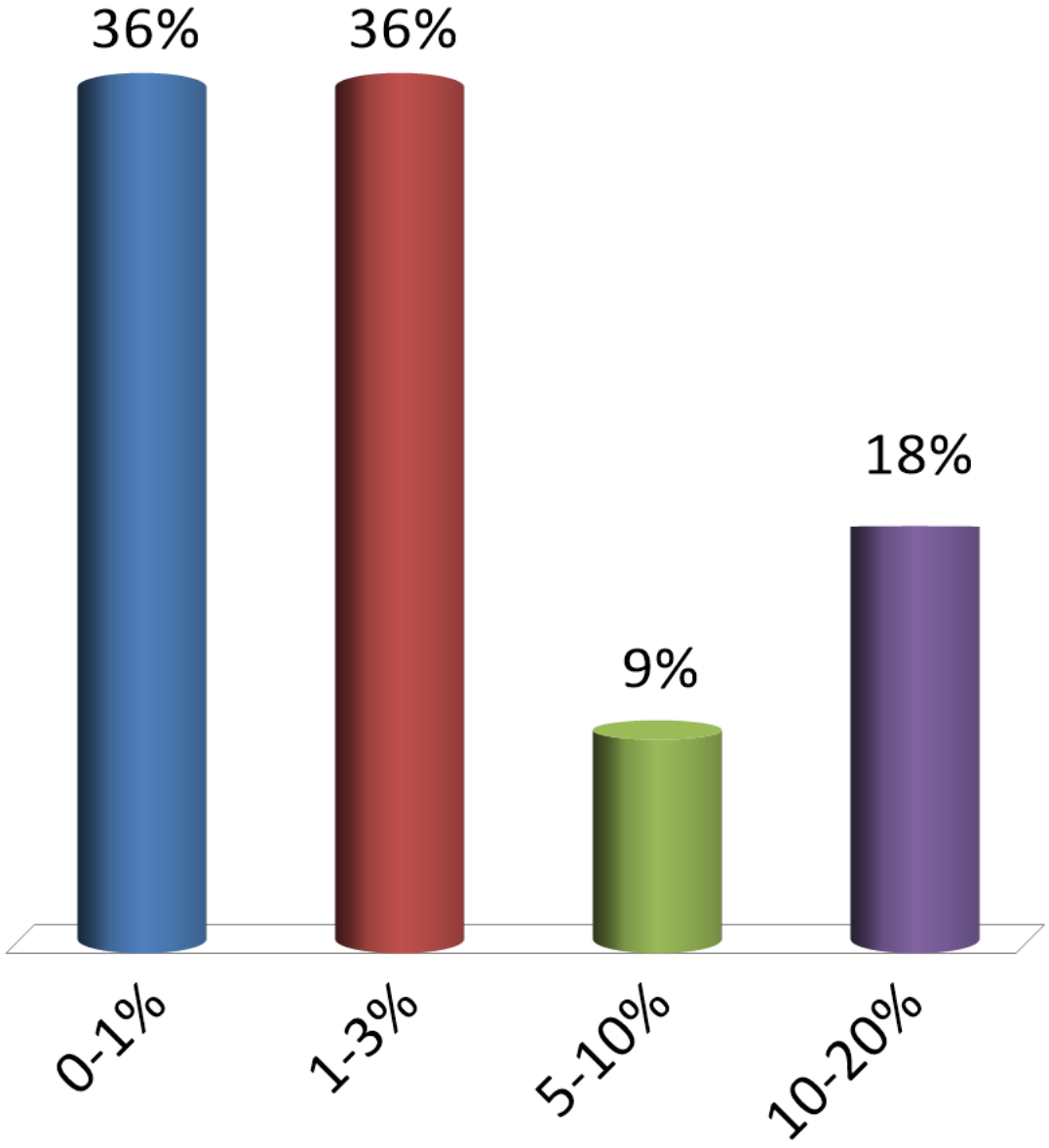
Which dose deviation is clinically relevant?

A. 0-1%

B. 1-3%

C. 5-10%

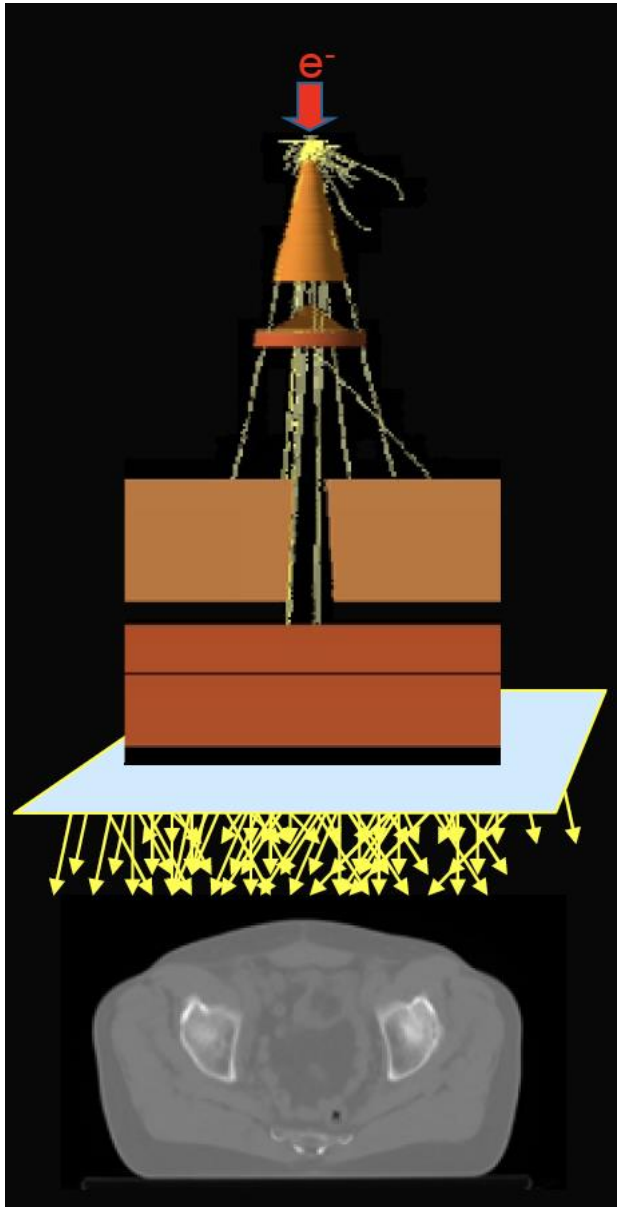
D. 10-20%



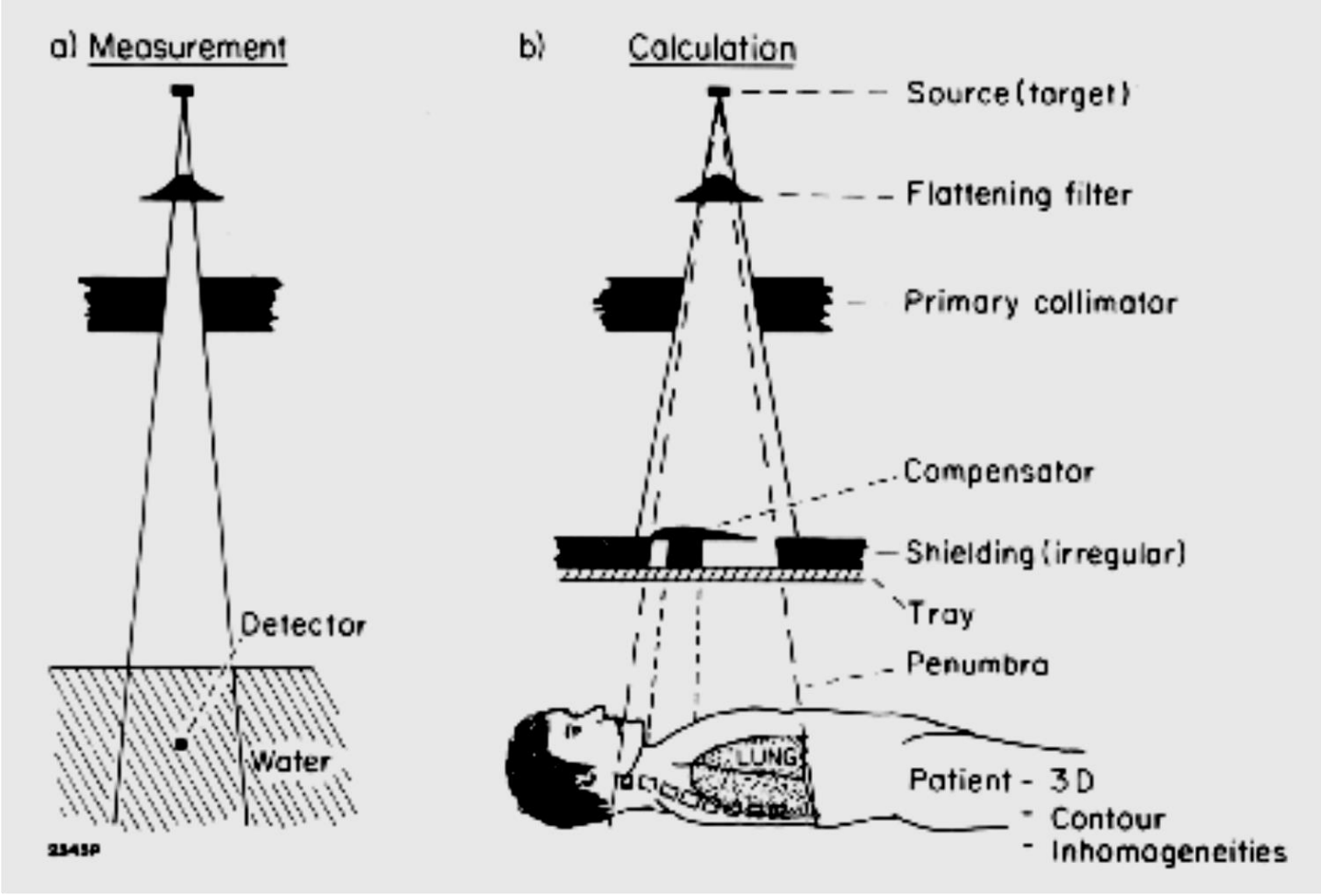
www.responseware.eu
session ID: atp18

Motivation

- **accuracy of dose calculations** is crucial to quality of treatment planning and consequently to doses delivered to patients
- evidence exists that dose differences on the order of <u>7%</u> are clinically detectable. Moreover, several studies have shown that 5% changes in dose can result in 10%–20% changes in tumor control probability (TCP) or up to 20–30% changes in normal tissue complication probabilities (NCTP)
- The problem is:
  - To model the treatment machine (**source models** or **MC**)
  - To model dose deposition in patient



Relate dose calculation in patient to beam calibration conditions

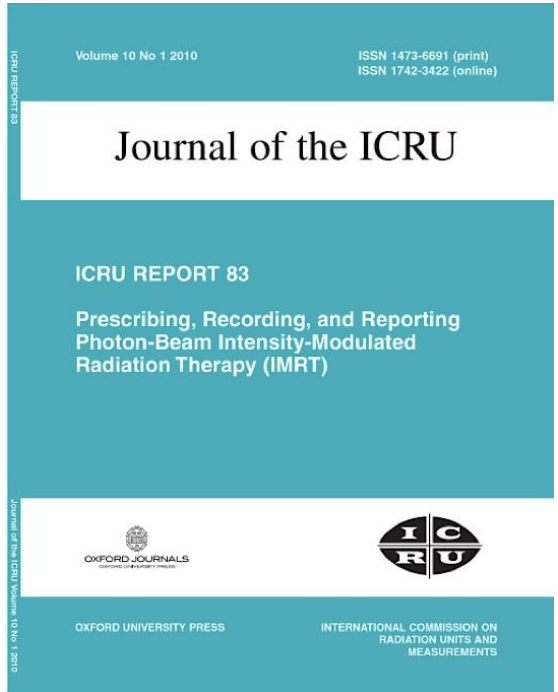


Papanikolaou, et al- 2004 - AAPM Task Group 65

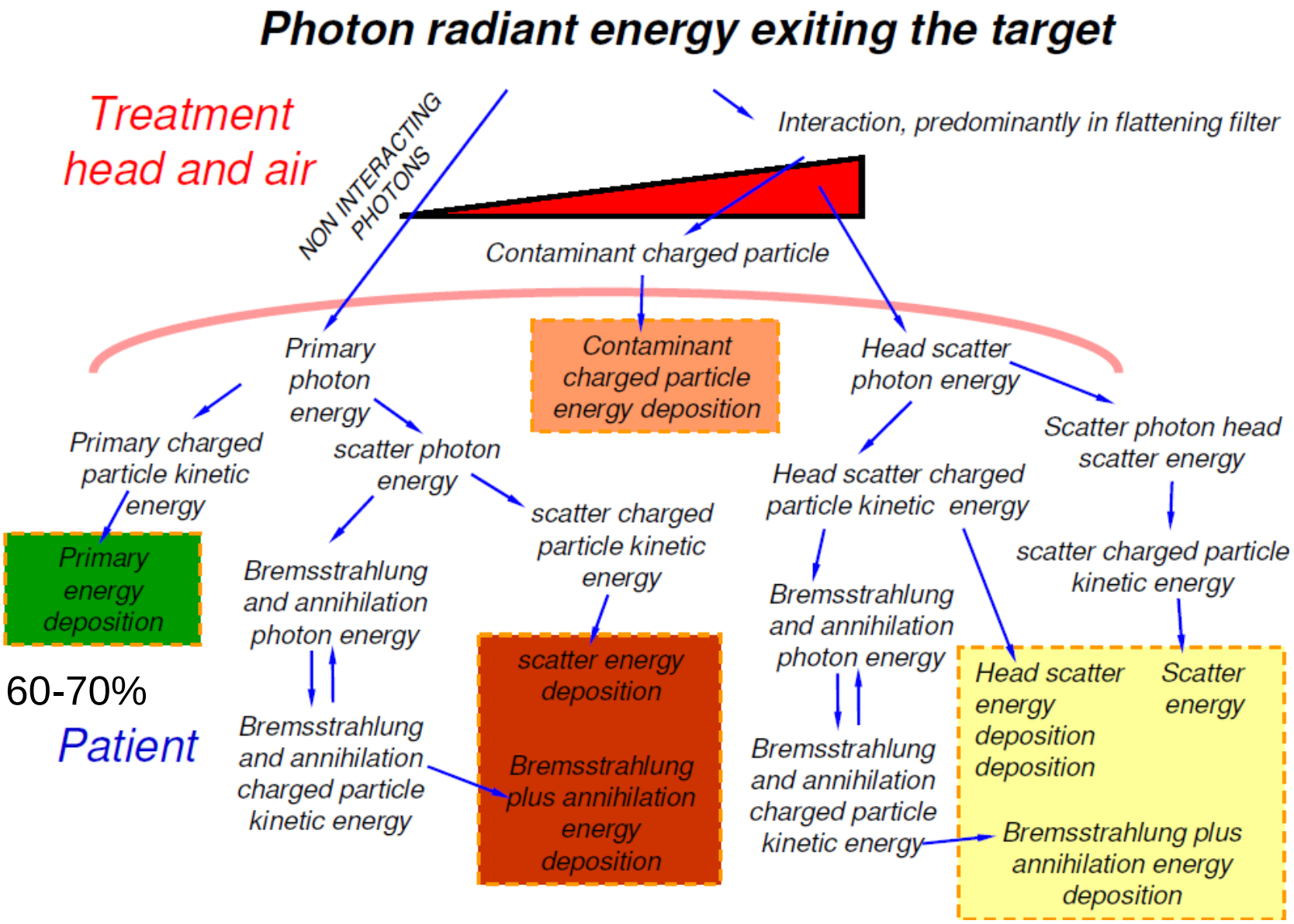
Expectations

- *More demanding treatment techniques as well as more complex delivery 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



Complexity of dose calculation



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Physics considerations

SCATTER SOURCES

primary collimator

flattening filter

collimator scatter

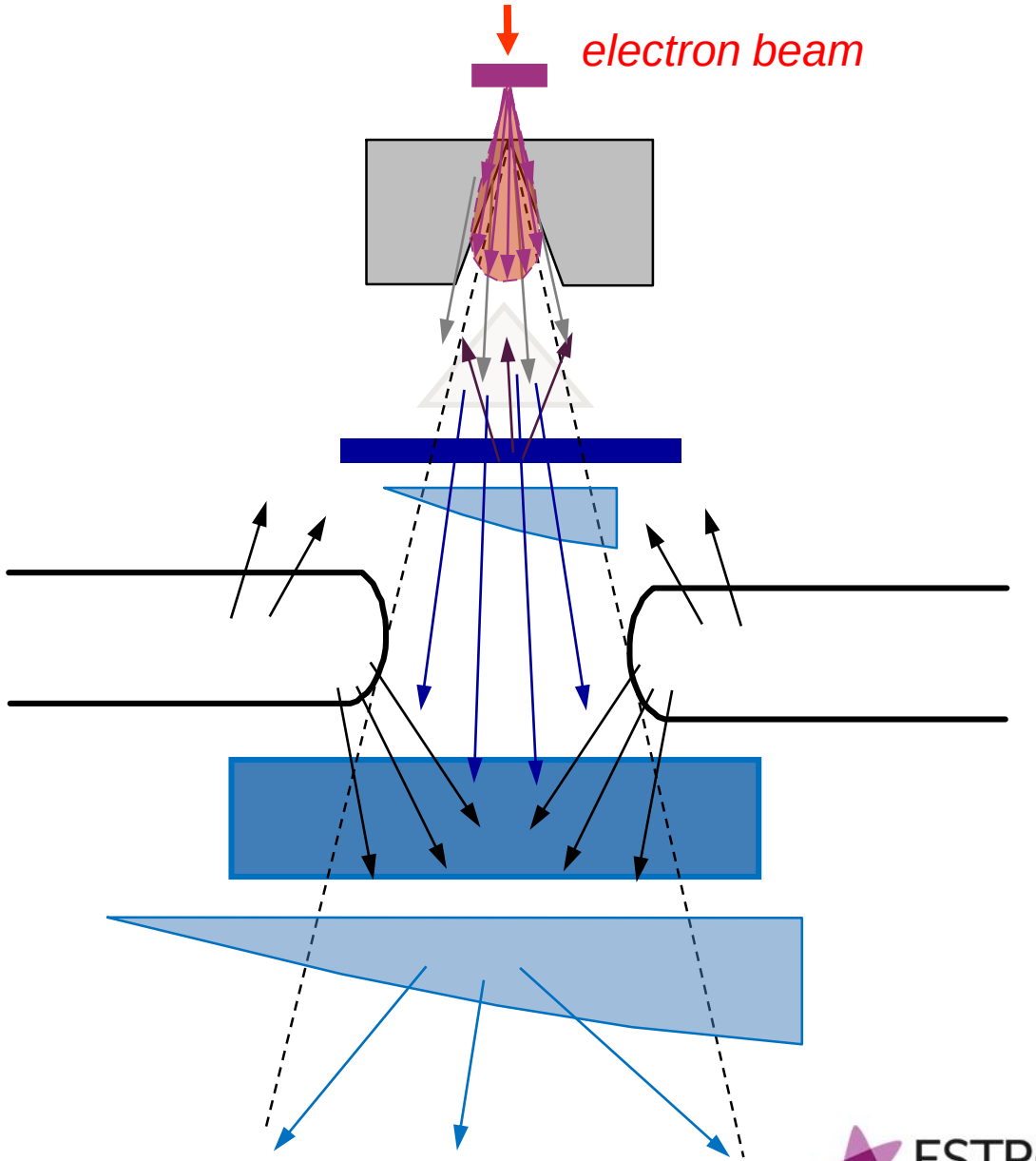
(secondary coll., blocks, MLC)

backscatter into monitor chamber

wedges, compensators

blocks, trays, ...

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



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X-Rays: Energy Deposition in a Nutshell

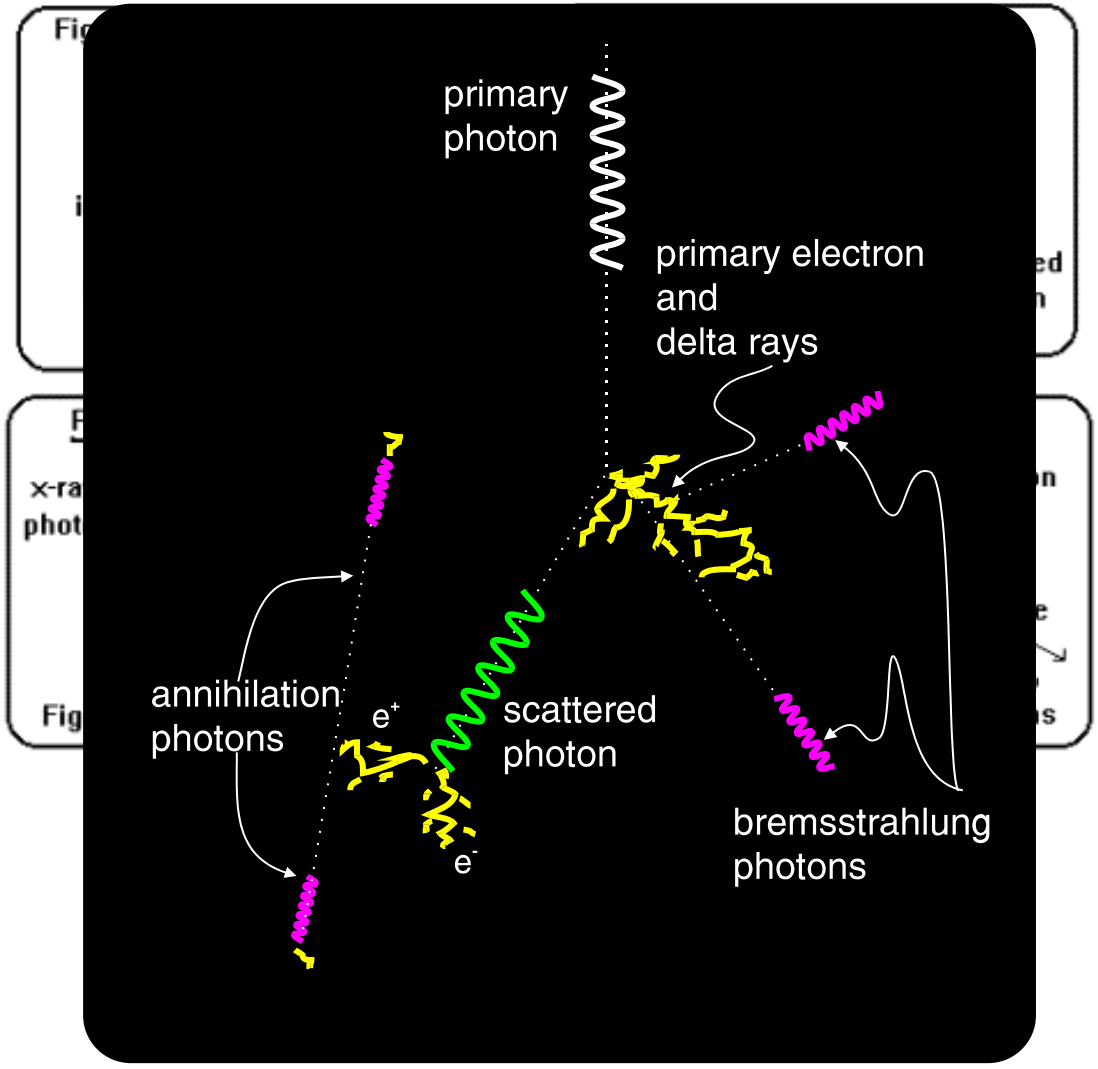
X rays do ionize *indirectly.*

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 (2 Gy) requires ~$10^{8\text{-}9}$ incident x rays per mm^2.



Dose Calculation Methods

Absolute Calibration
in water

Relative Distribution in water

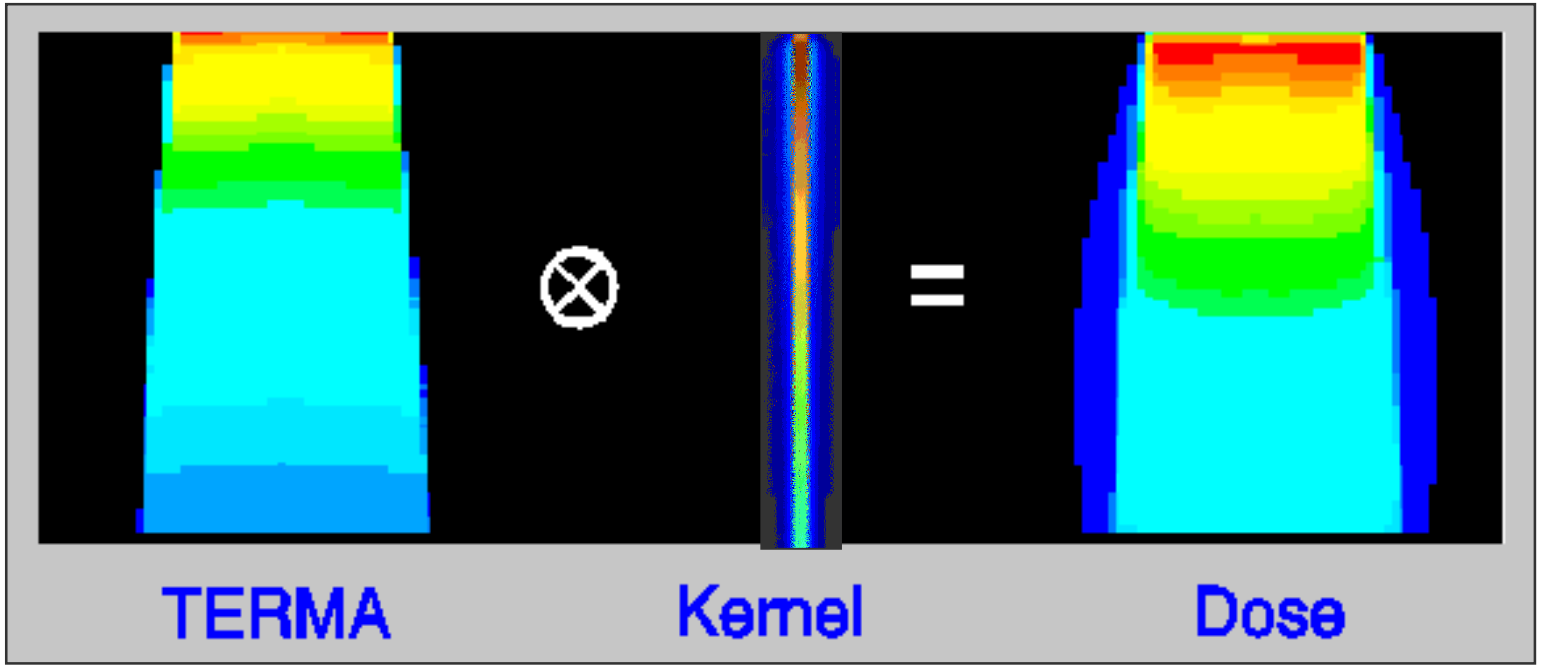
Tabulate & Interpolate	Model & fit parameters to emulate measurements
Reconstitute distribution in water by distance, depth, & field size	Compute dose directly from beam geometry & CT images
Apply correction factors (inhomogeneity, contour)	

"Correction" based methods

"Model" based methods

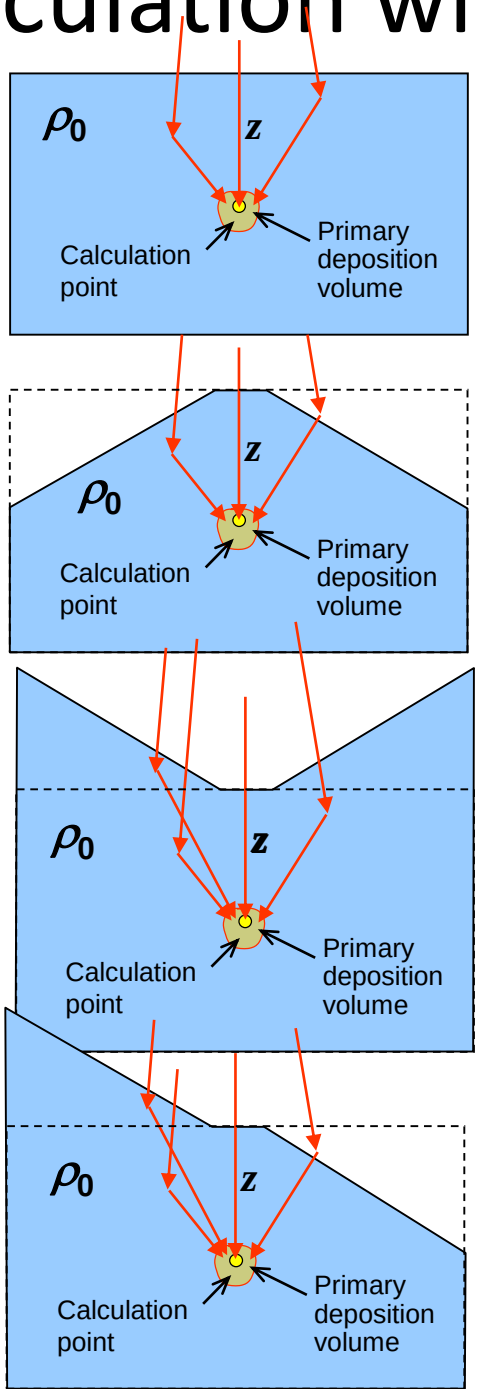
Convolution – Pencil Beam Kernel

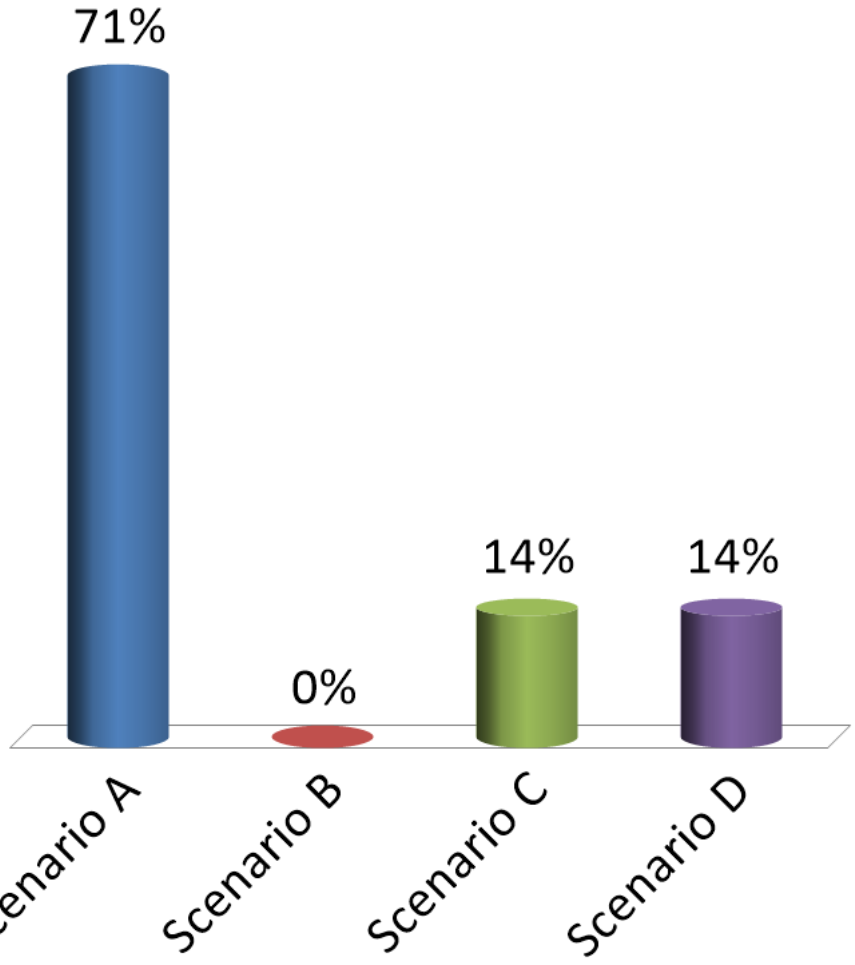
$$D(x,y,z) = \int\int F(x',y',z) K_z(x - x', y - y') dx\, dy$$



Correct calculation with a PB algorithm?

A. Scenario A
B. Scenario B
C. Scenario C
D. Scenario D





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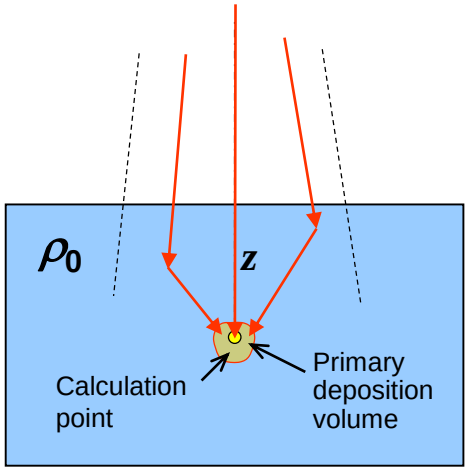
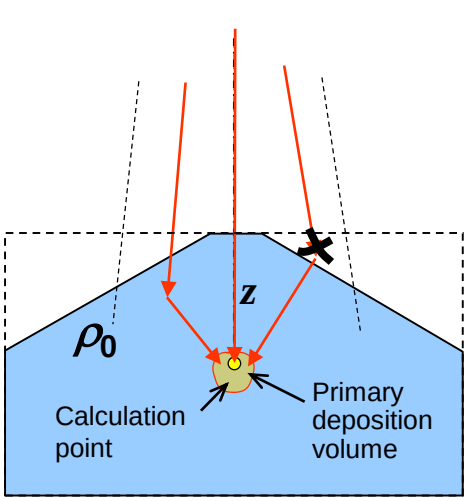
Pencil beam kernel

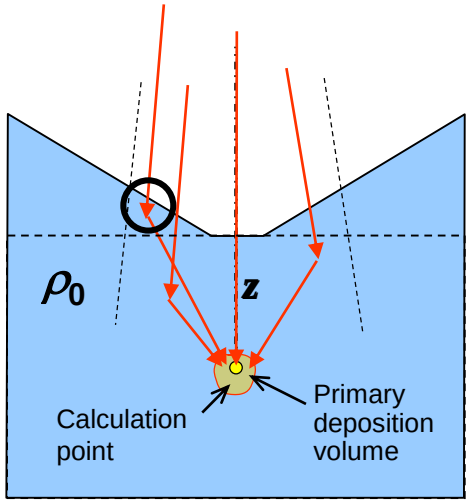
Calculation object approximations



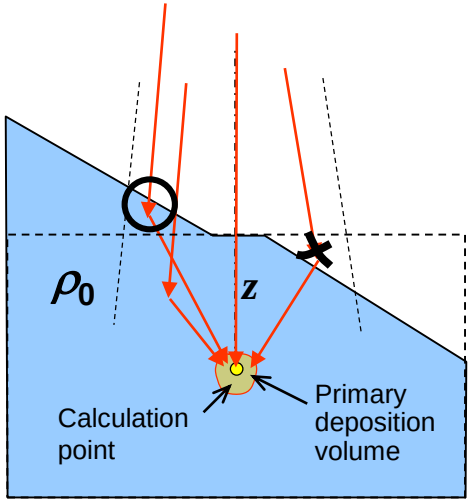
The depth (z) is generally assumed to be constant within the lateral integration plane during calculation of the scatter dose to a point.



Scatter overestimated



Scatter underestimated



Errors cancel (roughly)

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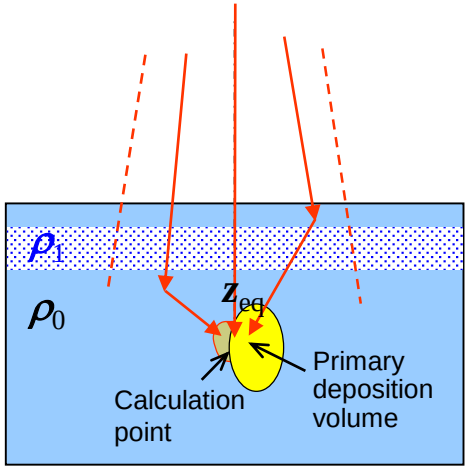
Pencil beam kernel

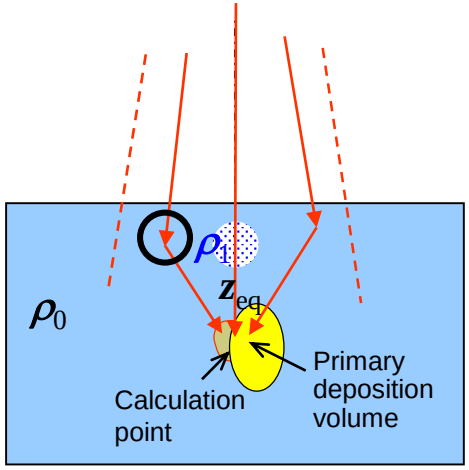
Calculation object approximations with heterogeneities

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

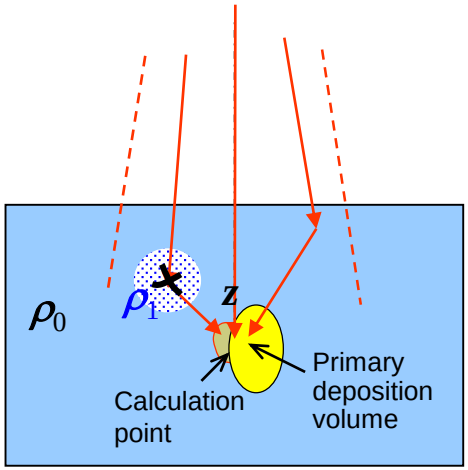


Heterogeneous slab phantom

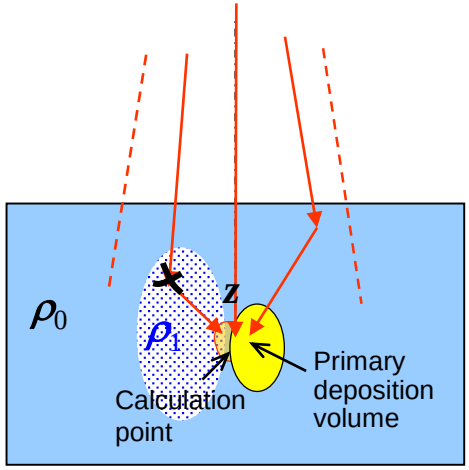
Effects of heterogeneities are generally modelled in pencil kernel algorithms through depth scaling along rayline (and no lateral scaling). Correct handling of heterogeneities requires proper 3D modelling of the secondary particle transport.



Scatter underestimated



Scatter overestimated



Scatter and primary overestimated

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Analytical Anisotropic Algorithm (AAA)

superposition of pencil beams, which are modified/scaled anisotropically based on tissue electron densities (3D PB kernel)

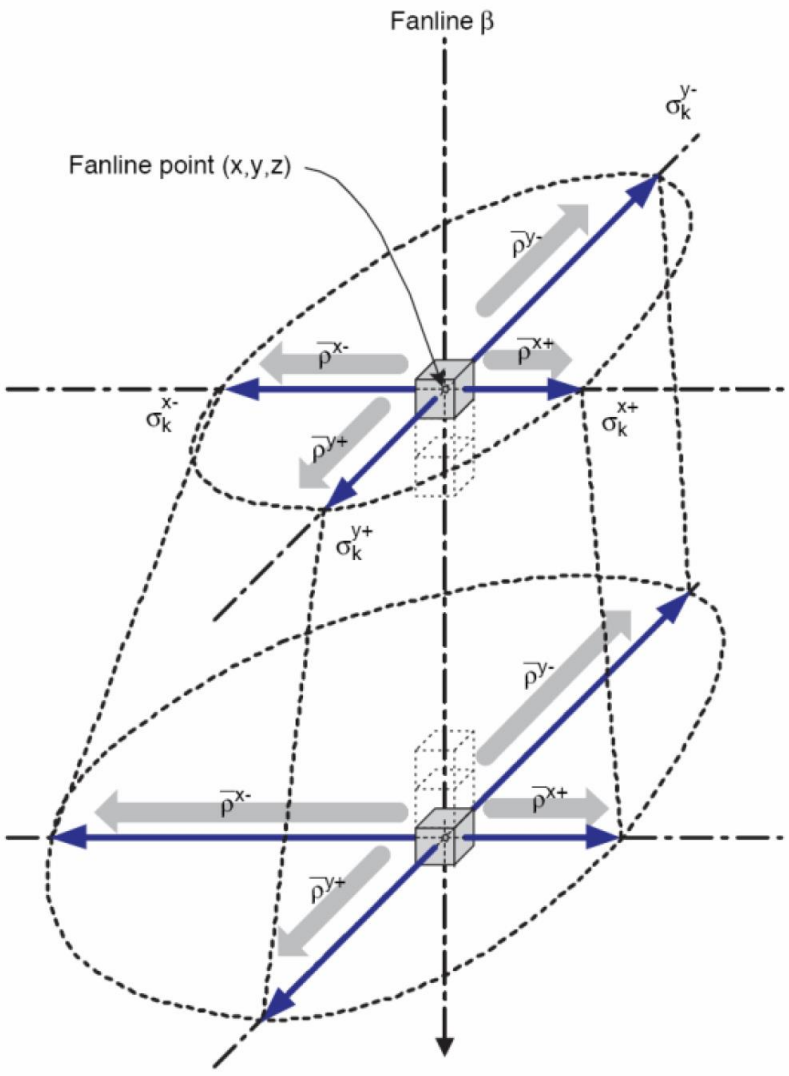
- PB separated into depth-directed (total energy deposited by the pencil beam) and lateral components (sum of N radial exponential function)

Build up and down correction needed

source model for

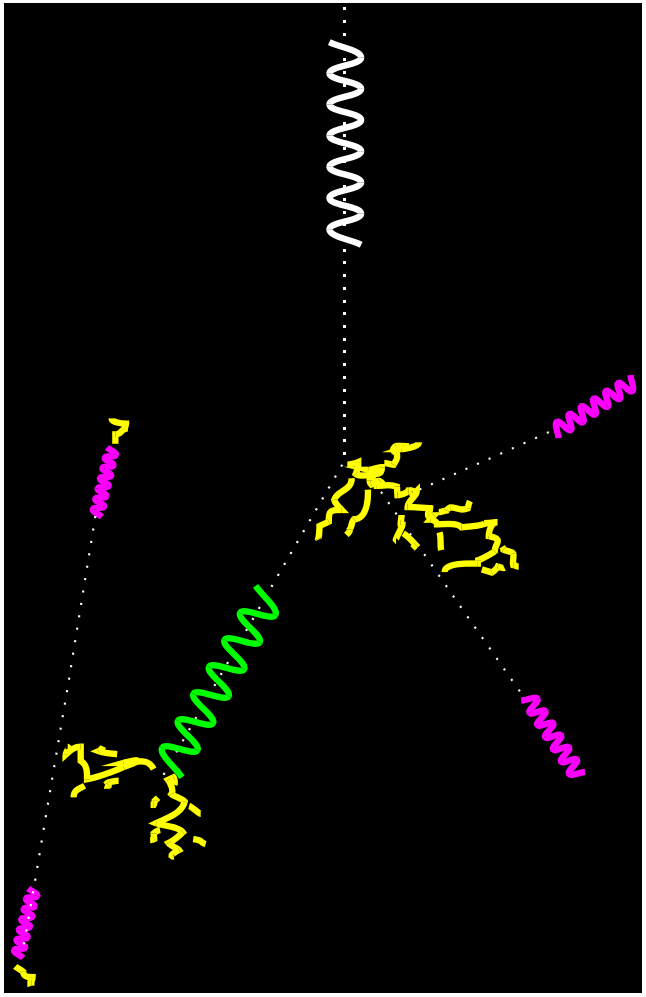
- Primary photon source
- extra-focal source for photons scattered in accelerator head
- electron contamination source

- Reduced computation time



Dose Spread Point Kernel

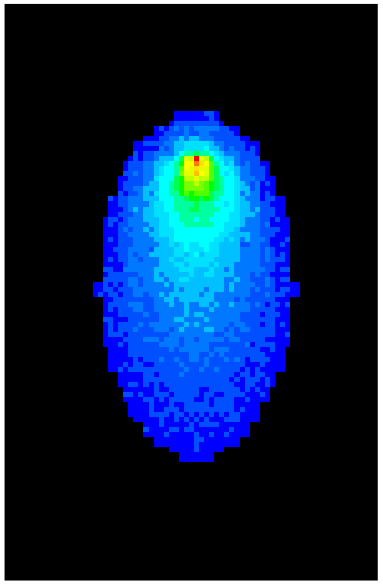
Mackie *et al*, PMB **33**(1) (1988).



One incident photon interacts at a point

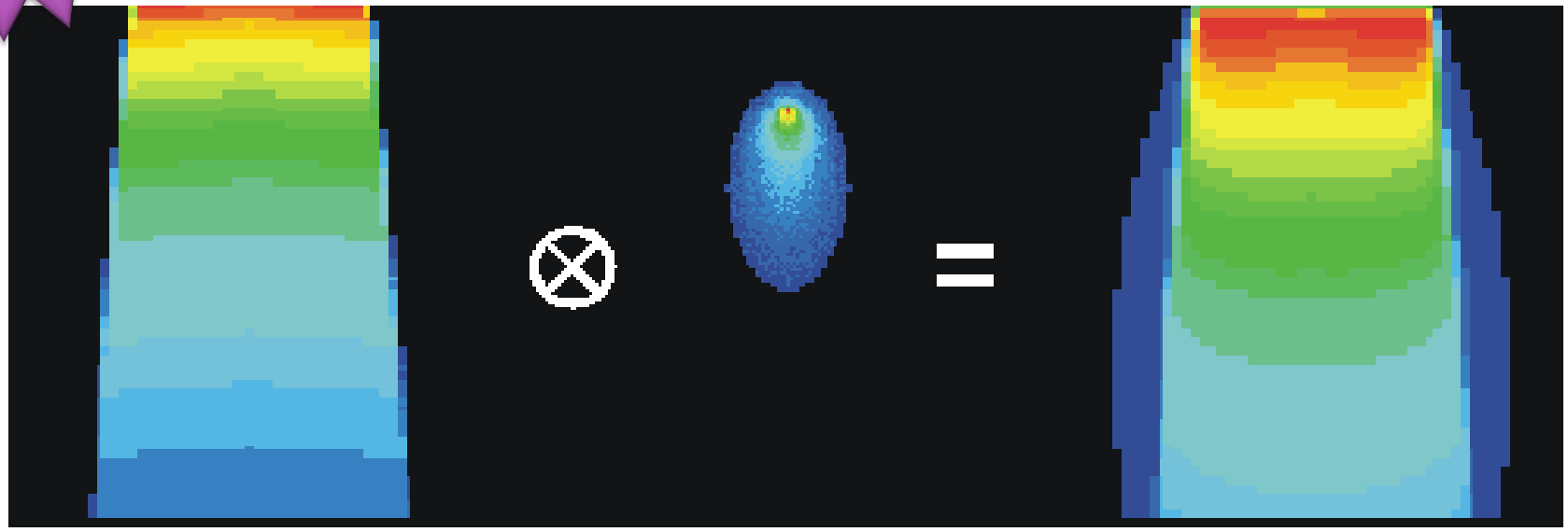
Average energy deposition pattern (10^6 interacting photons)

Monte Carlo Simulation



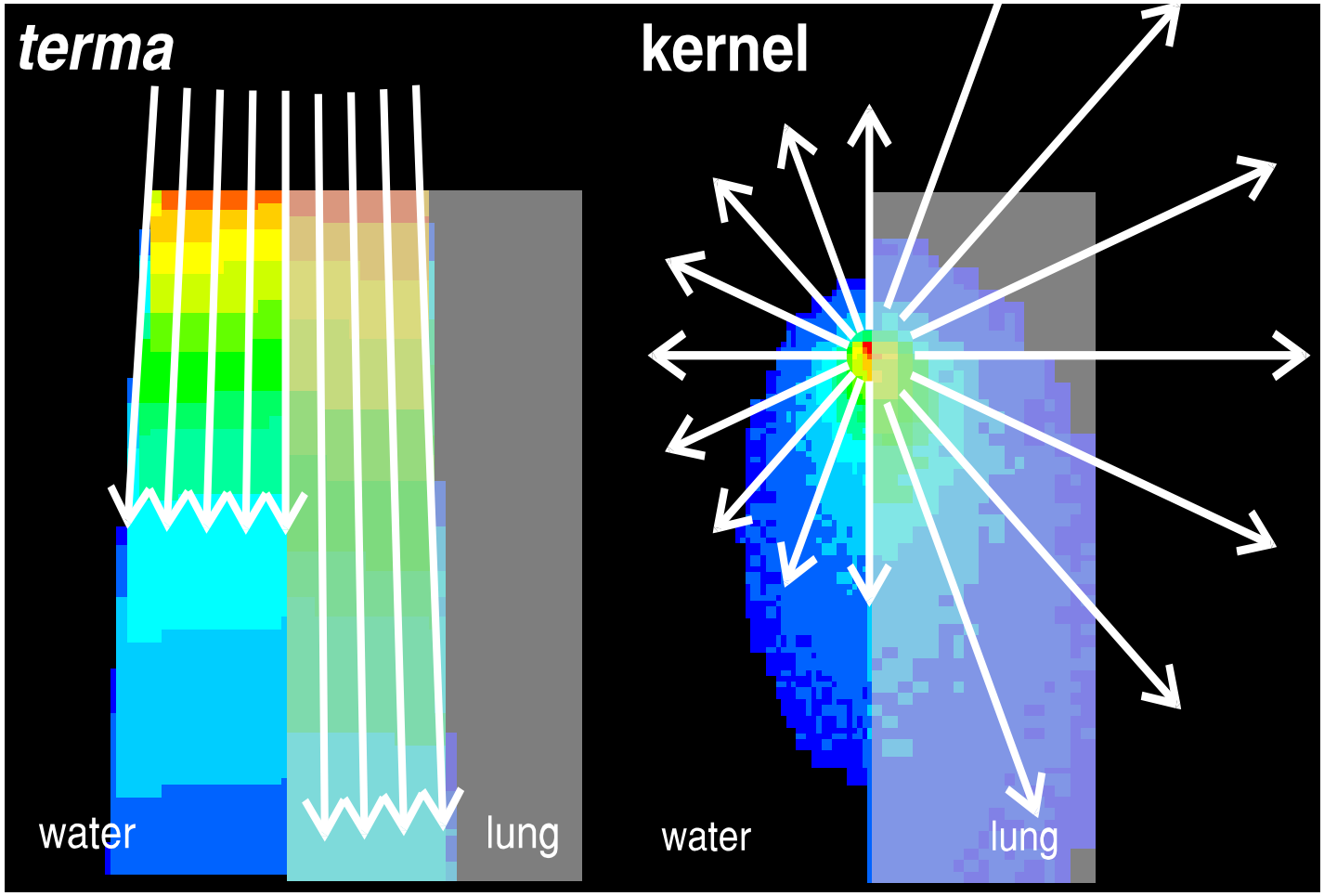
Ideal Conditions Only

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

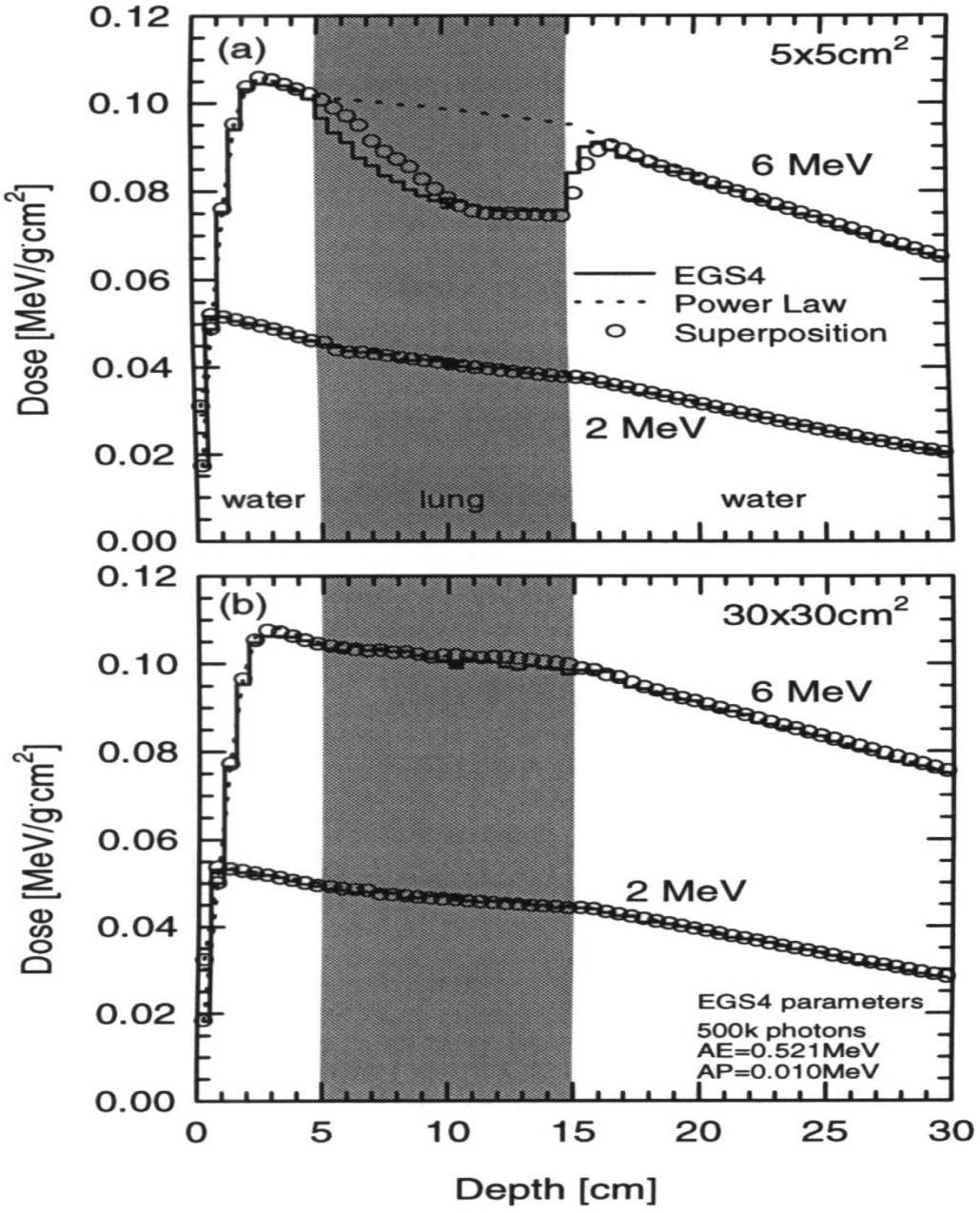


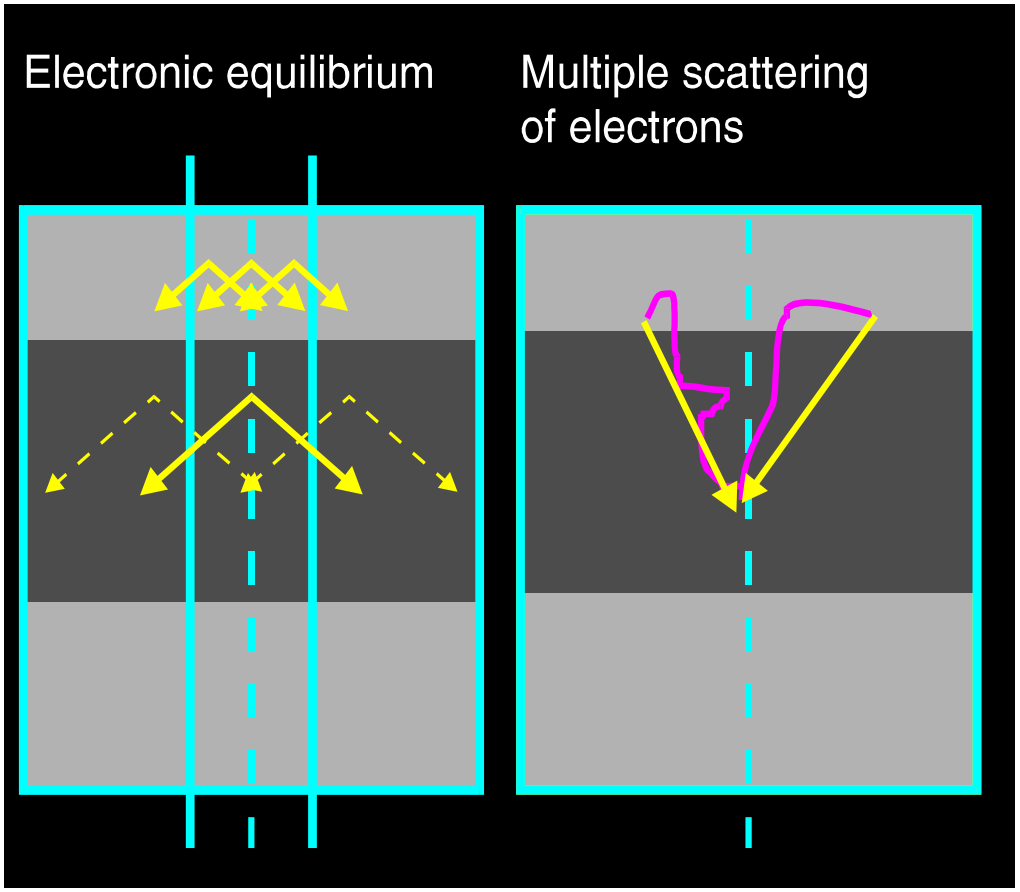
Density Scaling Approximation

TERMA and kernel are computed for water and scaled by the average density computed along raylines.



Electronic Disequilibrium





Deterministic linear Boltzmann transport equation (D-LBTE) algorithm

- Model based approach have problem to account for the **effect of electron transport** - **secondary electron transport** only modeled macroscopically by **scaling of kernels**
- **LBTE** is the governing equation that describes the macroscopic behavior of ionizing particles as they travel through and interact with media

$$\hat{\Omega} \cdot \vec{\nabla} \Phi^{\gamma} + \sigma_t^{\gamma} \Phi^{\gamma} = q^{\gamma\gamma} + q^{\gamma},$$

$$\hat{\Omega} \cdot \vec{\nabla} \Phi^{e} + \sigma_{\mathrm{t}}^{e} \Phi^{e} - \frac{\partial}{\partial E}(S_{\mathrm{R}} \Phi^{e}) = q^{ee} + q^{\gamma e} + q^{e}$$

- system of the **coupled LBTE is solved** to determine the **energy deposition of photon and electron transport**
- once the **electron angular fluence** is solved, the dose in any region, i, of the problem may be obtained through the following

$$D_i = \int_0^{\infty} \mathrm{d}E \int_{4\pi} \mathrm{d}\hat{\Omega} \frac{\sigma_{\mathrm{ED}}^{e}(\vec{r}, E)}{\rho} \Phi^{e}(\vec{r}, E, \hat{\Omega})$$

- Commercialized as Acuros XB

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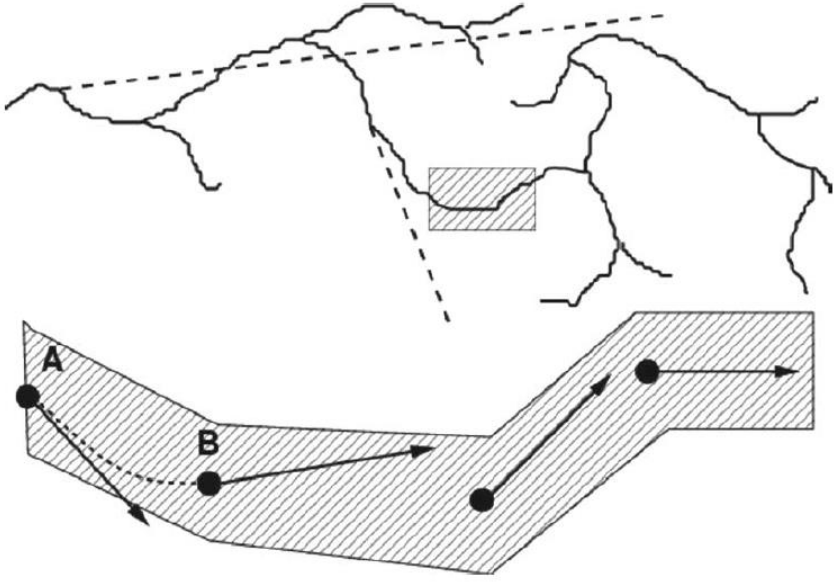
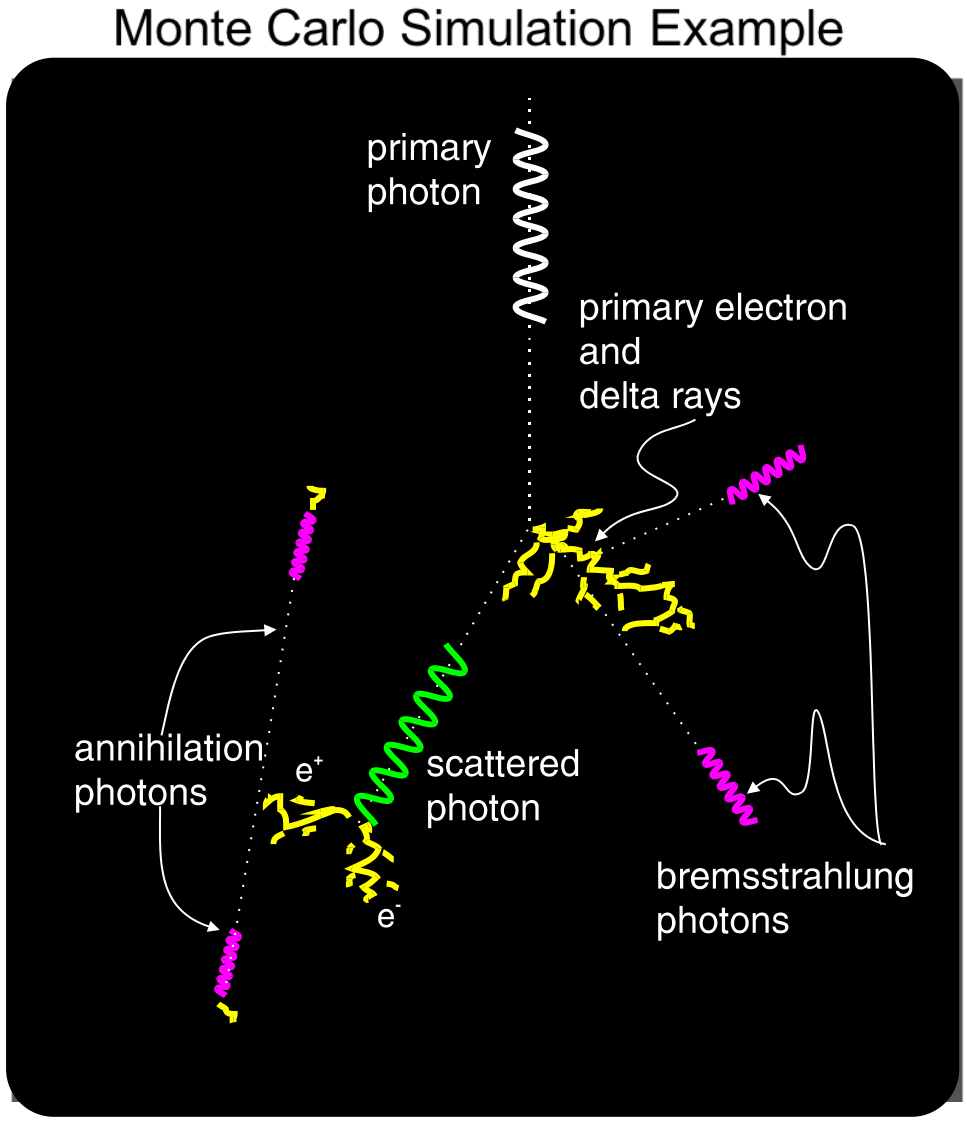
Monte Carlo Simulation

- developed and named at the end of the second world war. The motivation was to apply MC techniques to radiation transport, specifically for nuclear weapons.
- Uses photon & electron transport physics
- **Condensed history** simulation to speed up





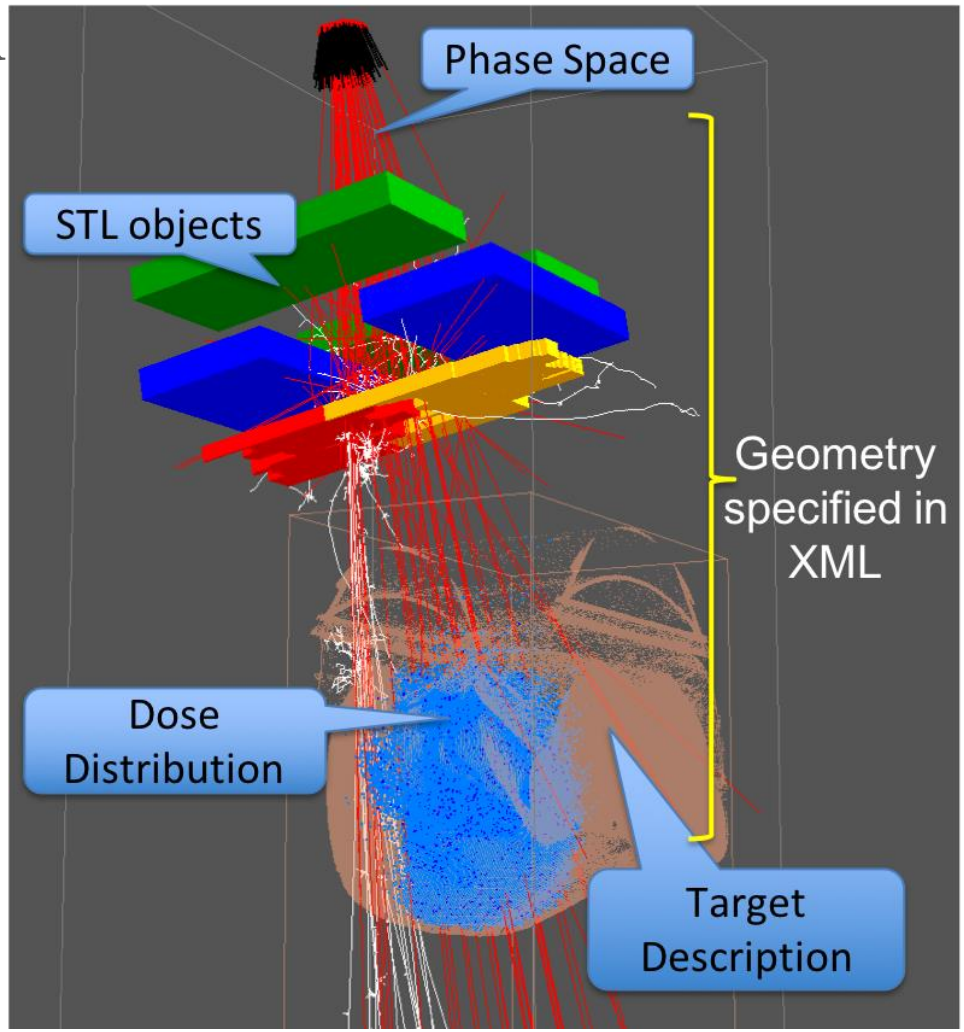
radyalis.com

AAPM TG Report 105

Monte Carlo Simulation

- More efficient by performing the simulation of patient-independent structures and to store what is called a **phase-space file** → can be reused as often as necessary
- **Variance reduction** techniques (low interest particles like electrons created from photon interactions in treatment head are eliminated with a given probability) help to speed up
- Parallelization via GPU improves speed as well
- Example codes are: EGS, ITS, PEREGRINE (first FDA approved), VMC (Monaco, PrecisePlan, iPlan) , MCNP, PENELOPE, GEANT4

Monte Carlo Simulation Example

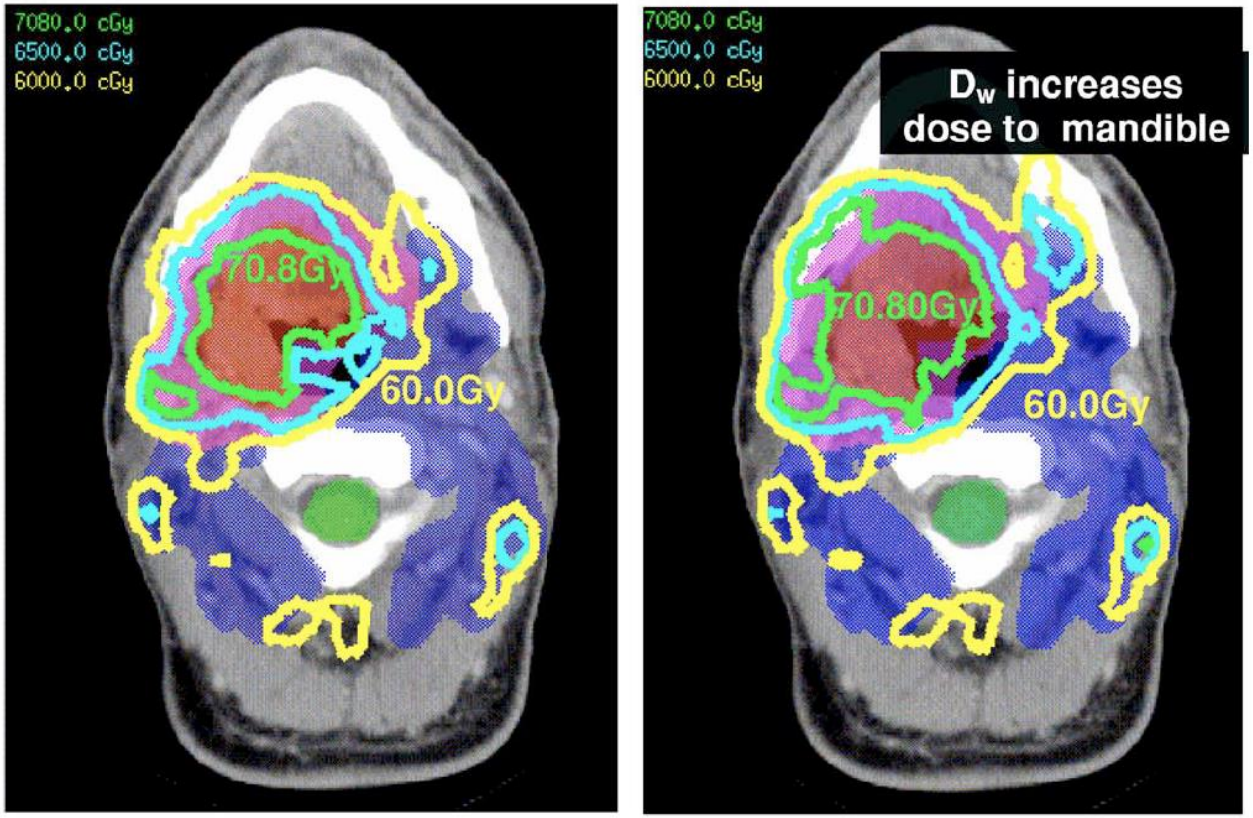


radyalis.com

AAPM TG Report 105

Monte Carlo - D_w vs D_m

- MC per nature **delivers D_m**
- For higher density materials, such as cortical bone, the difference in dose can be as large as 15%
- To use MC simulation in the current clinical practice so as to be able to **compare D_m with historical D_w** results, requires a **conversion of D_m to D_w** for dose prescriptions, isodose coverage, dose-volume histograms
- converted D_w represents the dose to a small volume of water embedded in the actual medium



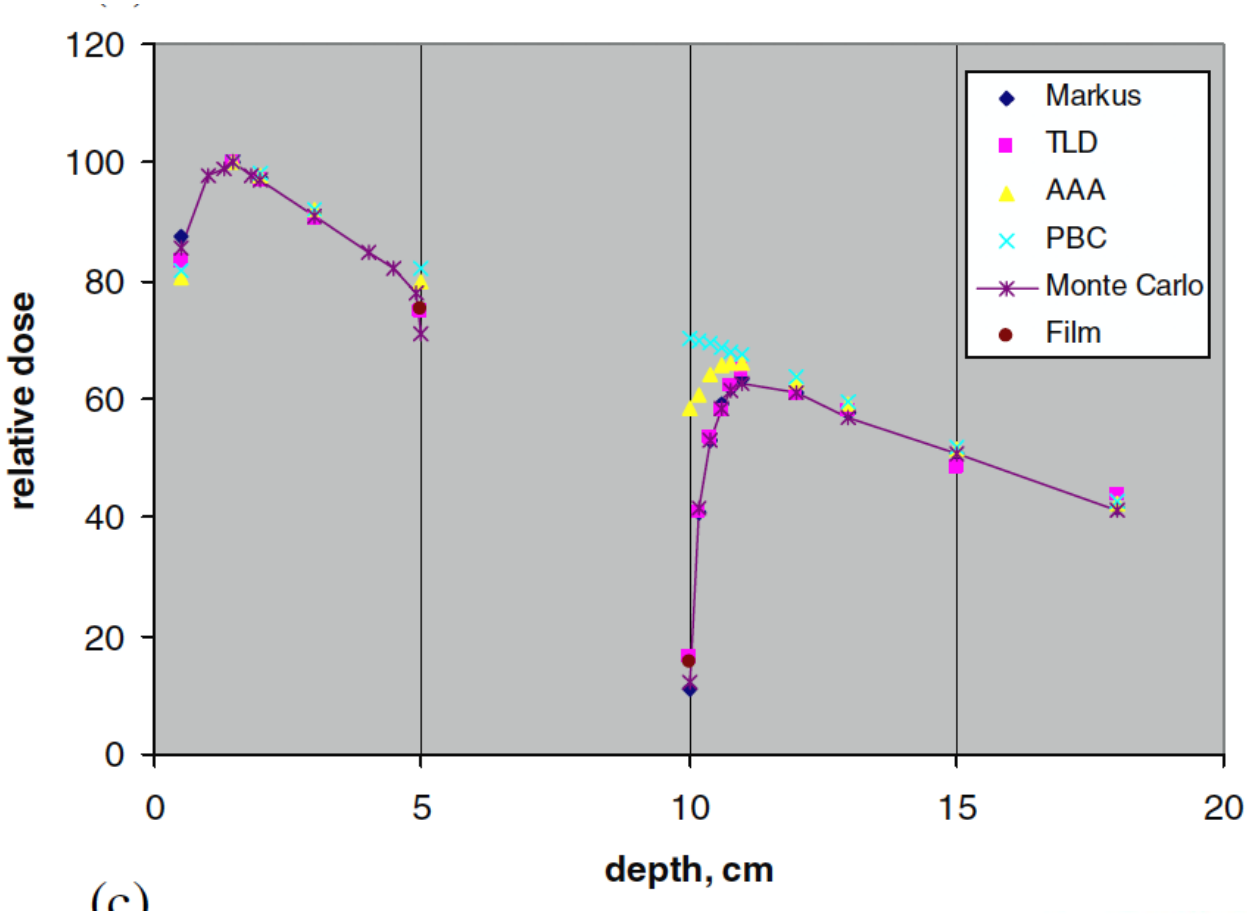
AAPM TG Report 105

Analytical Anisotropic Algorithm (AAA)

2x2 cm^2 field with 6MV at air-cavity phantom

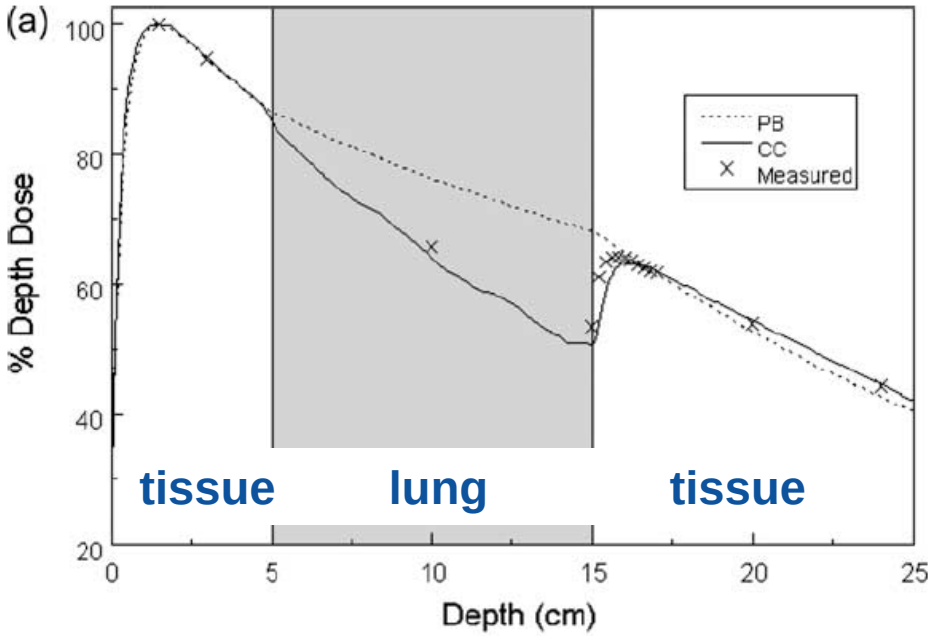
AAA overestimates dose (5-8%) near air–tissue interface when small beam segments are used with the presence of large air cavities.

Kan – PMB 2011

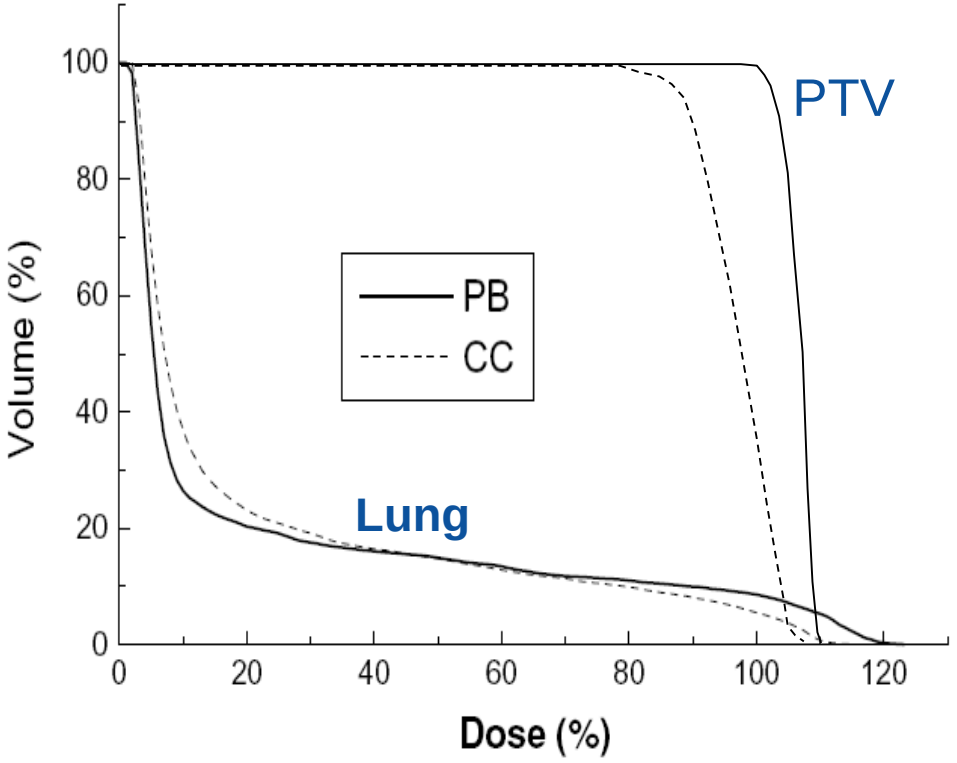


Clinical impact of dose calculation

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

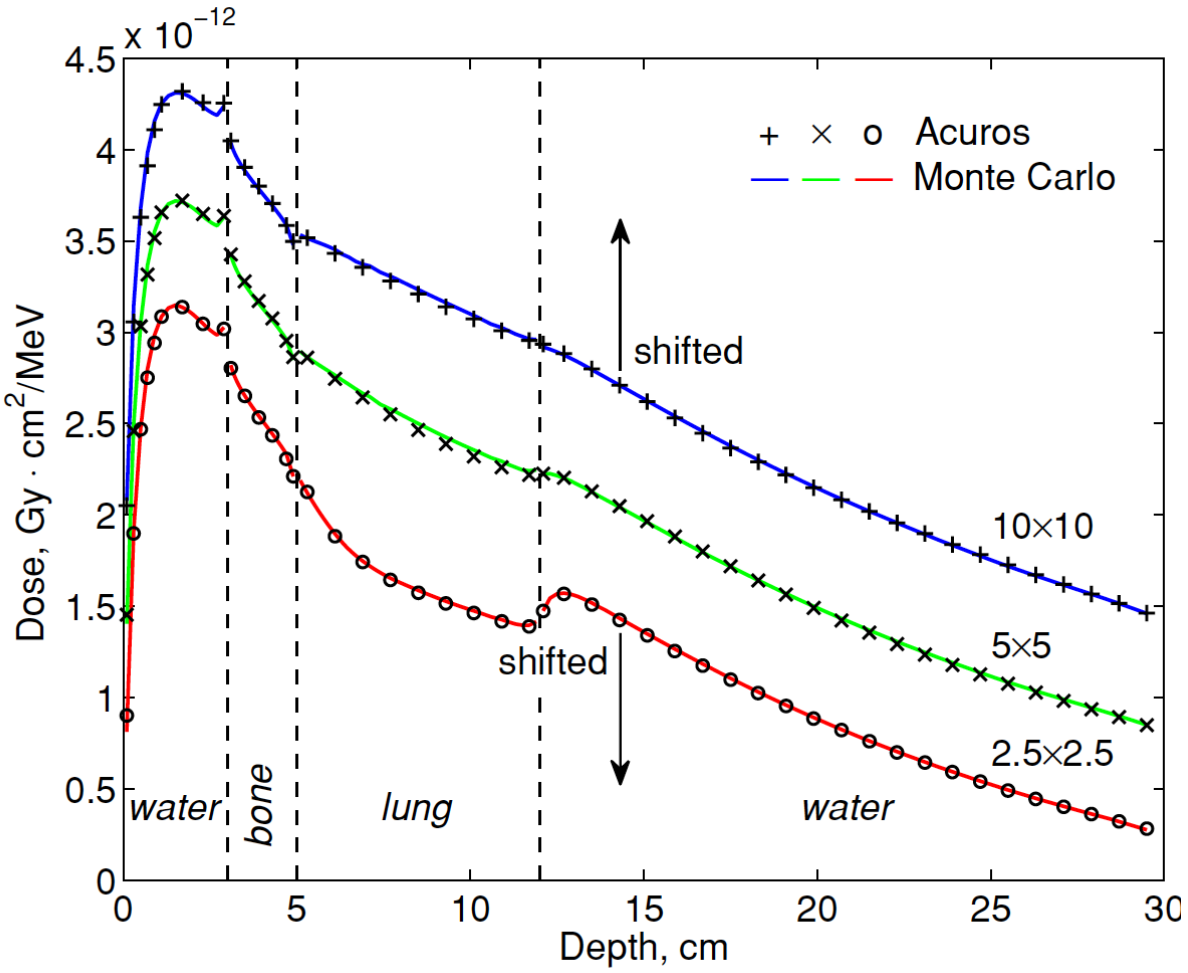


Nisbet *et al* RadOnc 73 (2004) p79
TMS

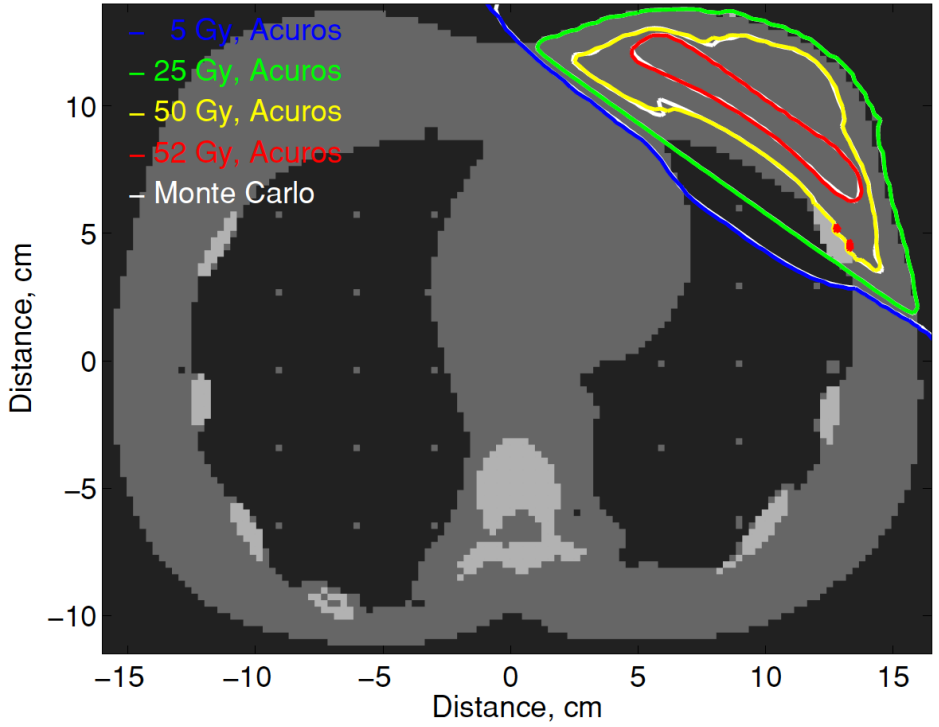


Irvine *et al* ClinOnc 16 (2004) p148

Deterministic linear Boltzmann transport equation (D-LBTE) algorithm



- For 6MV maximum relative differences between Acuros and Monte Carlo were less than 1.5% (local dose difference) and 2.3% for 18MV
- excellent agreement between both Acuros and Monte Carlo

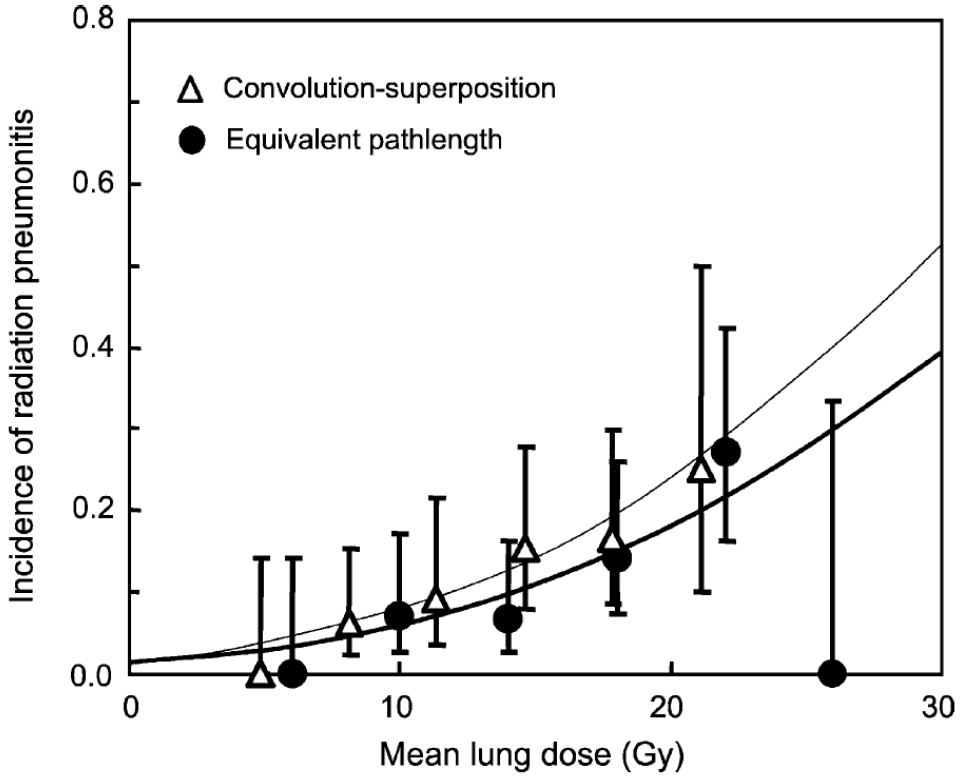


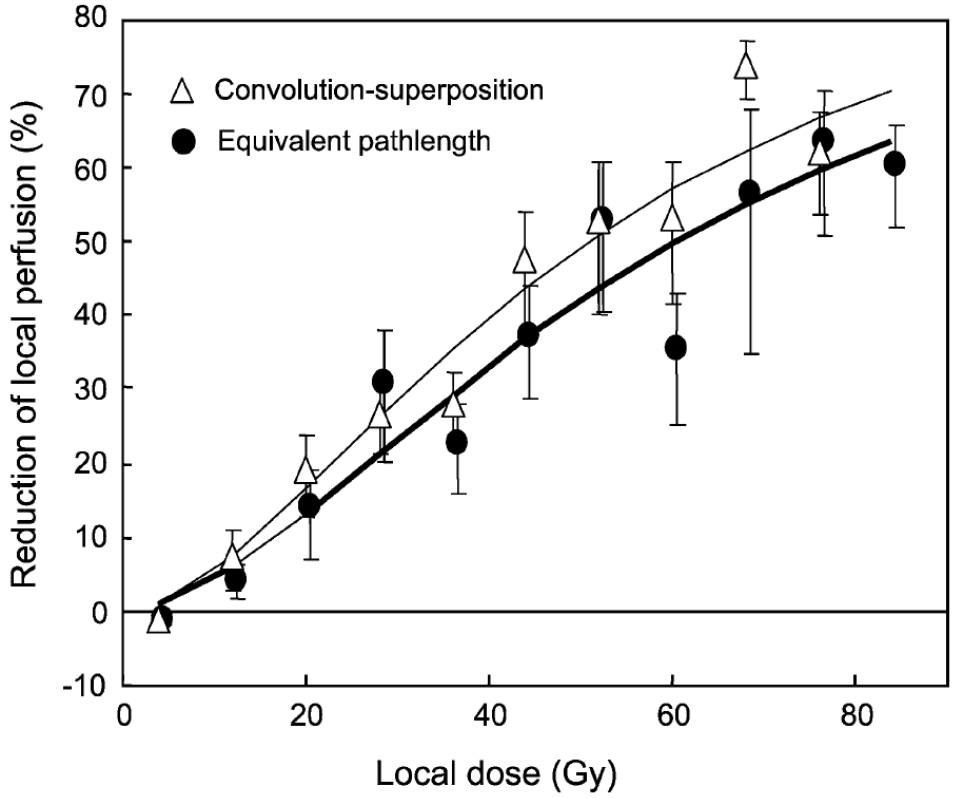
Vassiliev *et al* PMB 55 (2010) 581

De Jäger Radiother Oncol 2003

Clinical Impact - Conversion

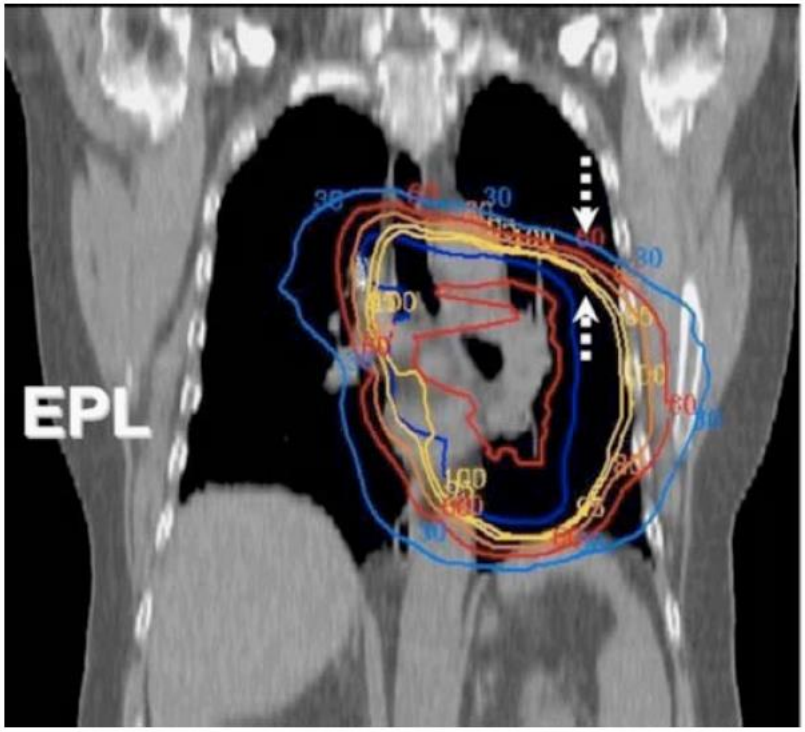
- PB Algorithm is not able to account for the electron transport in lung tissue → underestimate penumbra width and overestimate dose to the lung
- Dosimetric parameters for lung injury (like the MLD and V20) calculated with the two algorithms, are strongly correlated thus allowing a straightforward conversion of these parameters.

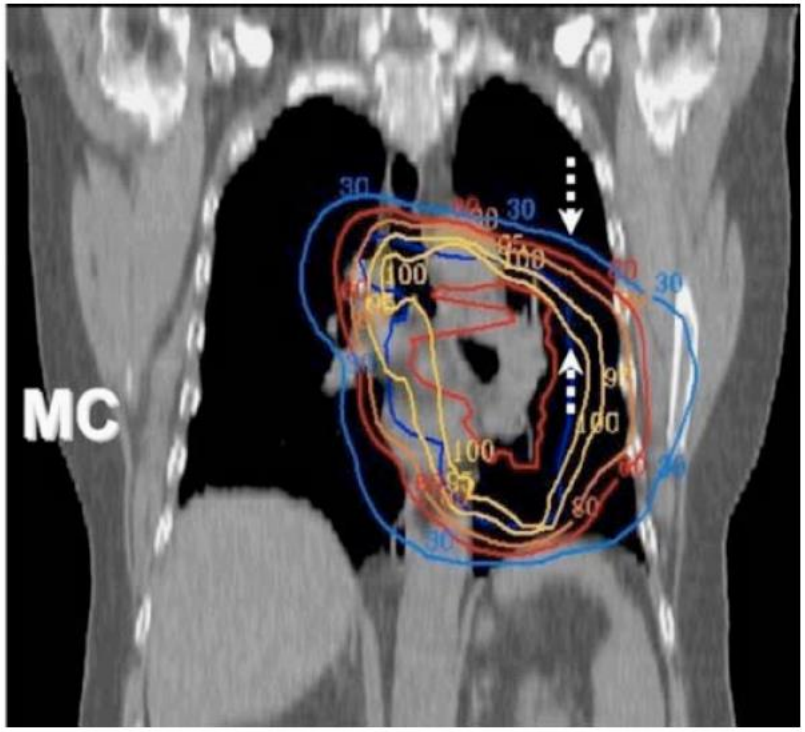




Clinical Impact

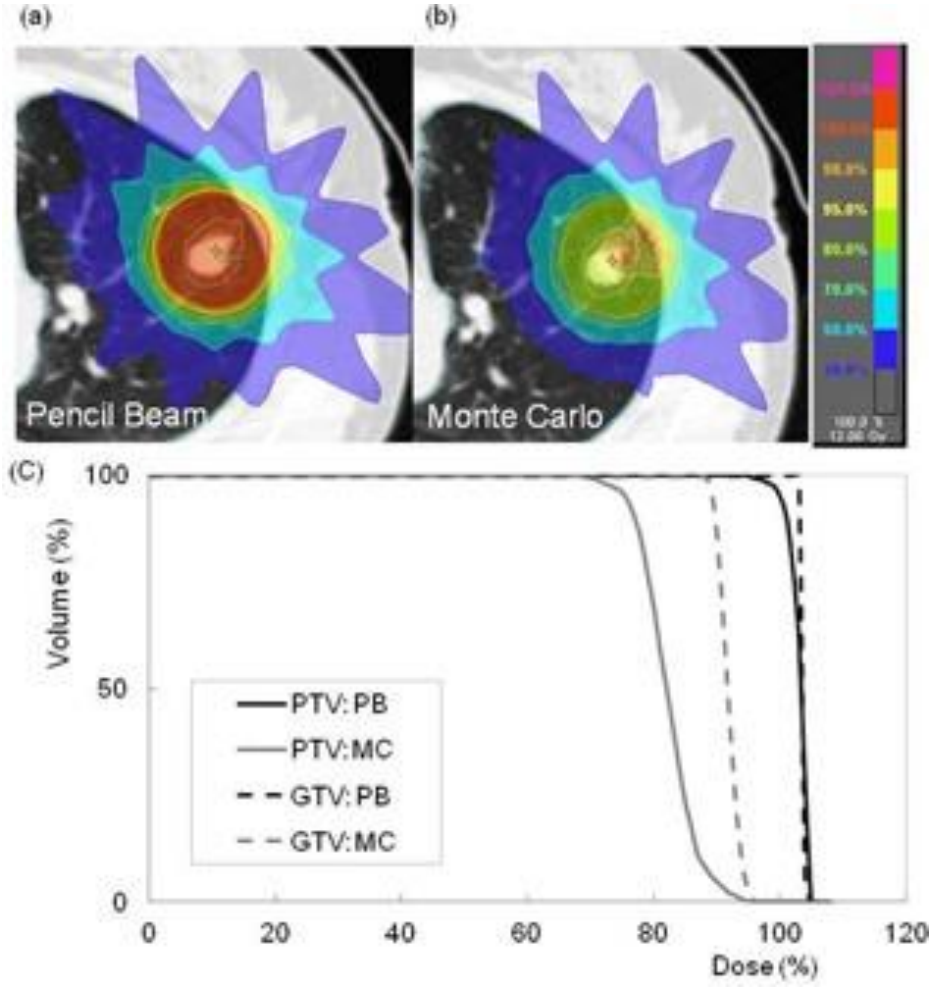
- MC method is likely to add a higher degree of accuracy to the dose-effect relationships.
- To address clinical impact of more accurate dose calculation can be done by using retrospective dose assessments of already existing local tumor control and normal tissue complications, using doses recalculated with MC algorithms.





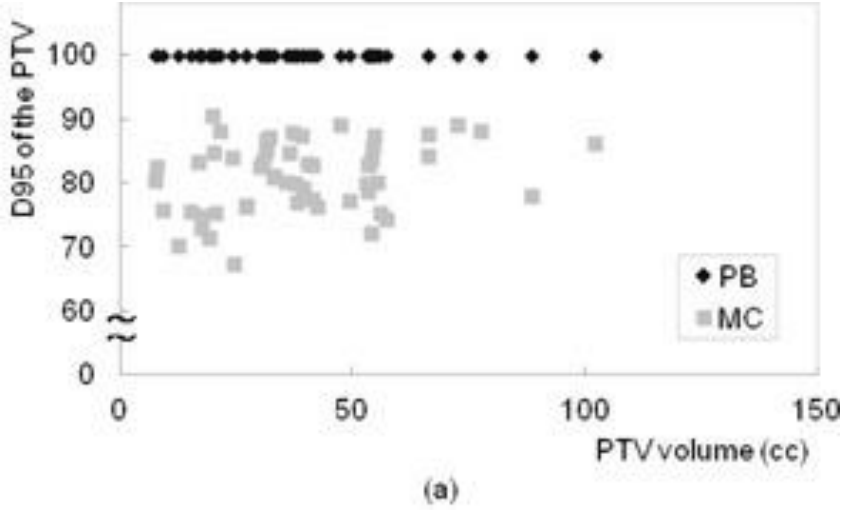
SBRT of lung tumor – PB vs MC

- Impact of algorithm on dose prescription



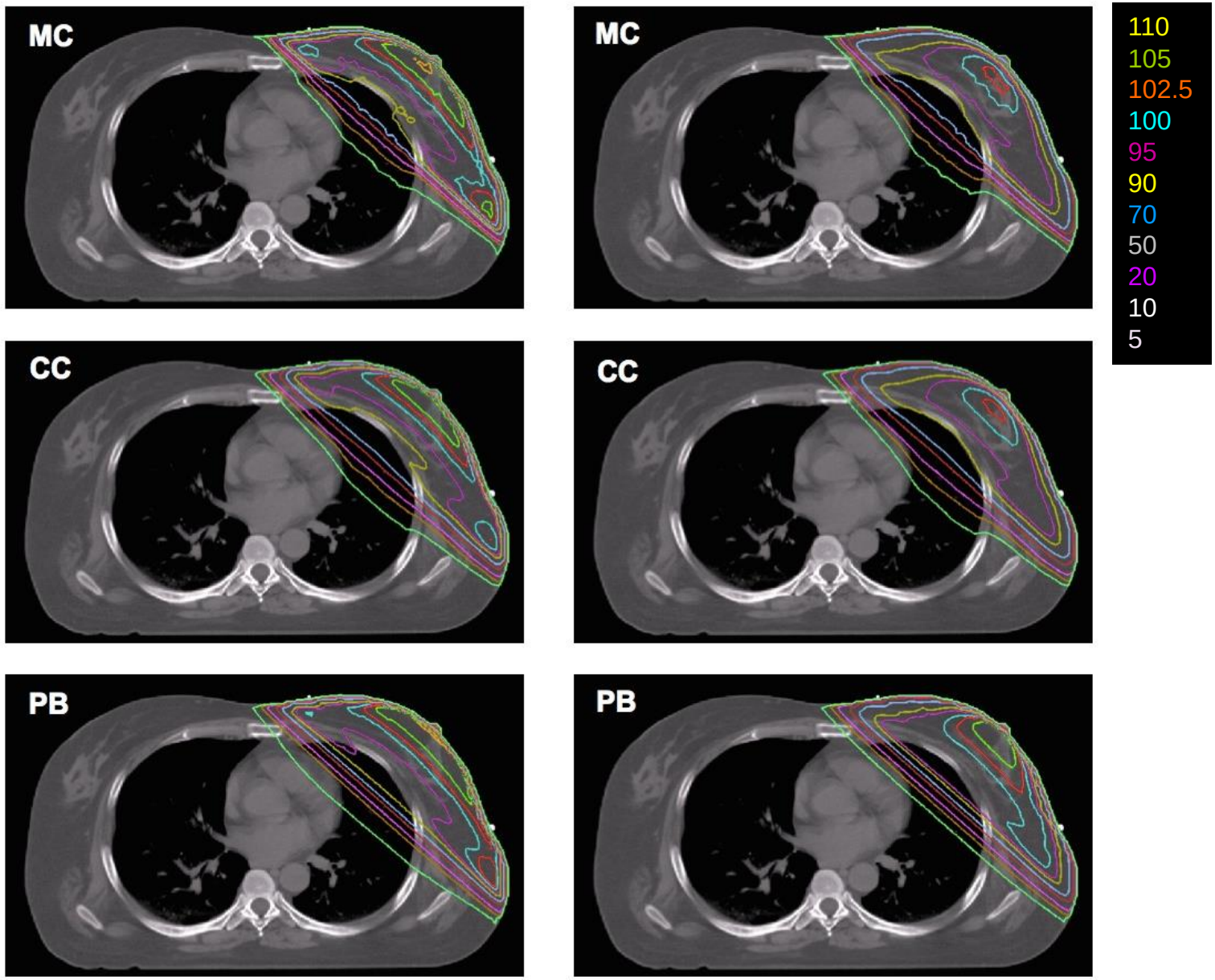
JACMP 15(1) 38

- Decrease in dose to the target for MC
- D_{95} of PTV



- Need to be cautious for multicenter clinical trials

Breast Tangent Example



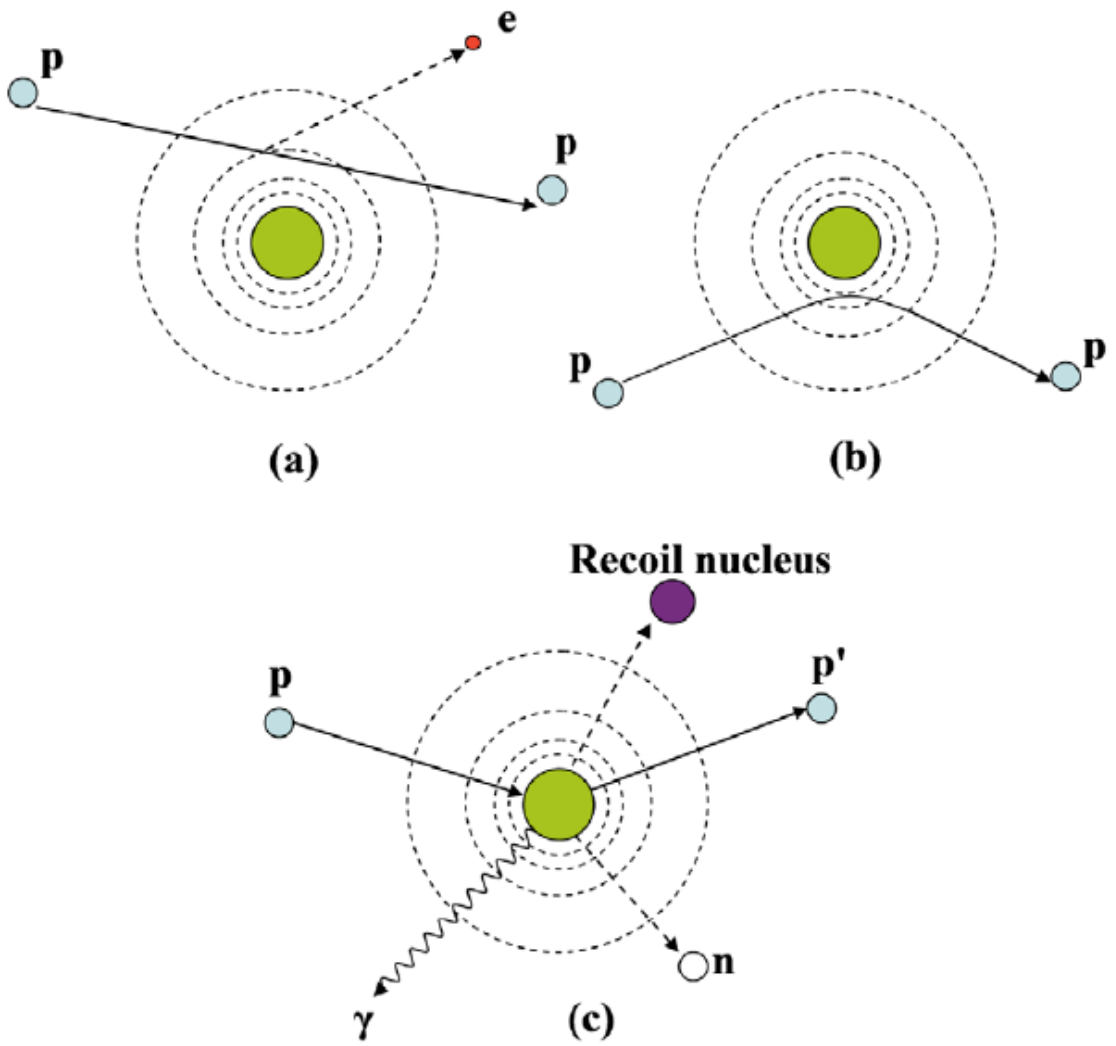
6 MV 18 MV

Proton interaction mechanism

Energy loss via **inelastic Coulomb interaction** with **electron**

deflection of proton trajectory by repulsive **Coulomb elastic scattering with nucleus** (small angle – Multiple Coulomb Scattering, large angle)

removal of primary proton and creation of secondary particles via non-elastic **nuclear interaction**



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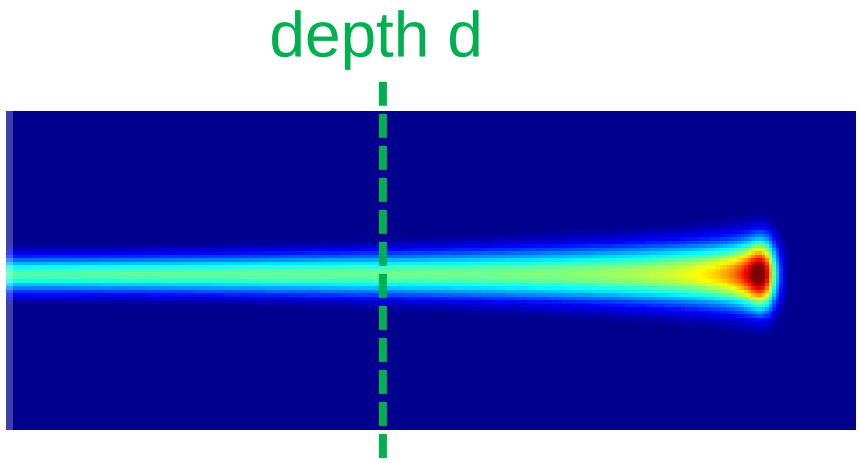
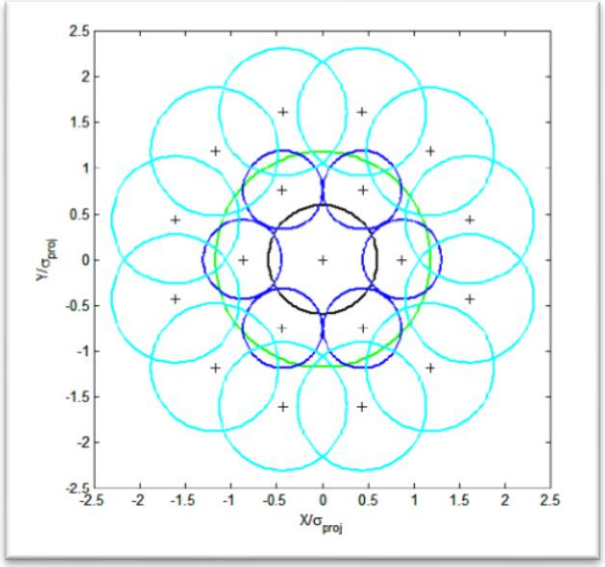
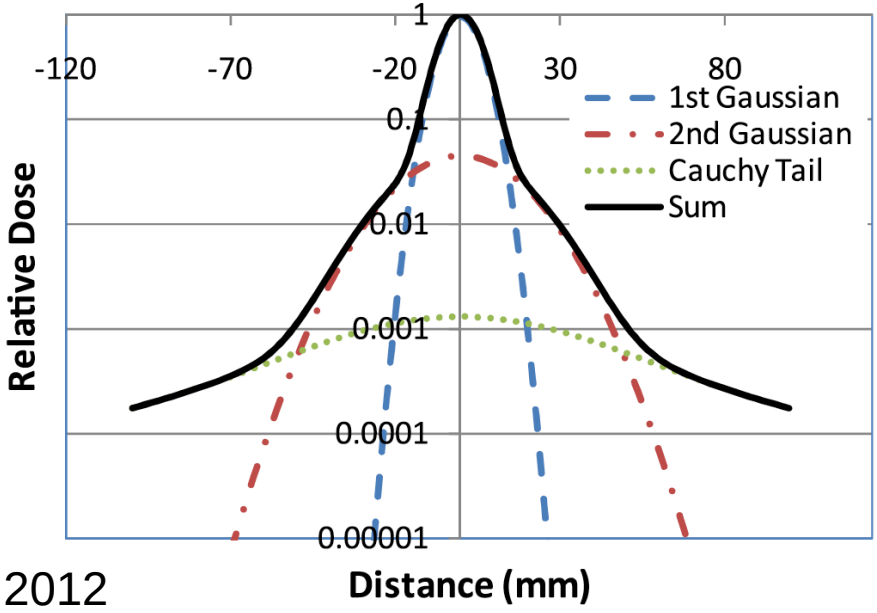
Analytical proton dose calculation

- $D(x,y,z) = I\big(d(z)\big) \times LAT\big(x,y,d(z)\big)$
- I(d) is integral depth dose
- LAT(x,y,d) is lateral dose profile
- Lateral has two components
  - Multiple Coulomb Scattering (1st and 2nd Gaussian)
  - Nuclear Interaction (Halo) due to large angle inelastic nuclear fragments (3rd Gaussian)
  - Usually multiple sub-PB







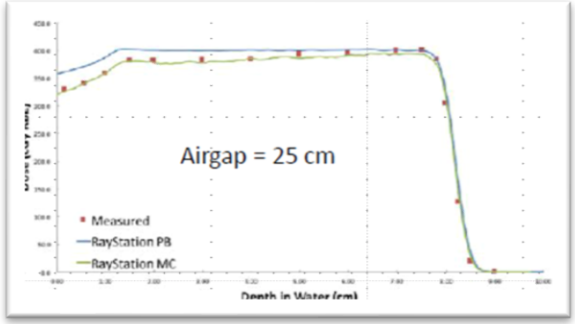
Li Med Phys 2012

Why switch to MC dose computation?

PB algorithm (especially in combination with range shifter) inaccurate for two reasons:

➢ Nuclear halo effect

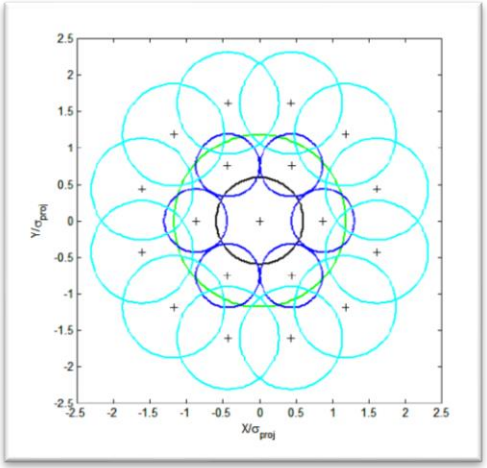
- Each pencil beam is modelled by 2 Gaussians (MCS, nuclear halo)
- Lack of handling nuclear halo properly within the range shifter, then transporting the beam through vacuum (instead of air) and large heterogeneities (patient surface): causes lack of modelling accuracy especially for low energies where a greater angular spread of the protons is expected.



Courtesy N. Schreuder, Provision Knoxville, 2017

➢ Lateral heterogeneities

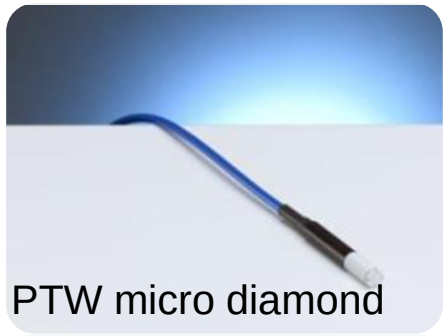
- Each spot is split into 19 sub-pencil beams.
- In case of large spot sizes (combination of range shifter and larger gaps) the distance between subspots becomes larger than anatomic density variations within the patient.



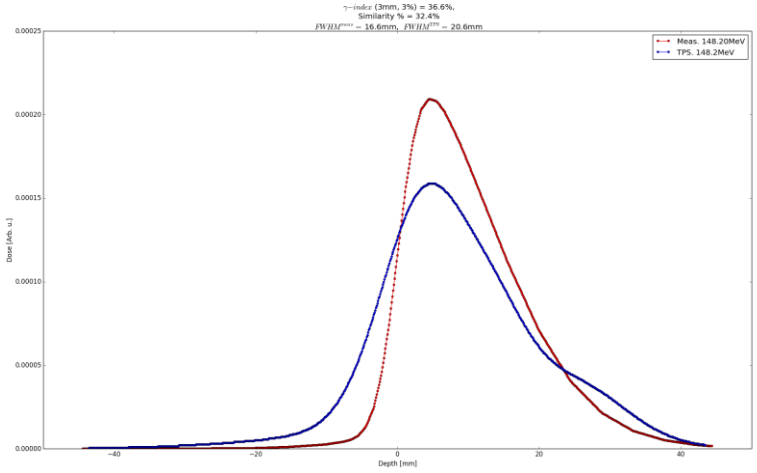
Source: RS5 reference manual, RSL

Validation of algorithms

- Lateral profiles


PTW micro diamond

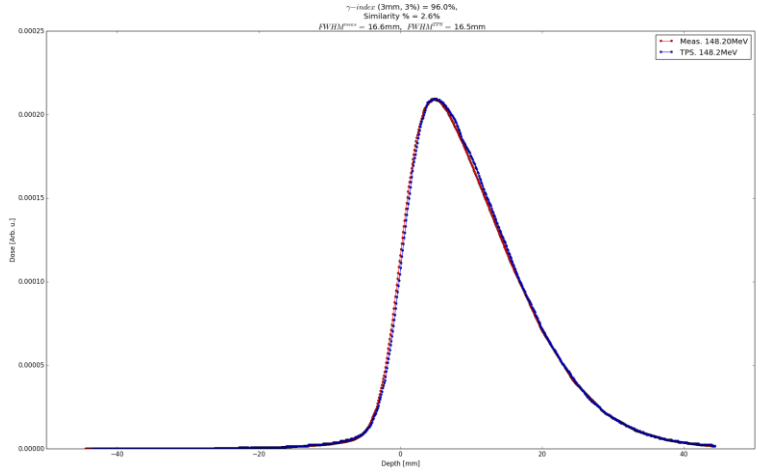
PBv4.1



1cm bone | 1cm air

148,2 MeV, with RaShi

MCv4.0

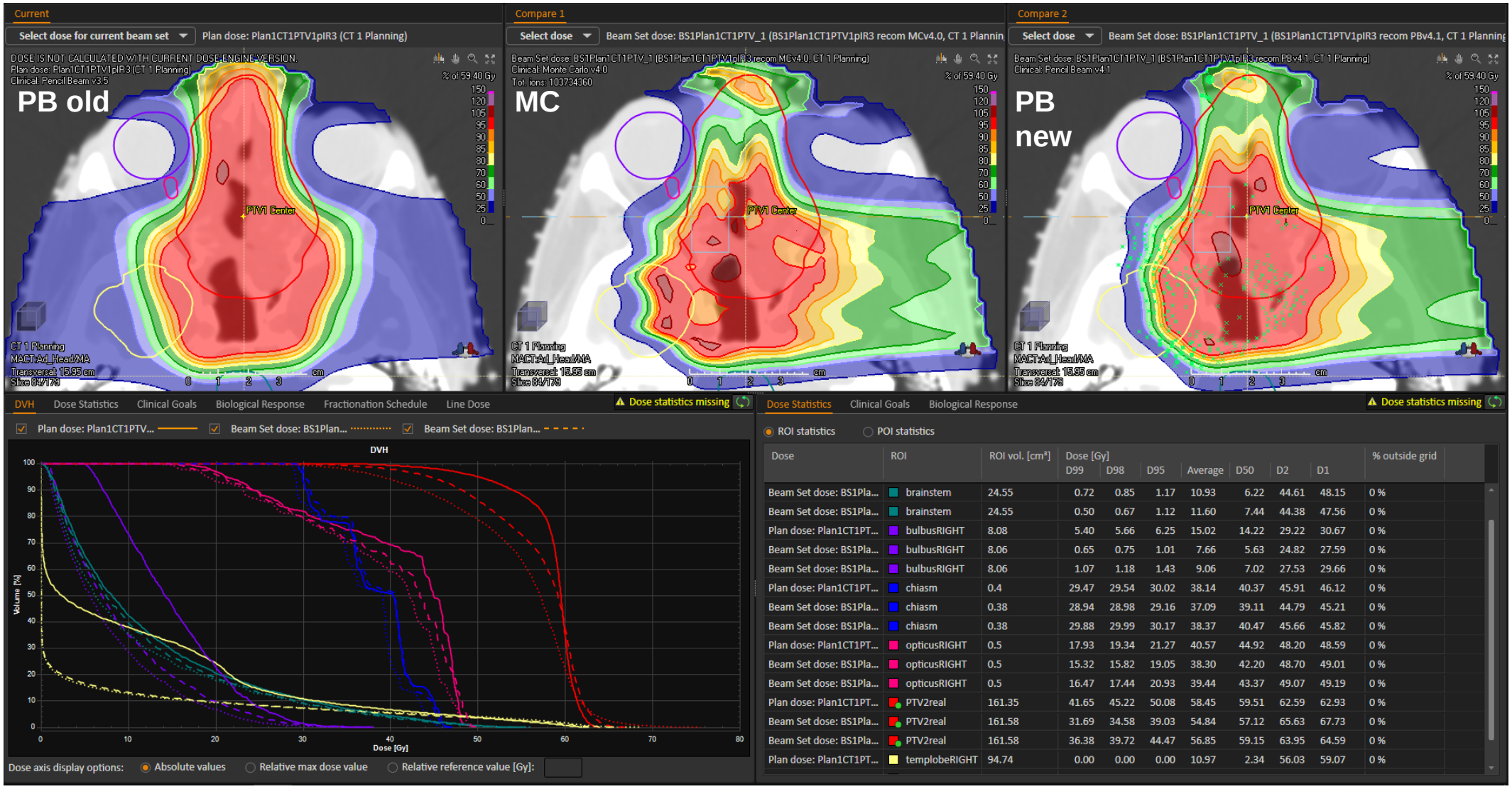


1cm bone | 1cm air

148,2 MeV, with RaShi

Comparison MC vs PB

Complex Case



Dose	ROI	ROI vol. [cm³]	Dose [Gy] D99	D98	D95	Average	D50	D2	D1	% outside grid
Beam Set dose: BS1Pla...	brainstem	24.55	0.72	0.85	1.17	10.93	6.22	44.61	48.15	0 %
Beam Set dose: BS1Pla...	brainstem	24.55	0.50	0.67	1.12	11.60	7.44	44.38	47.56	0 %
Plan dose: Plan1CT1PT...	bulbusRIGHT	8.08	5.40	5.66	6.25	15.02	14.22	29.22	30.67	0 %
Beam Set dose: BS1Pla...	bulbusRIGHT	8.06	0.65	0.75	1.01	7.66	5.63	24.82	27.59	0 %
Beam Set dose: BS1Pla...	bulbusRIGHT	8.06	1.07	1.18	1.43	9.06	7.02	27.53	29.66	0 %
Plan dose: Plan1CT1PT...	chiasm	0.4	29.47	29.54	30.02	38.14	40.37	45.91	46.12	0 %
Beam Set dose: BS1Pla...	chiasm	0.38	28.94	28.98	29.16	37.09	39.11	44.79	45.21	0 %
Beam Set dose: BS1Pla...	chiasm	0.38	29.88	29.99	30.17	38.37	40.47	45.66	45.82	0 %
Plan dose: Plan1CT1PT...	opticusRIGHT	0.5	17.93	19.34	21.27	40.57	44.92	48.20	48.59	0 %
Beam Set dose: BS1Pla...	opticusRIGHT	0.5	15.32	15.82	19.05	38.30	42.20	48.70	49.01	0 %
Beam Set dose: BS1Pla...	opticusRIGHT	0.5	16.47	17.44	20.93	39.44	43.37	49.07	49.19	0 %
Plan dose: Plan1CT1PT...	PTV2real	161.35	41.65	45.22	50.08	58.45	59.51	62.59	62.93	0 %
Beam Set dose: BS1Pla...	PTV2real	161.58	31.69	34.58	39.03	54.84	57.12	65.63	67.73	0 %
Beam Set dose: BS1Pla...	PTV2real	161.58	36.38	39.72	44.47	56.85	59.15	63.95	64.59	0 %
Plan dose: Plan1CT1PT...	templobeRIGHT	94.74	0.00	0.00	0.00	10.97	2.34	56.03	59.07	0 %

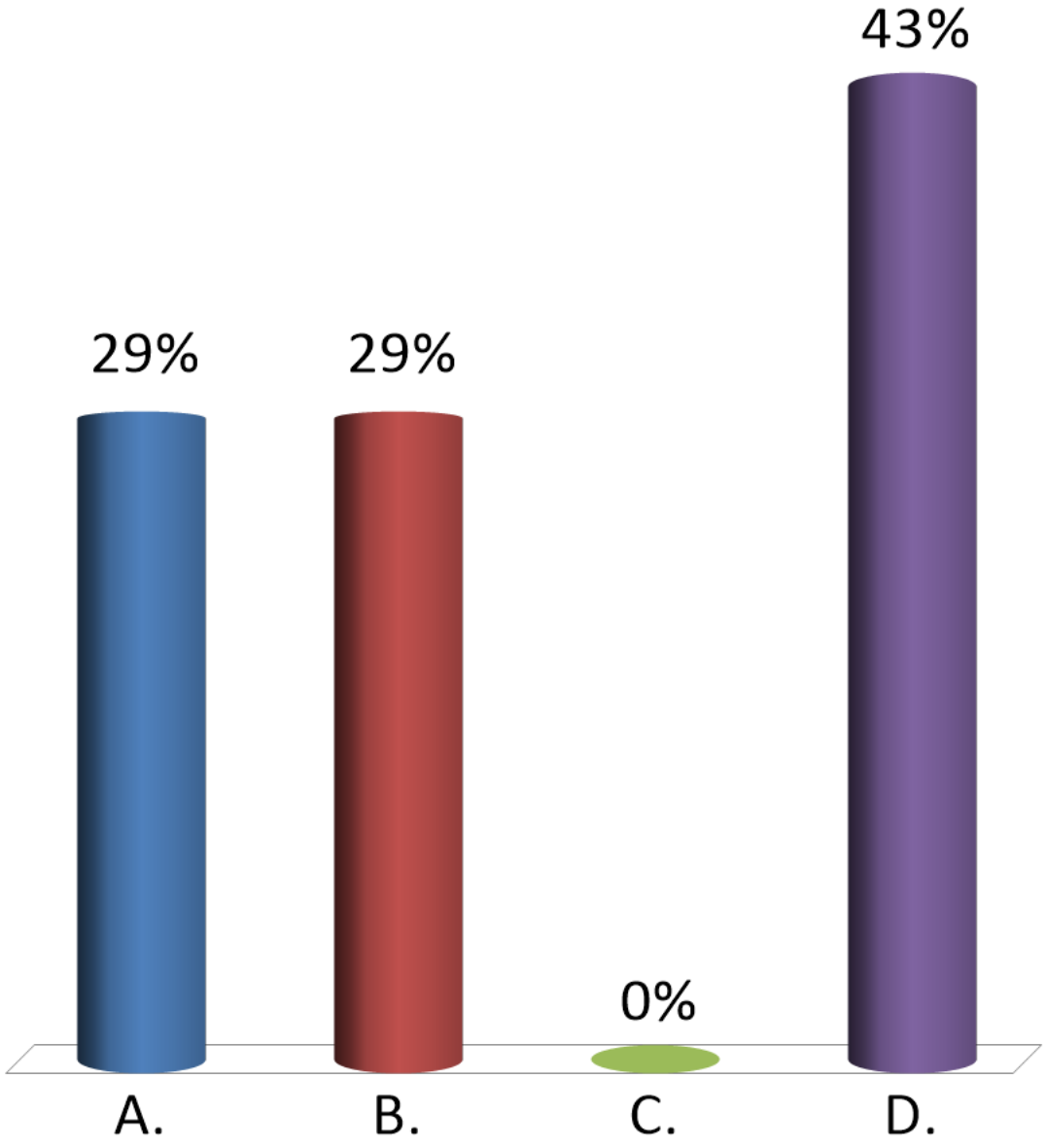
Order algorithms with increasing accuracy

A. MC, PK, AAA, PBK

B. PBK, AAA, PK, MC

C. AAA, PK, PBK, MC

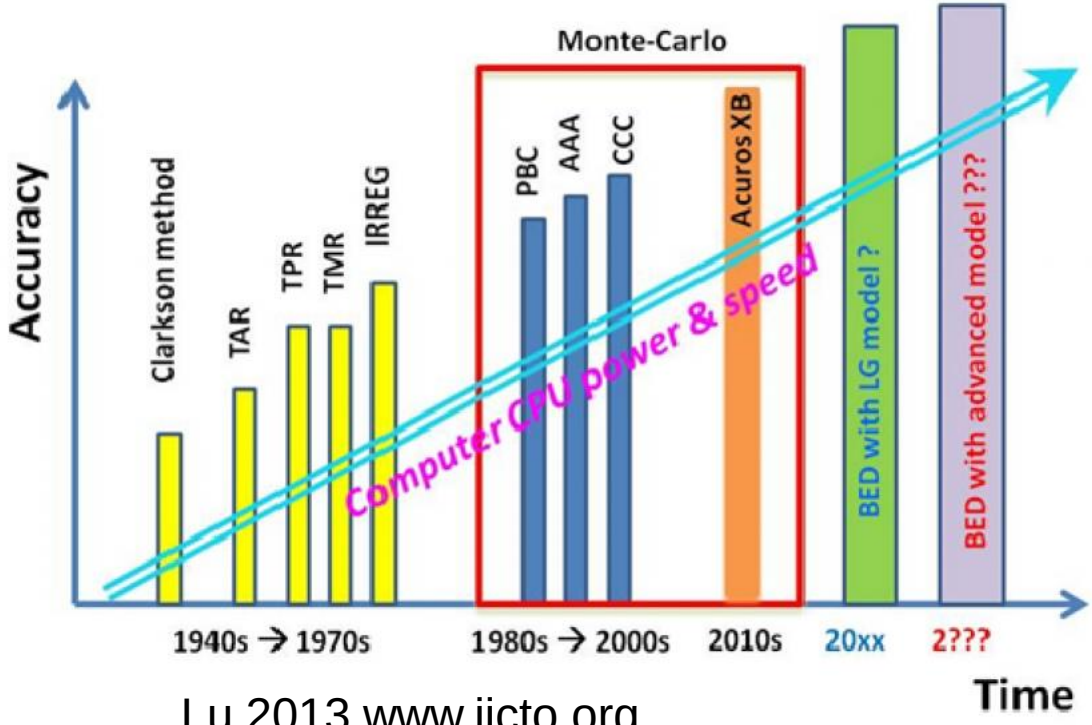
D. PBK, PK, MC, AAA



www.responseware.eu
session ID: atp18

Summary – Evolution, not Revolution

- Point Kernel algorithms more accurate than Pencil Kernel models
- Modern algorithms are hybrids of deterministic numerical and Monte Carlo methods. They can predict dose in heterogeneous tissues more accurately.
- Speed optimized MC clinically available without large compromise on accuracy – for photons, electrons and protons. Errors are stochastic.
- In both Monte Carlo and LBTE methods, a trade-off exists between speed and accuracy.



Lu 2013 www.ijcto.org

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WWW.ESTRO.ORG/SCHOOL

ICRU guidance on planning and prescribing

Neil Burnet

Manchester Cancer Research Centre,
University of Manchester and Christie Hospital,
Manchester, UK

ATP
Athens 2018

Summary

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

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The history of radiotherapy

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

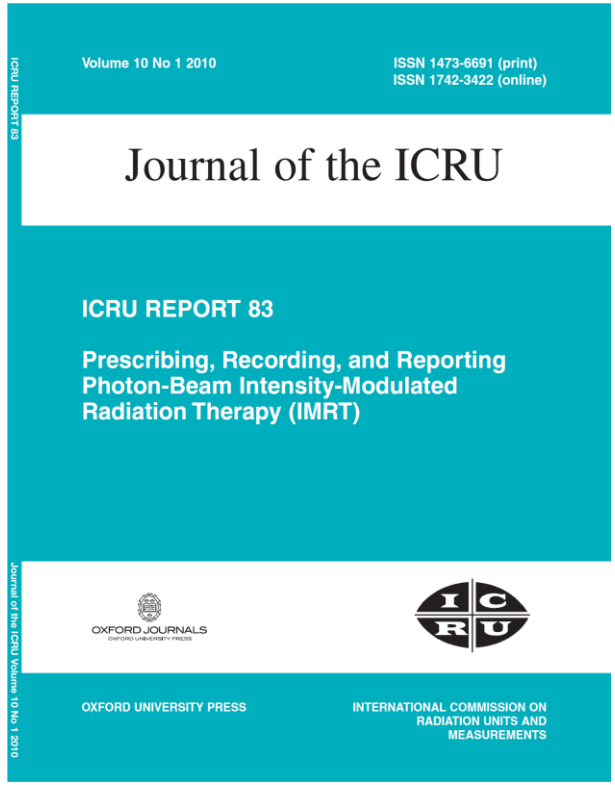
- 100+ years later the technology has changed!
- ICRU reports are here to help us

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

- ICRU 83 (2010) was 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

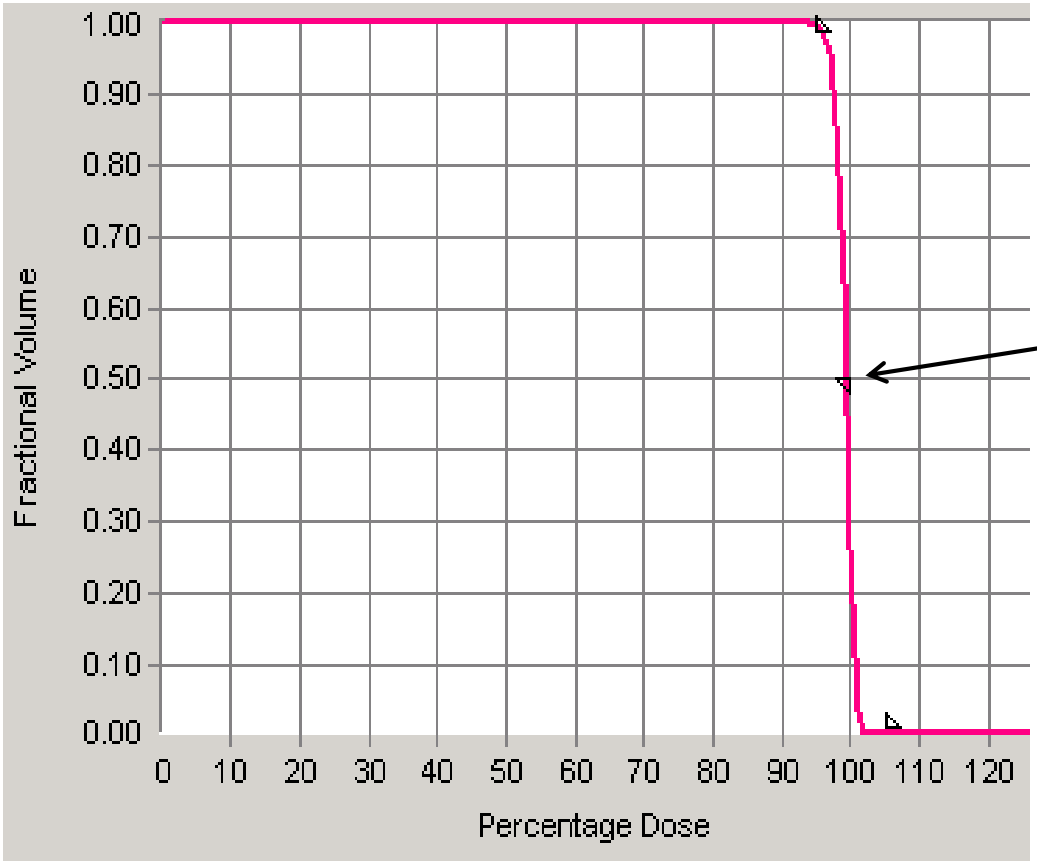
- Specify median dose - $D_{median} = D_{50\ \%}$
  - Corresponds best to previous ICRU reference point dose (≈ isocentre dose)
  - Often close to mean dose
  - Not influenced by 'tails' on the DVH
  - Accurately calculated in TPSs

  - 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

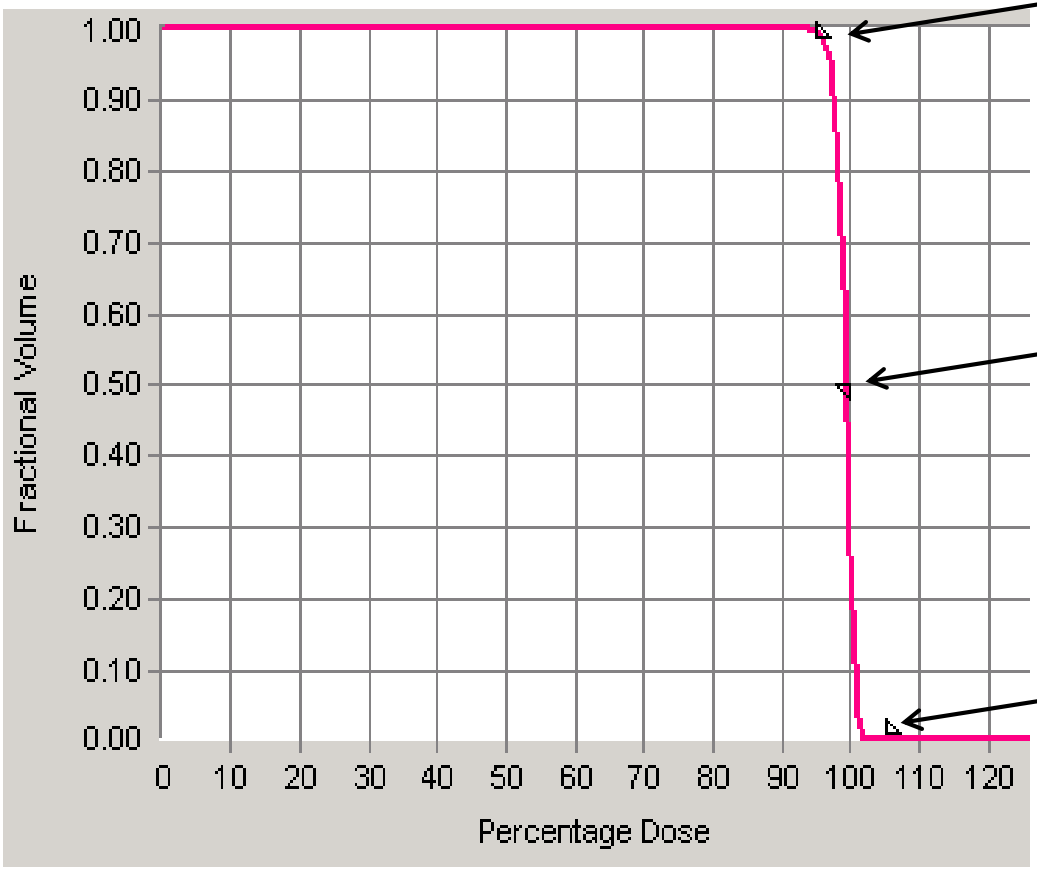
- Prescribing to median dose without some restriction on the slope of the target DVH could allow a shallow slope and low target minimum dose

- 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)

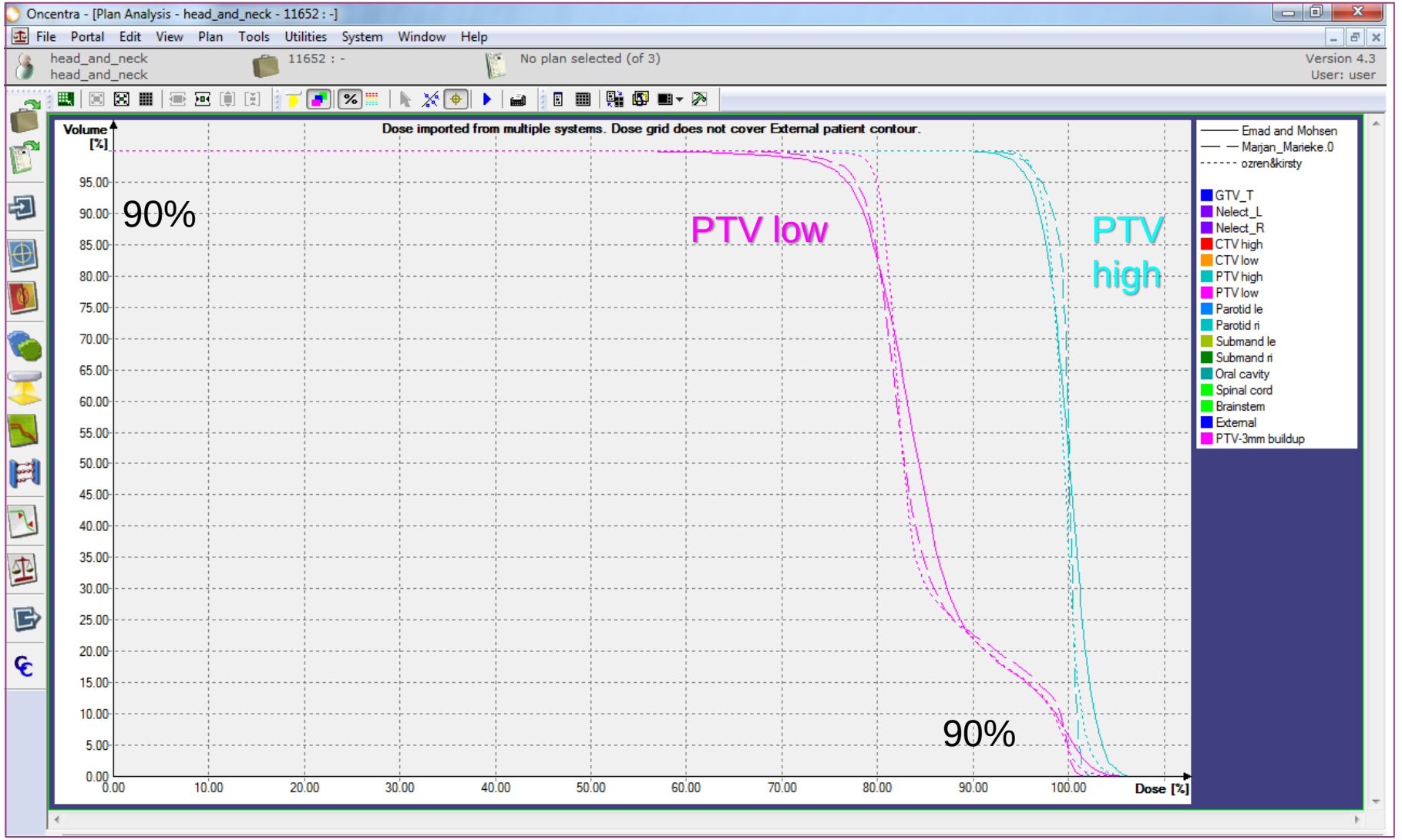


$V_{95\ \%}$

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

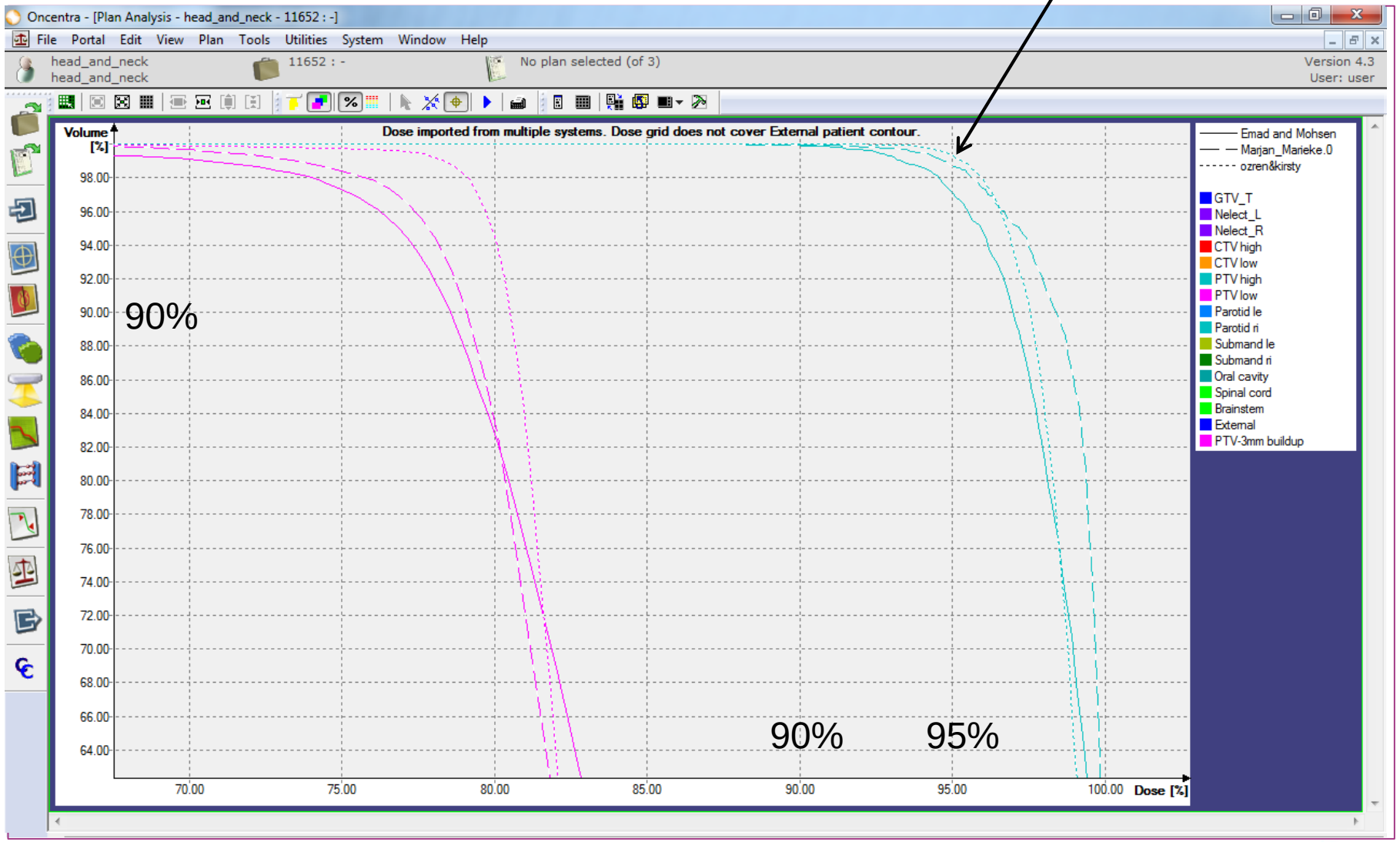
$V_{105\ \%}$

Prescribing



Prescribing

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



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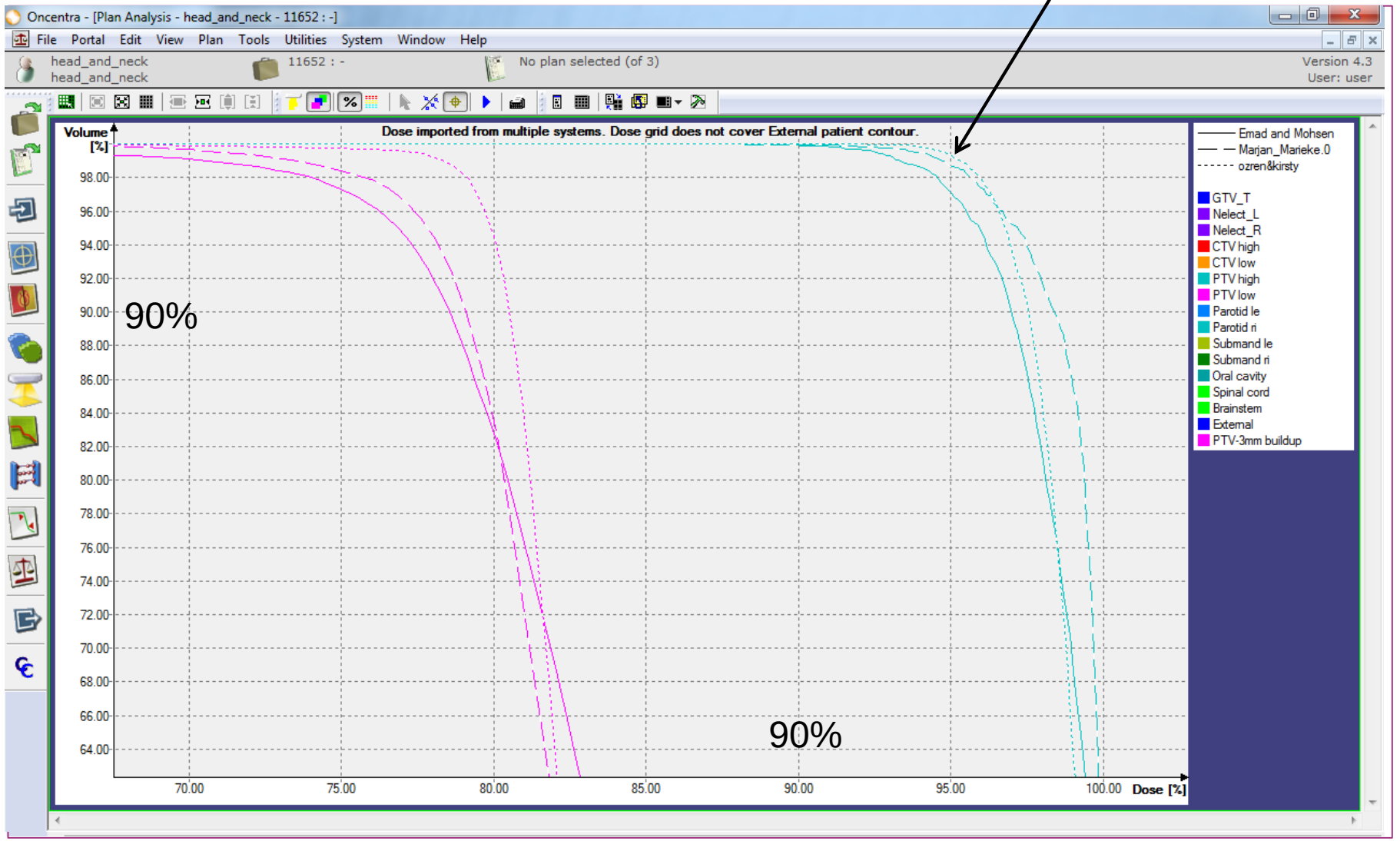
Prescribing

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

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



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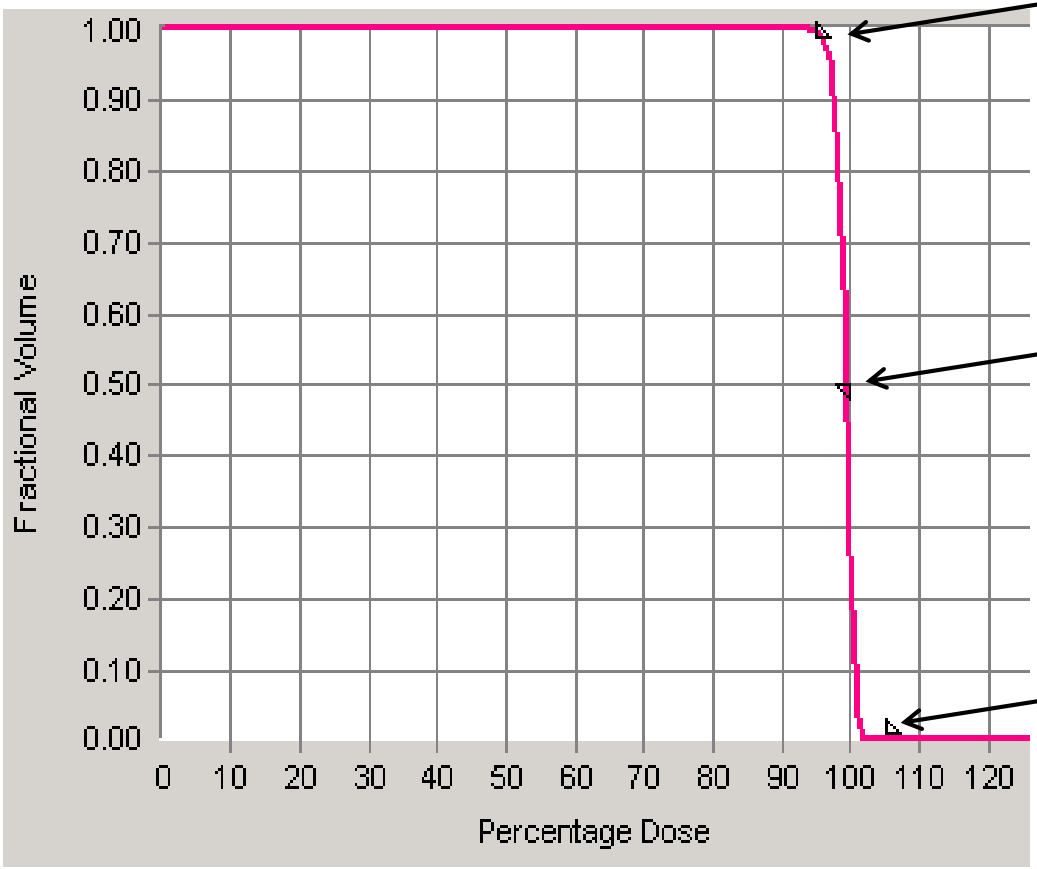
Prescribing

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



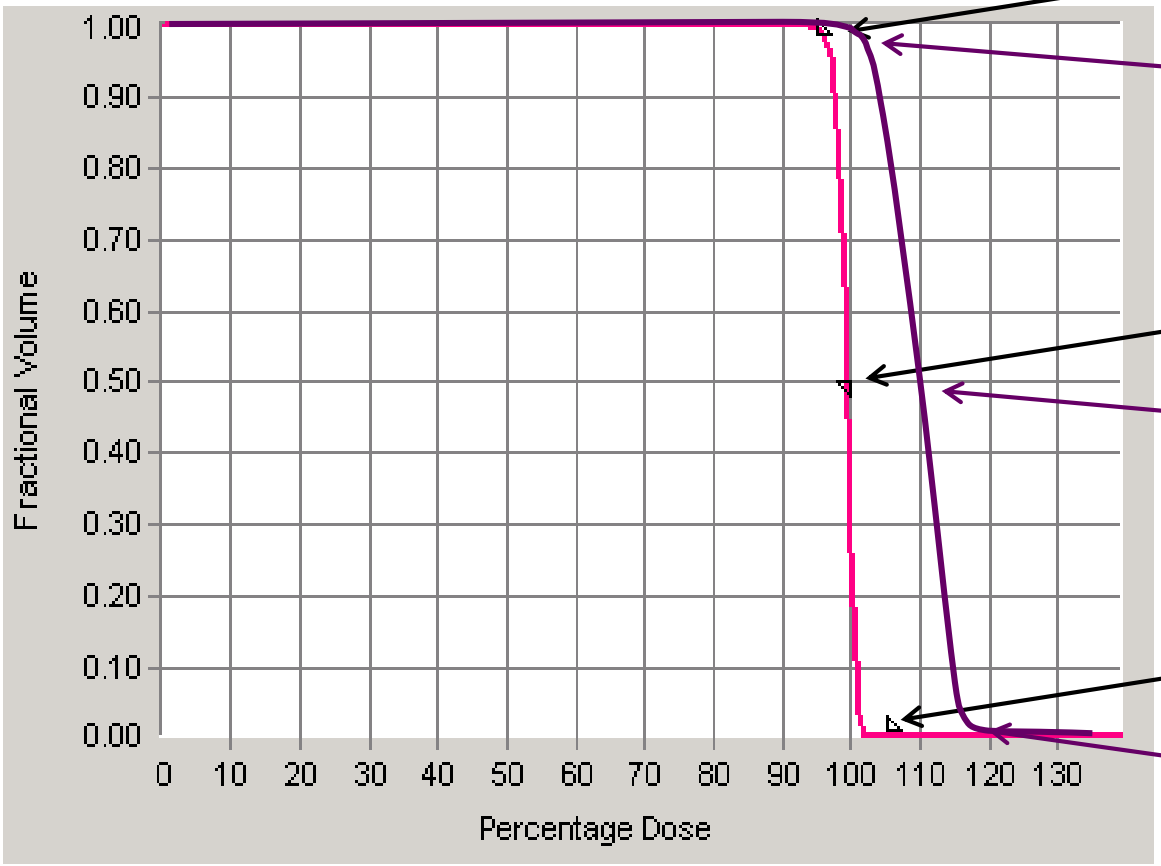
$V_{95\ \%}$

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

$V_{105\ \%}$

Prescribing

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



$V_{95\ \%}$

(Near) min dose increased

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

Median now too high

$V_{105\ \%}$

(Near) max very high

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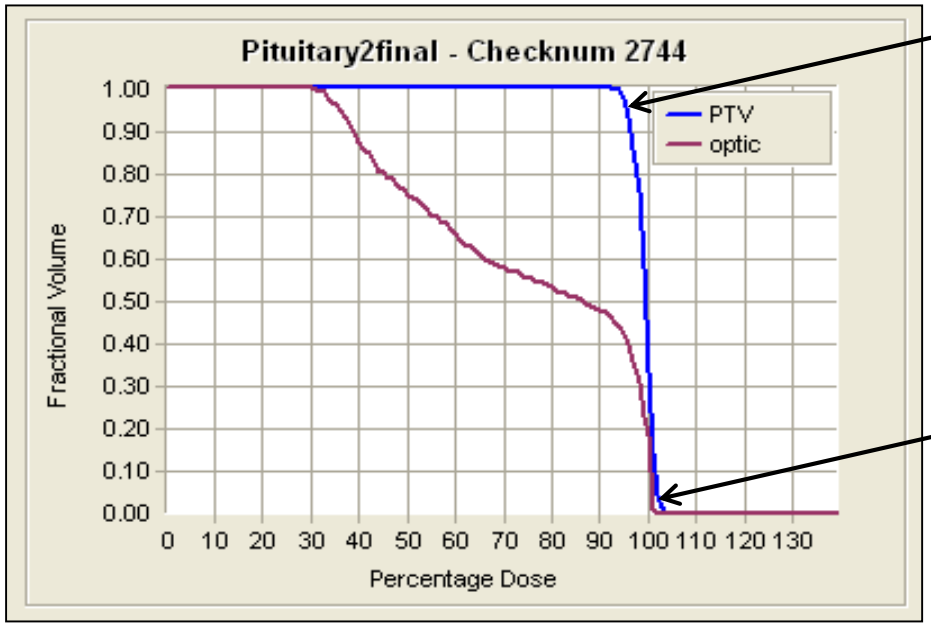
Prescribing

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

Prescribing

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



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

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

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Prescribing

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

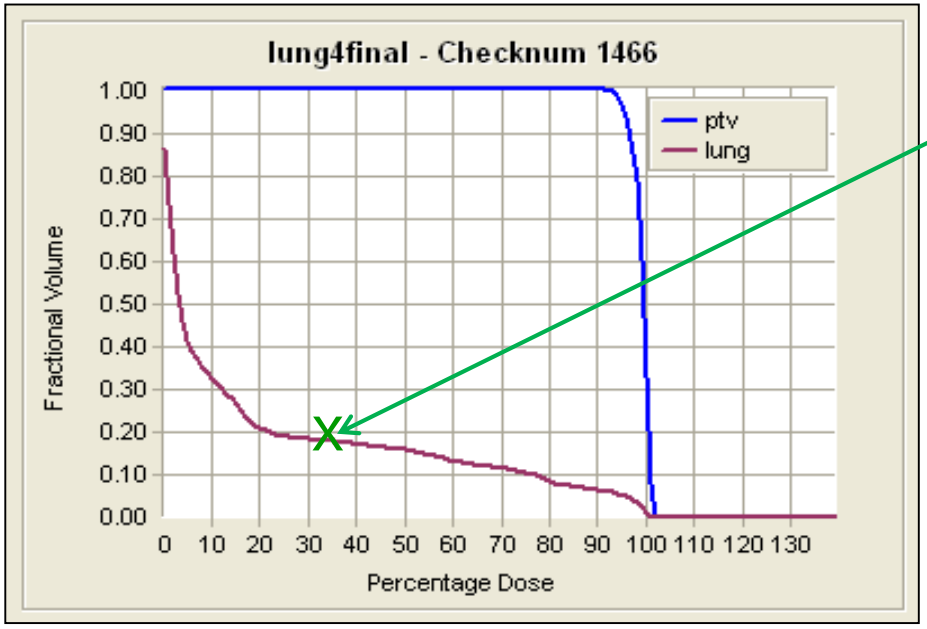
Prescribing

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

- Contains worked examples, which may be helpful

Prescribing

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



$V_{20\ Gy}$

Relates to clinical outcome

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

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Prescribing

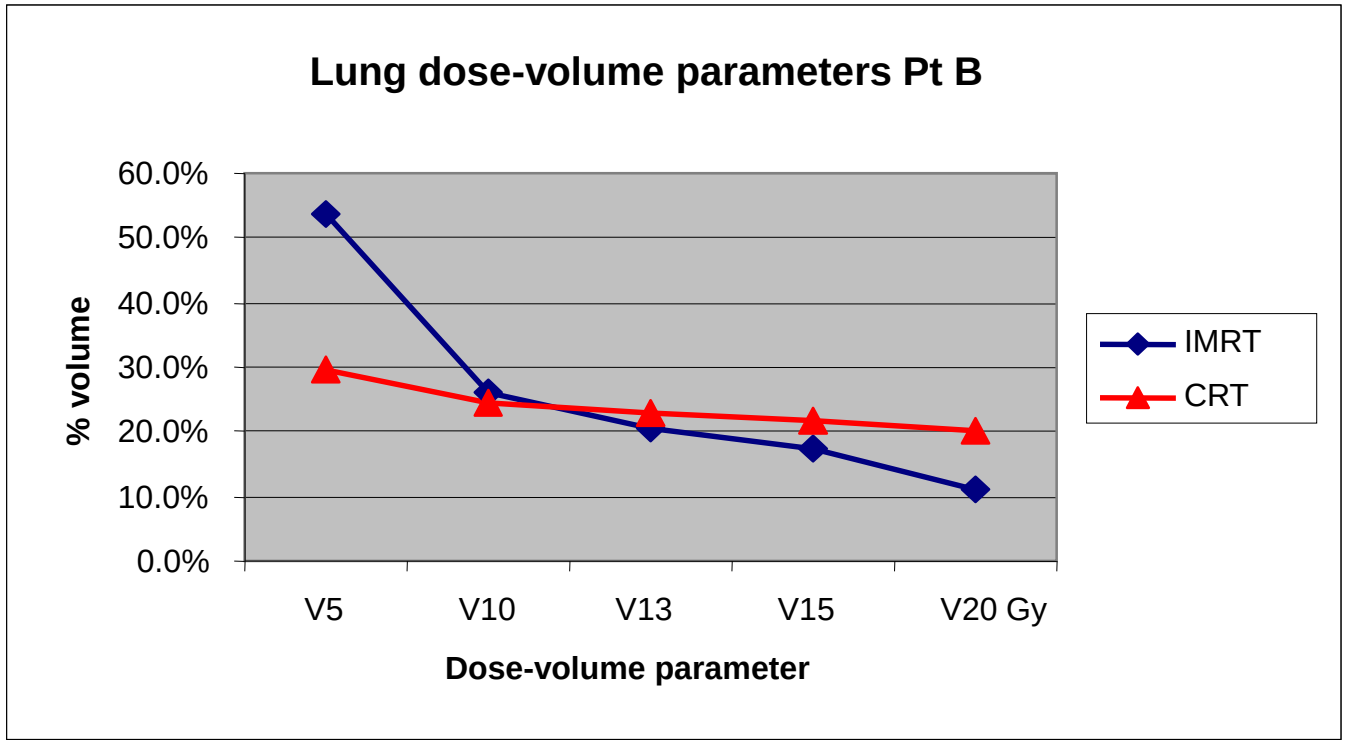
- Add volume parameters where relevant
  - e.g. $V_{20\ Gy}$ for lung

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

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

Lung doses

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



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Prescribing

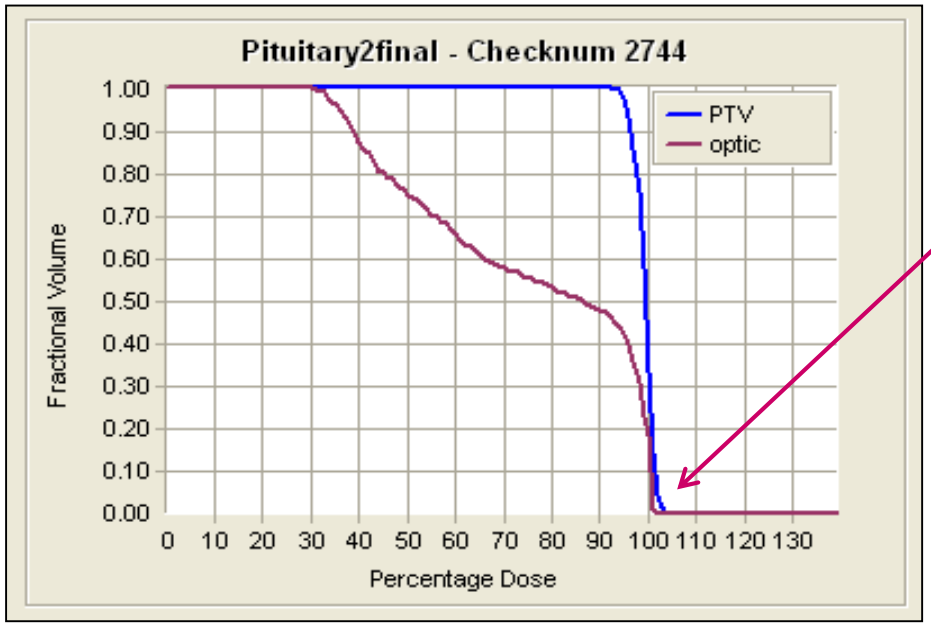
- For serial organs, maximum (near-max) dose is relevant parameter
  - ICRU recommends $D_{2\%}$ rather than D_{Max} ($D_{0\%}$)
  - Overcomes problem of defining (knowing!) what volume of the structure is important

  - Note that $D_{2\%}$ not validated (yet); caution given !
  - But … it is logical
  - However, effect will depend on total volume of structure

  - In gynae brachtherapy often use $D_{2\,cm^3}$

Prescribing

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



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

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

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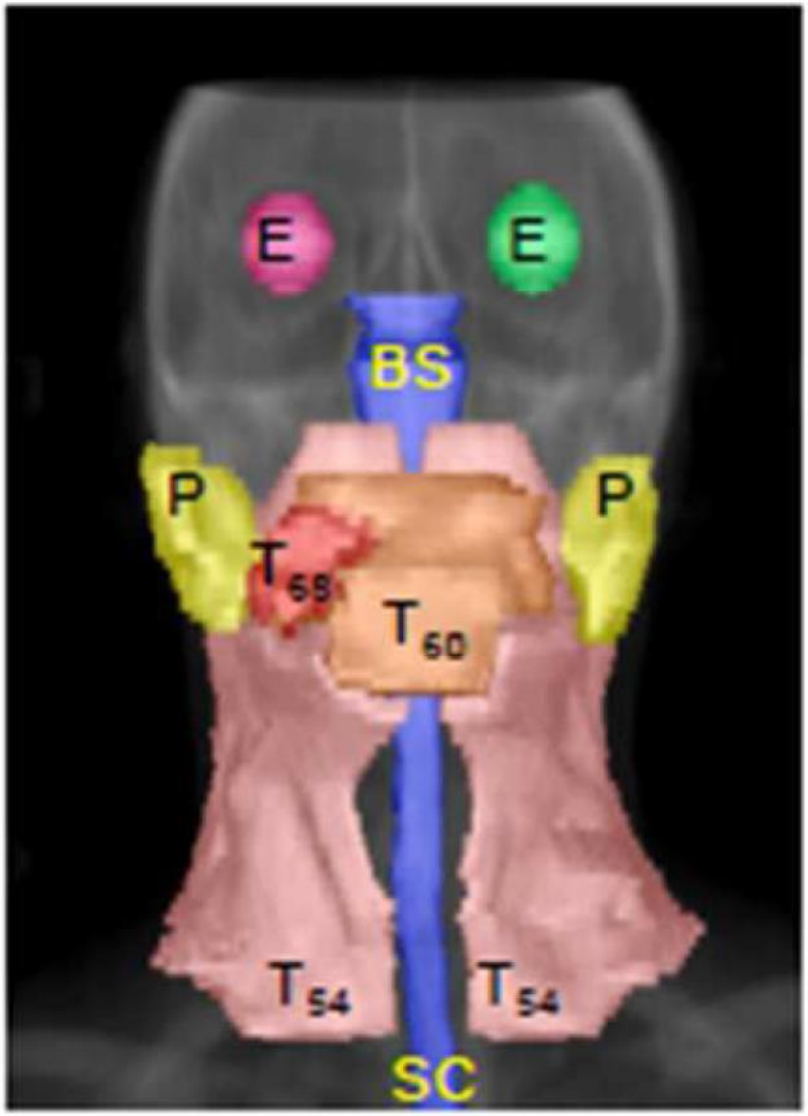
ICRU guidance

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

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

- Some details at end of lecture notes

Target volumes



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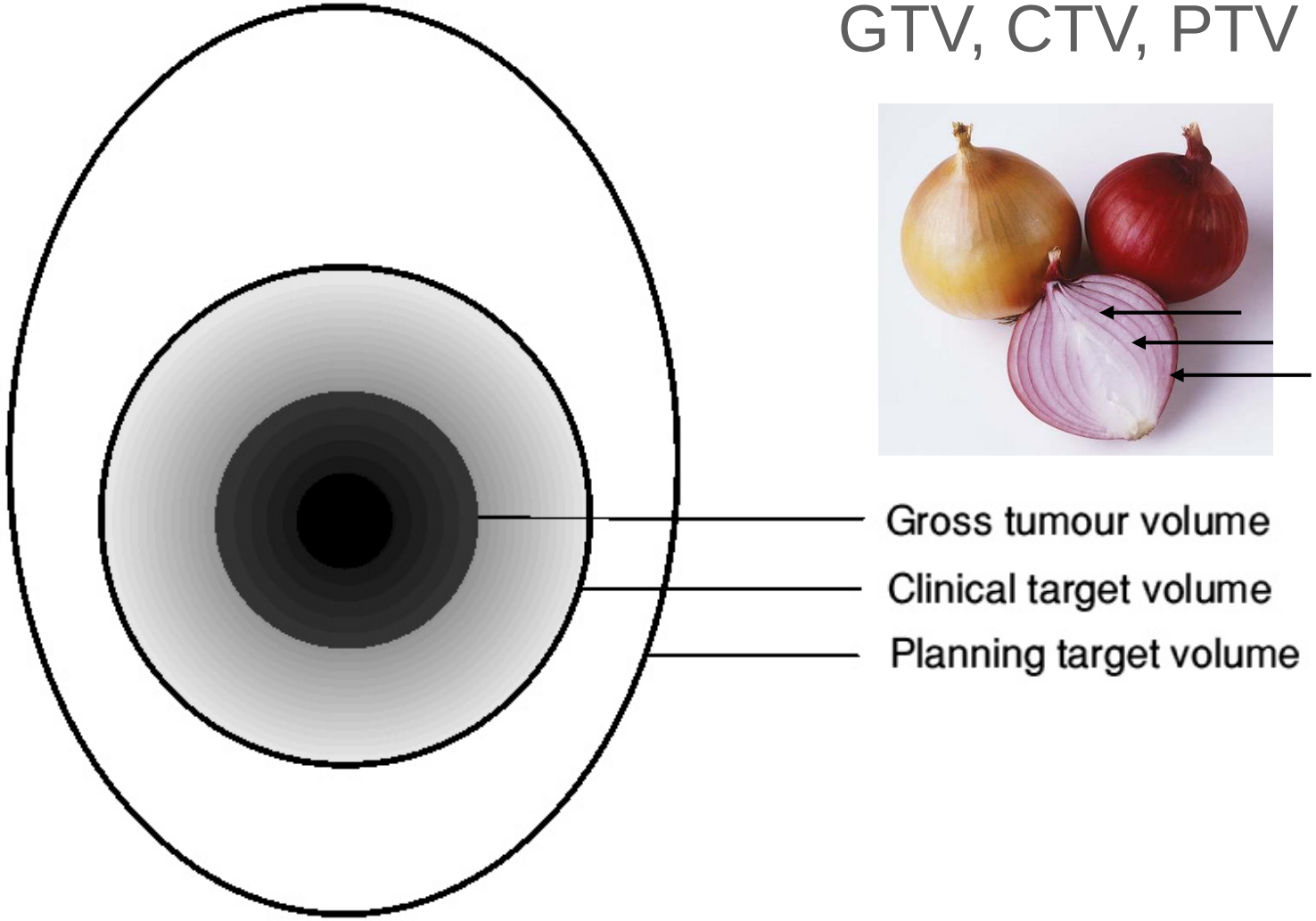
Target volumes

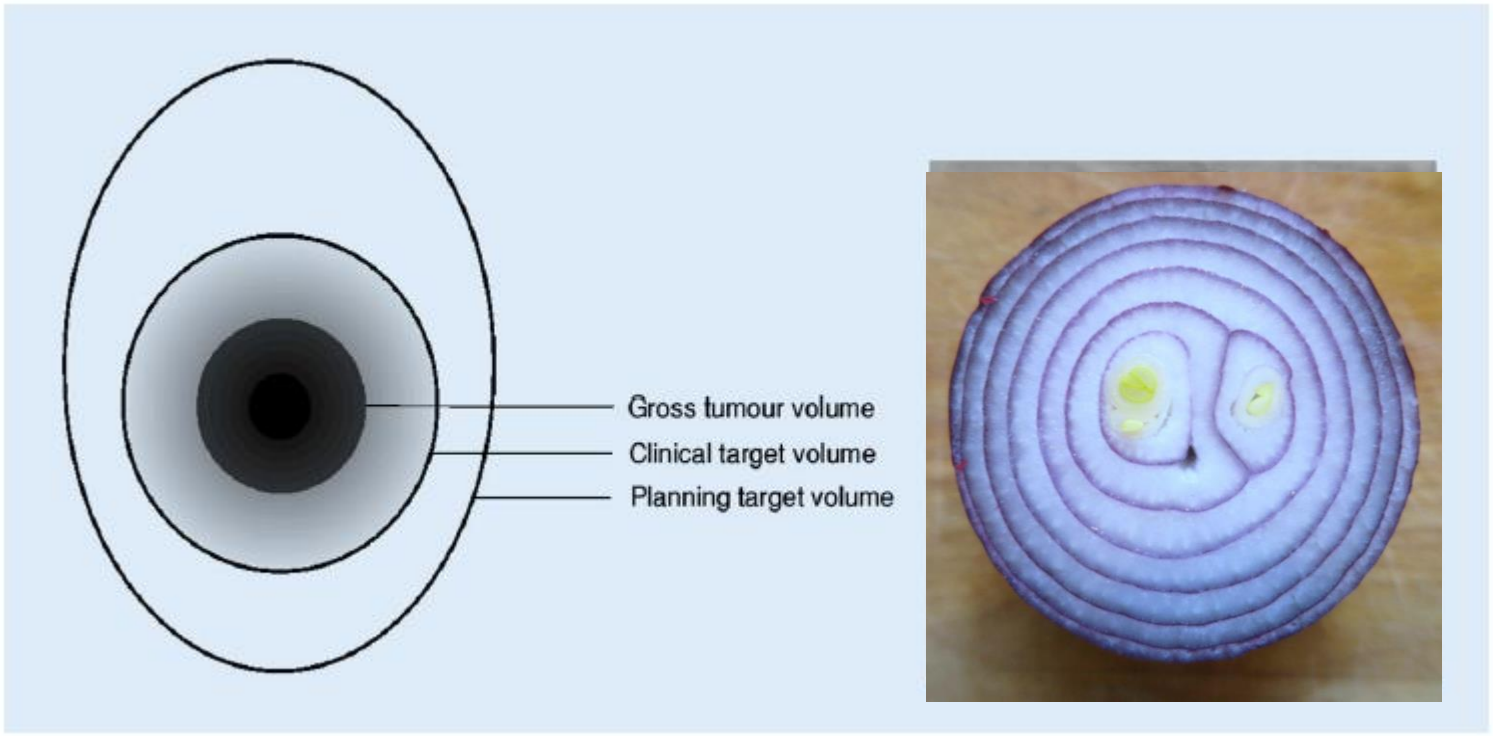
- ICRU 50 target volumes
- The PTV can be eccentric



Target volumes

Zielvolumenkonzepte in der Strahlentherapie und ihre Bedeutung für die Bildgebung

Burnet NG, Noble DJ, Paul A, Whitfield GA, Delorme S. Radiologe. 2018; 58(8): 708-721. Review. German.



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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 - CTV

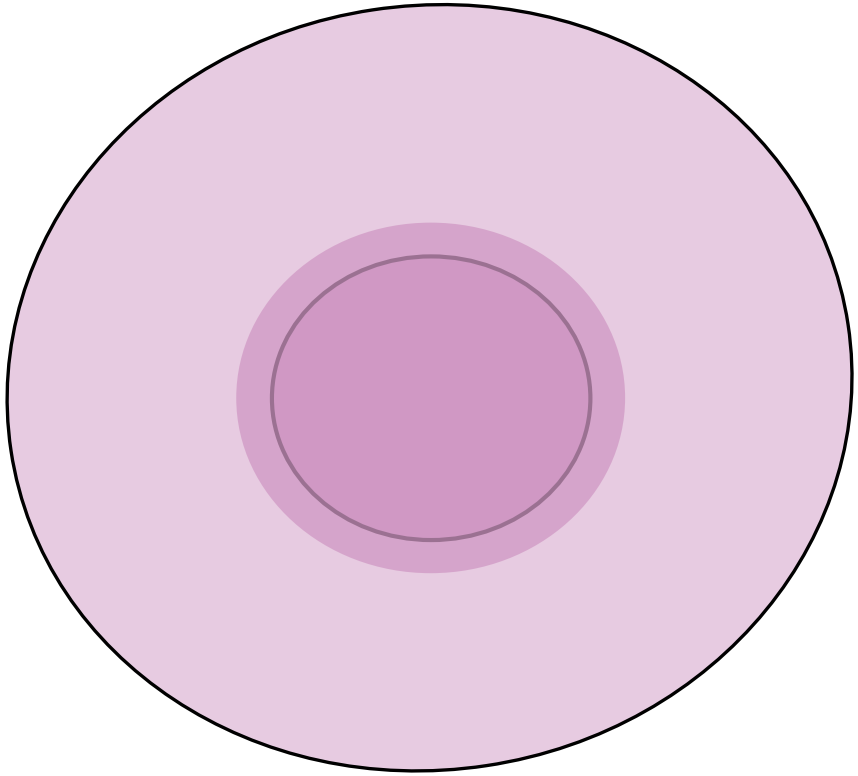
Target volumes - CTV

- CTV is based on historical data
  - Derived from population data
  - Margin *not* individualised

- Some individualisation according to anatomical boundaries is possible
  - Implies that isotropic growing is often not appropriate to derive the CTV

Target volumes - CTV

- Newer imaging may push the edge of the GTV outwards into the CTV
- If CTV stays the same, the margin will change
- May need new definitions
- Useful to define imaging used for GTV contouring



Target volumes - CTV

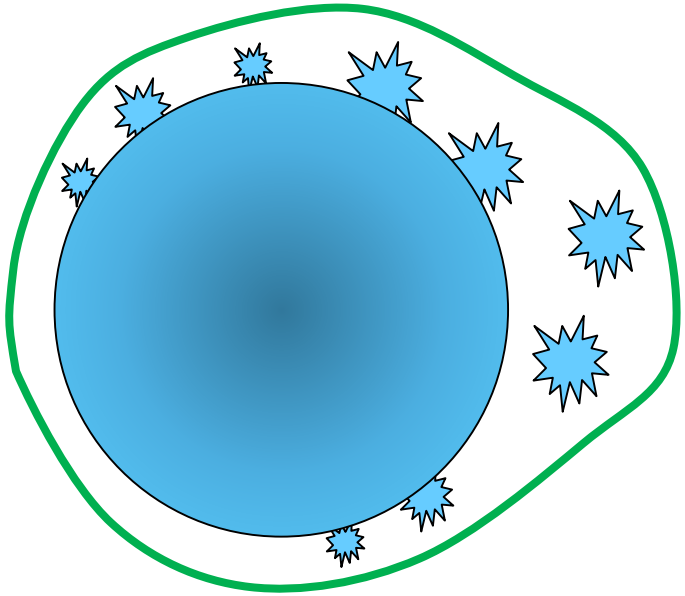
- Concept that the CTV contains all the sub-clinical disease with a certain probability
  - Introduced in ICRU 83 (2010)

- No consensus as to what that probability is
  - Probability of ~ 90-95% may be reasonable
  - Should it be lower or higher?
  - (i.e. don't treat if probability <5% or 10%)

- Might depend on dose at edge of treated volume …

Target volumes - CTV

- Microscopic disease not imageable
- Probability of all microscopic tumour included in CTV …
- Is there a dose gradient? Where?



100%
(good work!)

Adapted from: Radiation oncology in the era of precision medicine
Baumann M. et al. Nat Rev Cancer 2016; 16: 234-249

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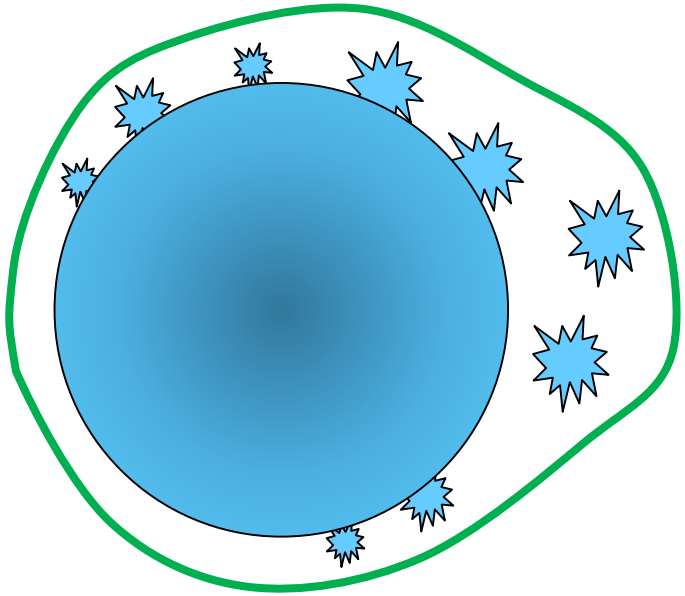
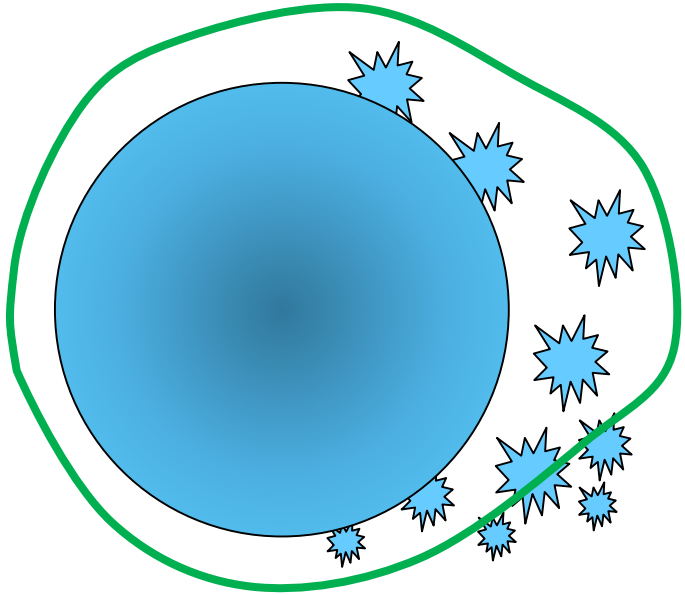
Target volumes - CTV

- Microscopic disease not imageable
- Probability of all microscopic tumour included in CTV …
- Is there a dose gradient? Where?



100%
(good work!)



95%
(not right)

Adapted from: Radiation oncology in the era of precision medicine
Baumann M. et al. Nat Rev Cancer 2016; 16: 234-249

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Target volumes - PTV

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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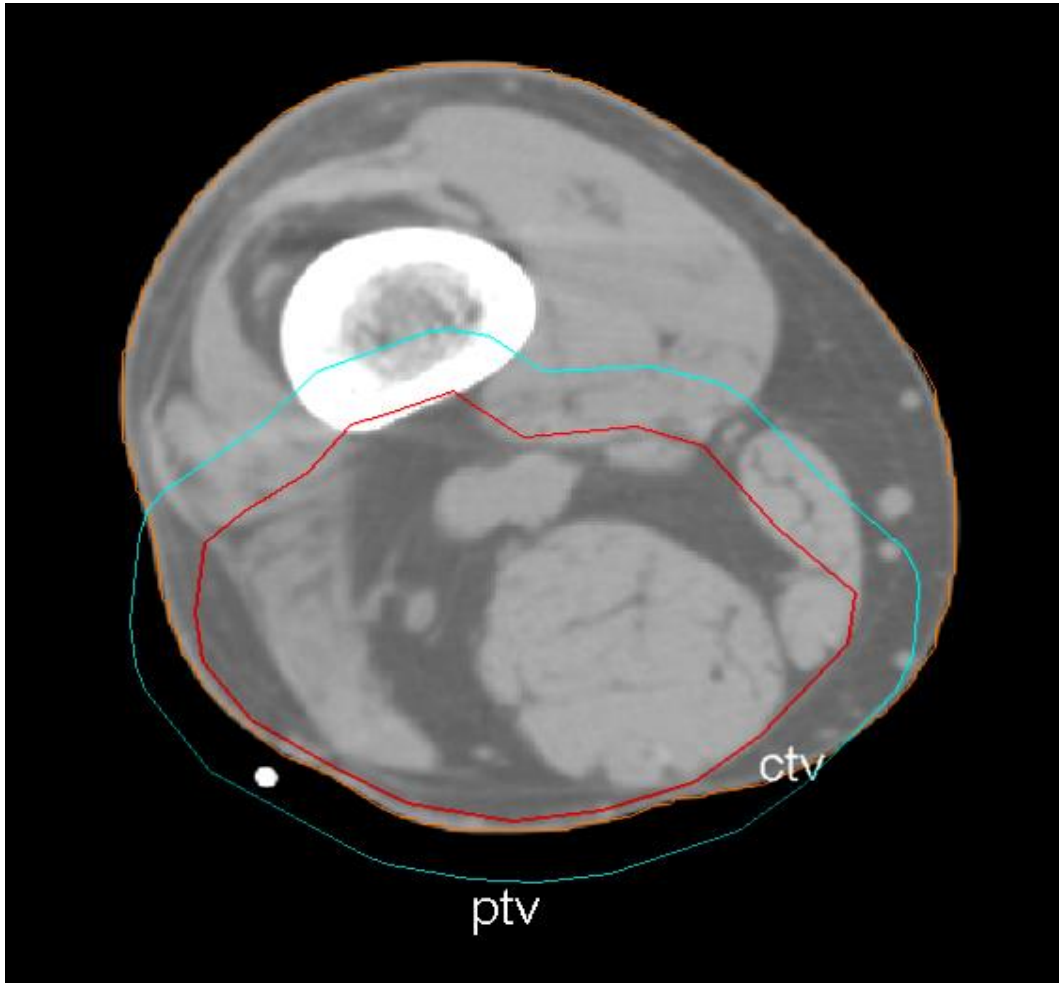
Target volumes - PTV

- PTV extend into
  - the build up region
  - outside the patient
- NB problem of IMRT optimisation
- Also a challenge in PBT



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

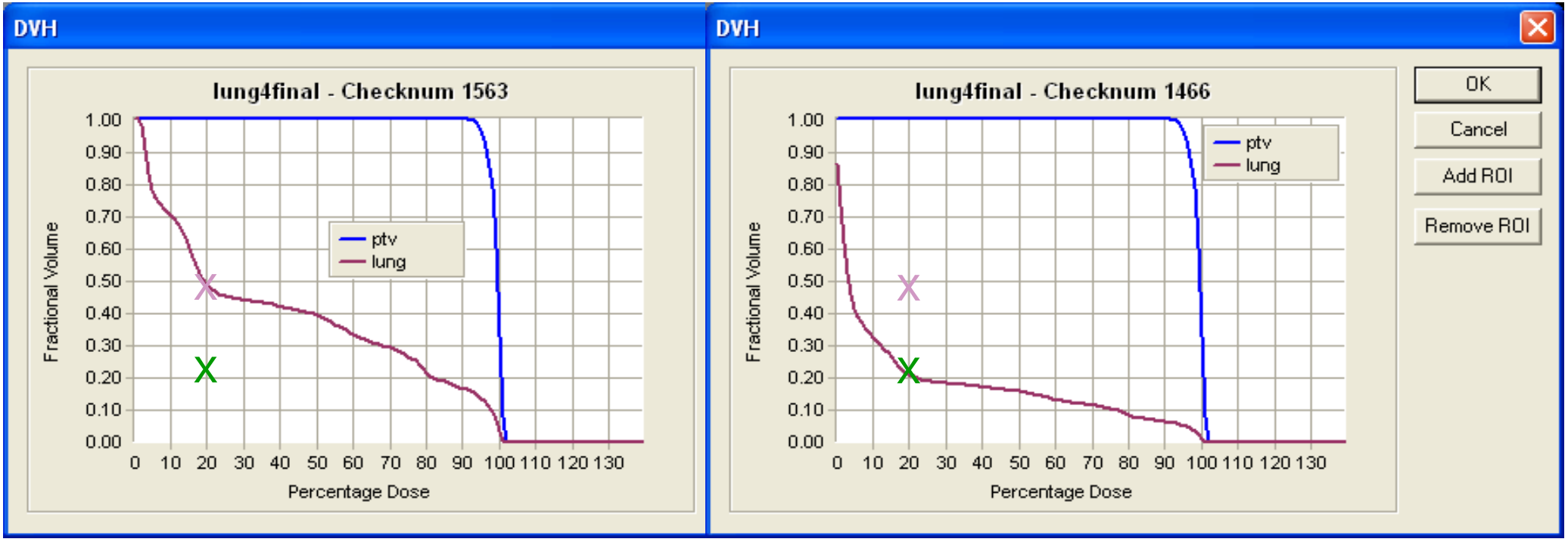
Target volumes – OARs

- 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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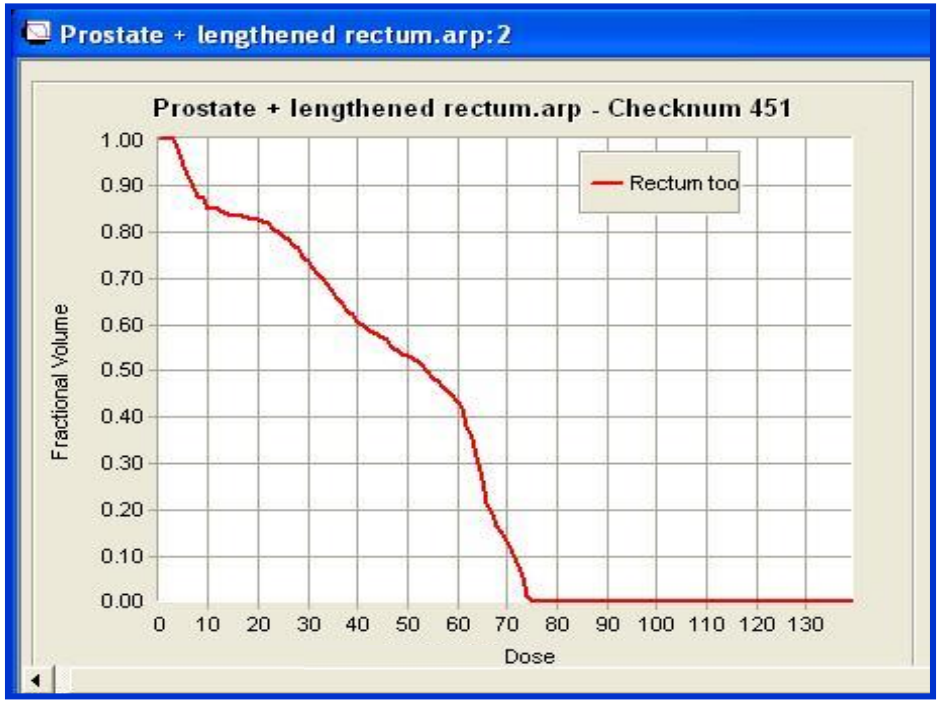
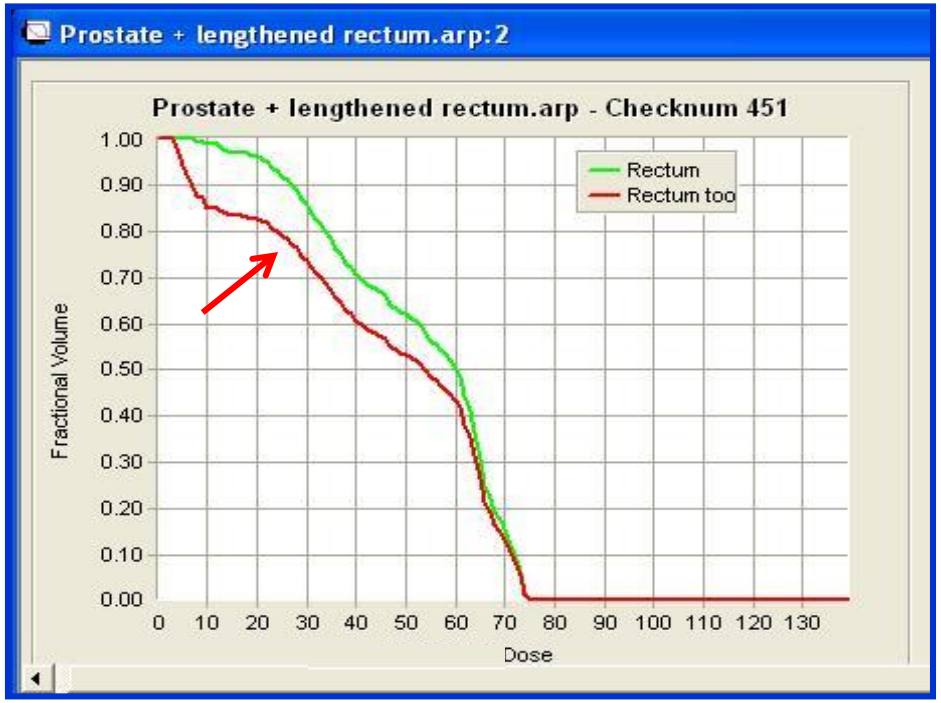
Target volumes – OARs

- 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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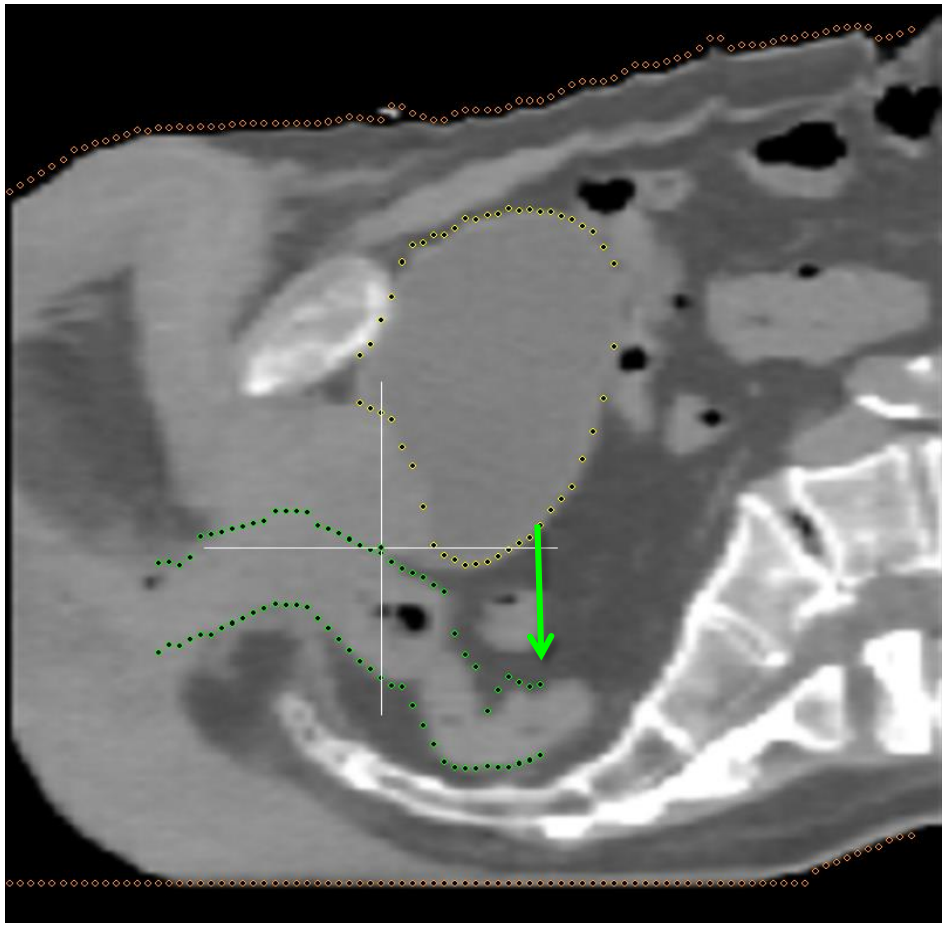
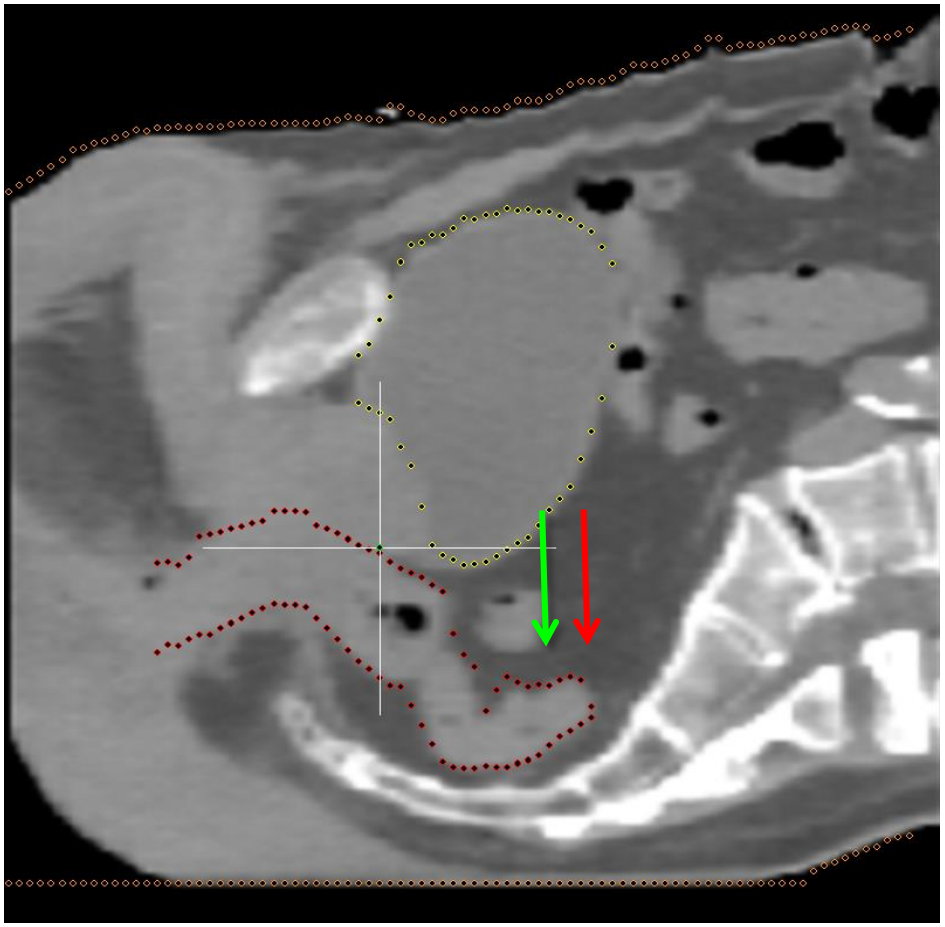
Target volumes – OARs

- Rectum–clear delineation, according to an agreed protocol



- Rectum correct



- Rectum on 4 slices more

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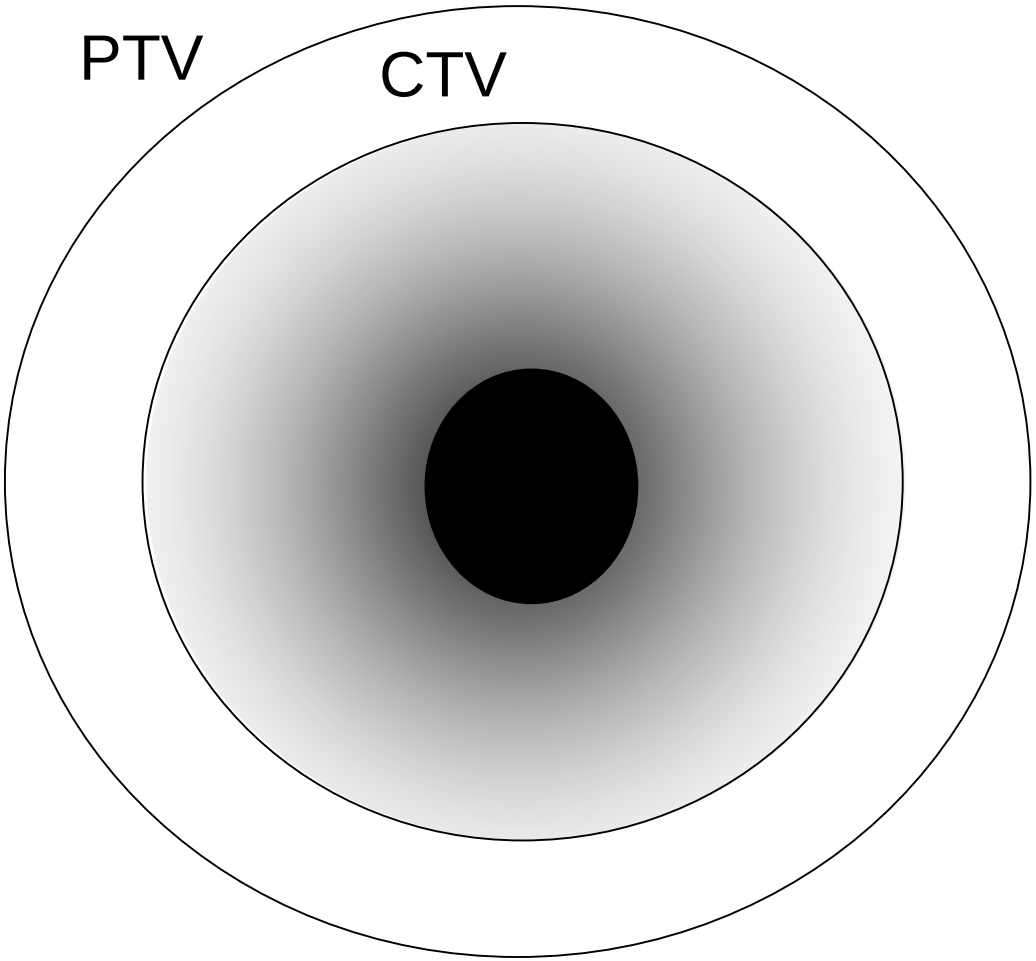
Target volumes – OARs + PRVs

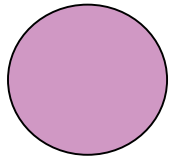
- Uncertainties apply to the OAR … so a 'PTV margin' can be added around it - to give the Planning organ at Risk Volume (PRV)

- 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

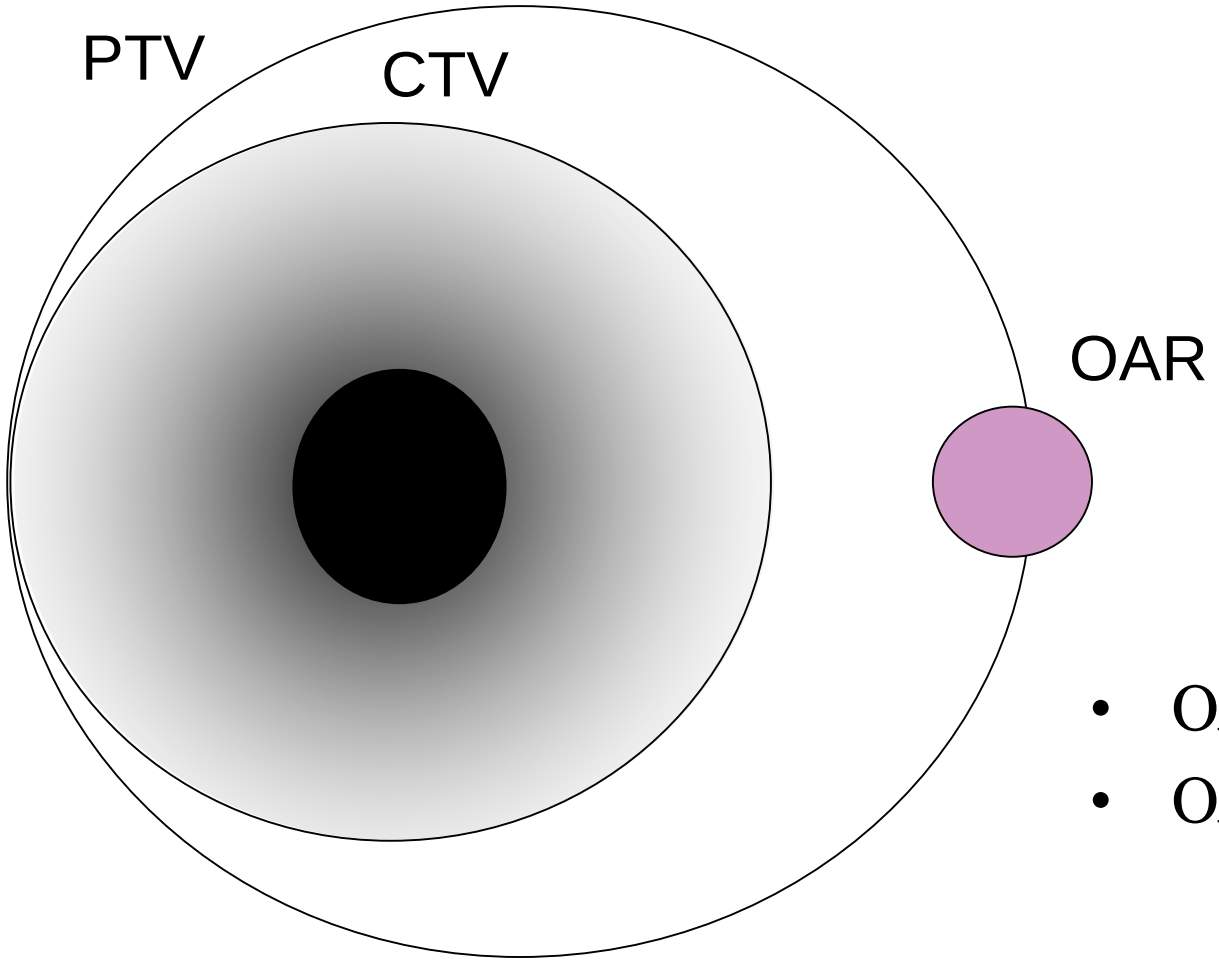
Target volumes – OARs + PRVs





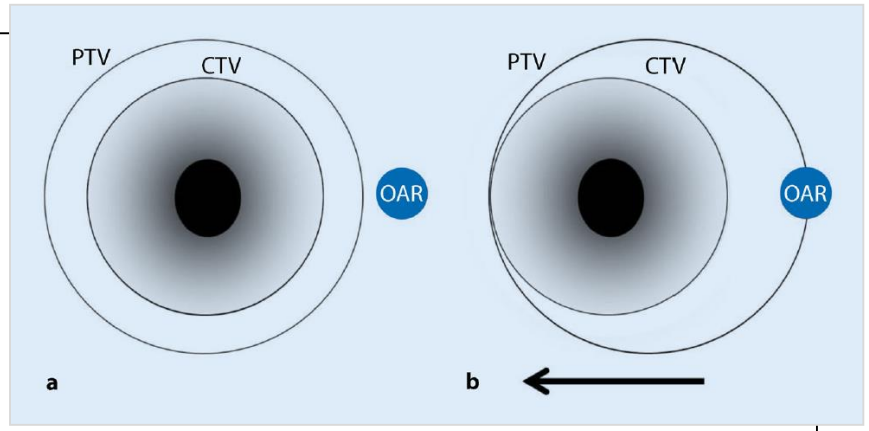
- OAR clear of PTV
- OAR safe …

Target volumes – OARs + PRVs



- OAR moves with CTV
- OAR not so safe …

Target volumes – OARs + PRVs



PTV

CTV

OAR

- OAR moves with CTV
- OAR not so safe …

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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

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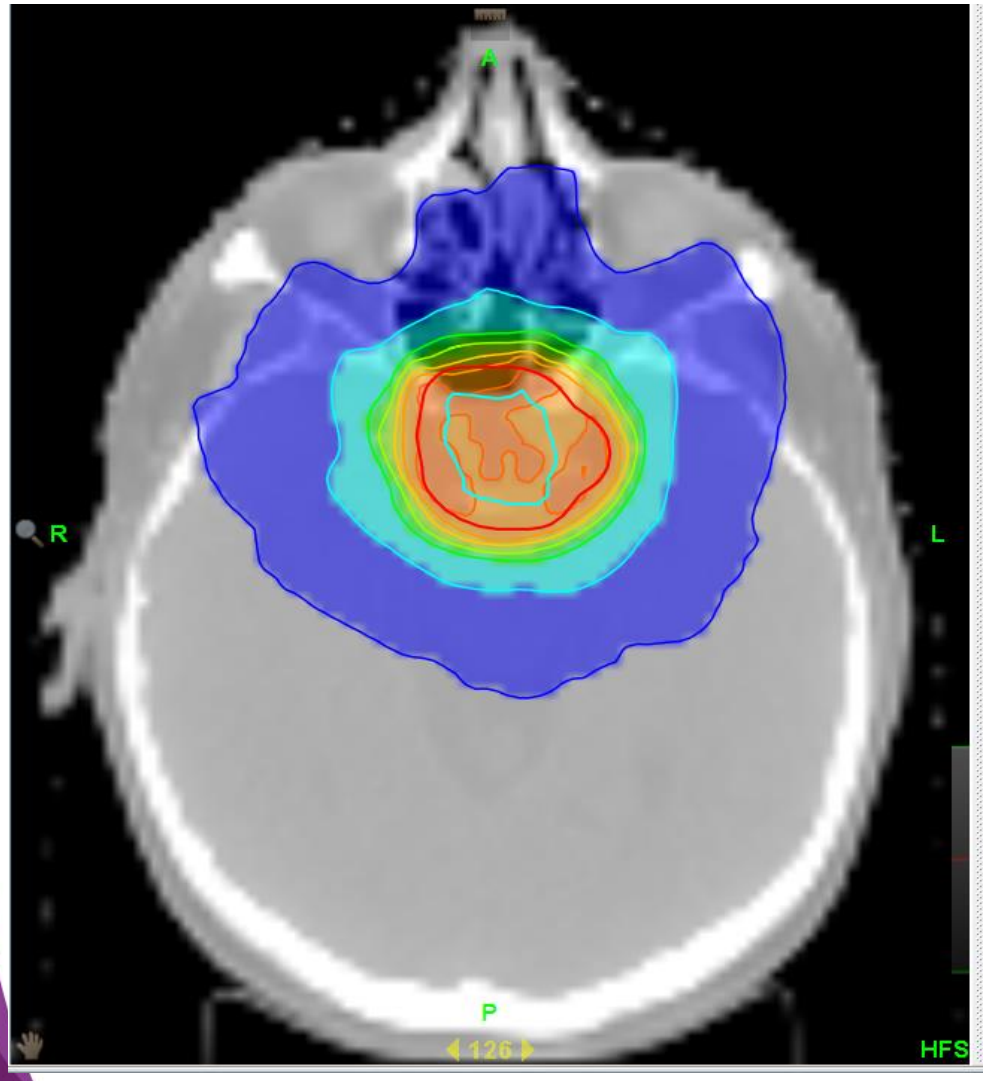
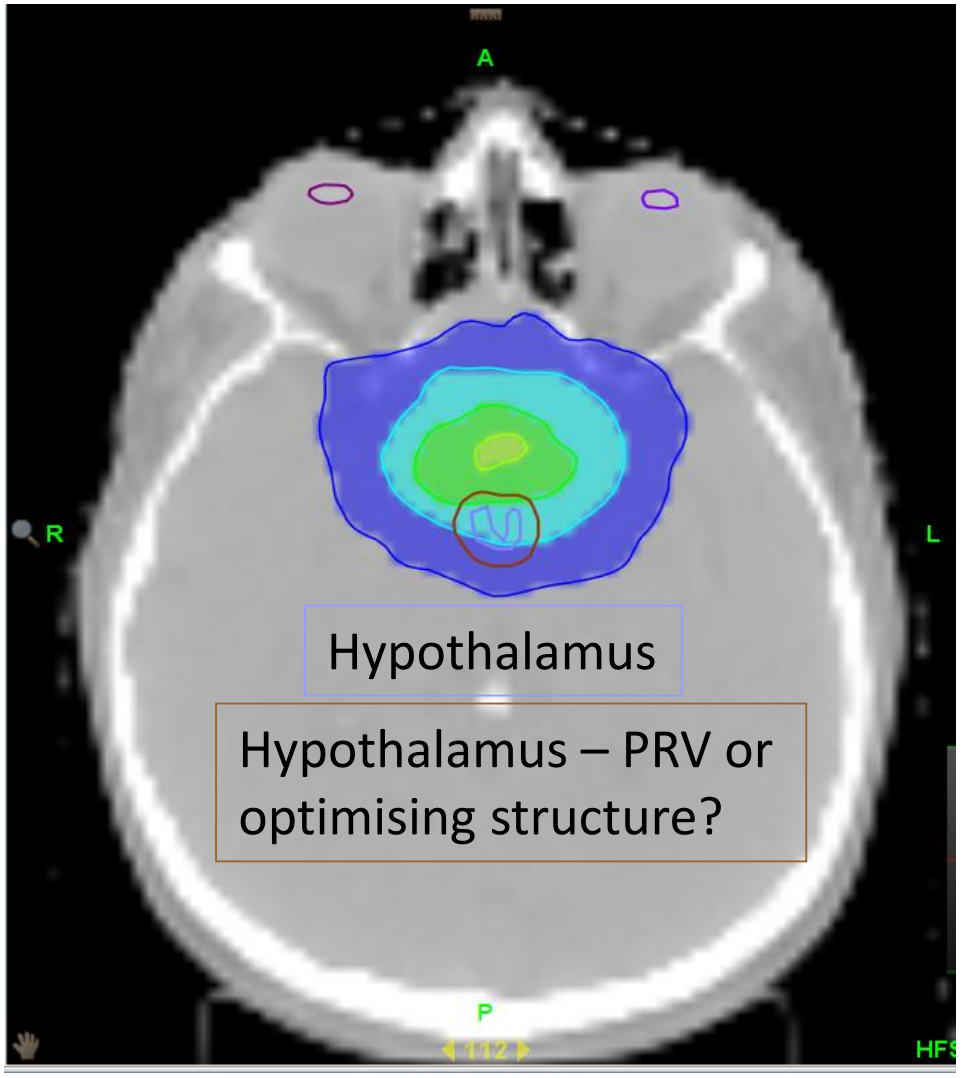
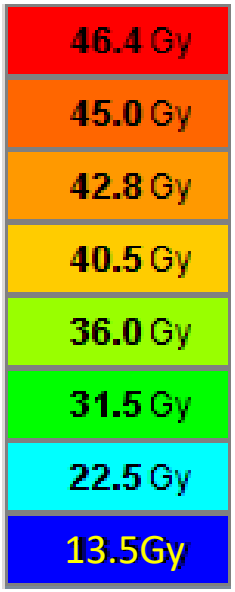
Target volumes – PRV or optimising structure?

Hypothalamus DVHs







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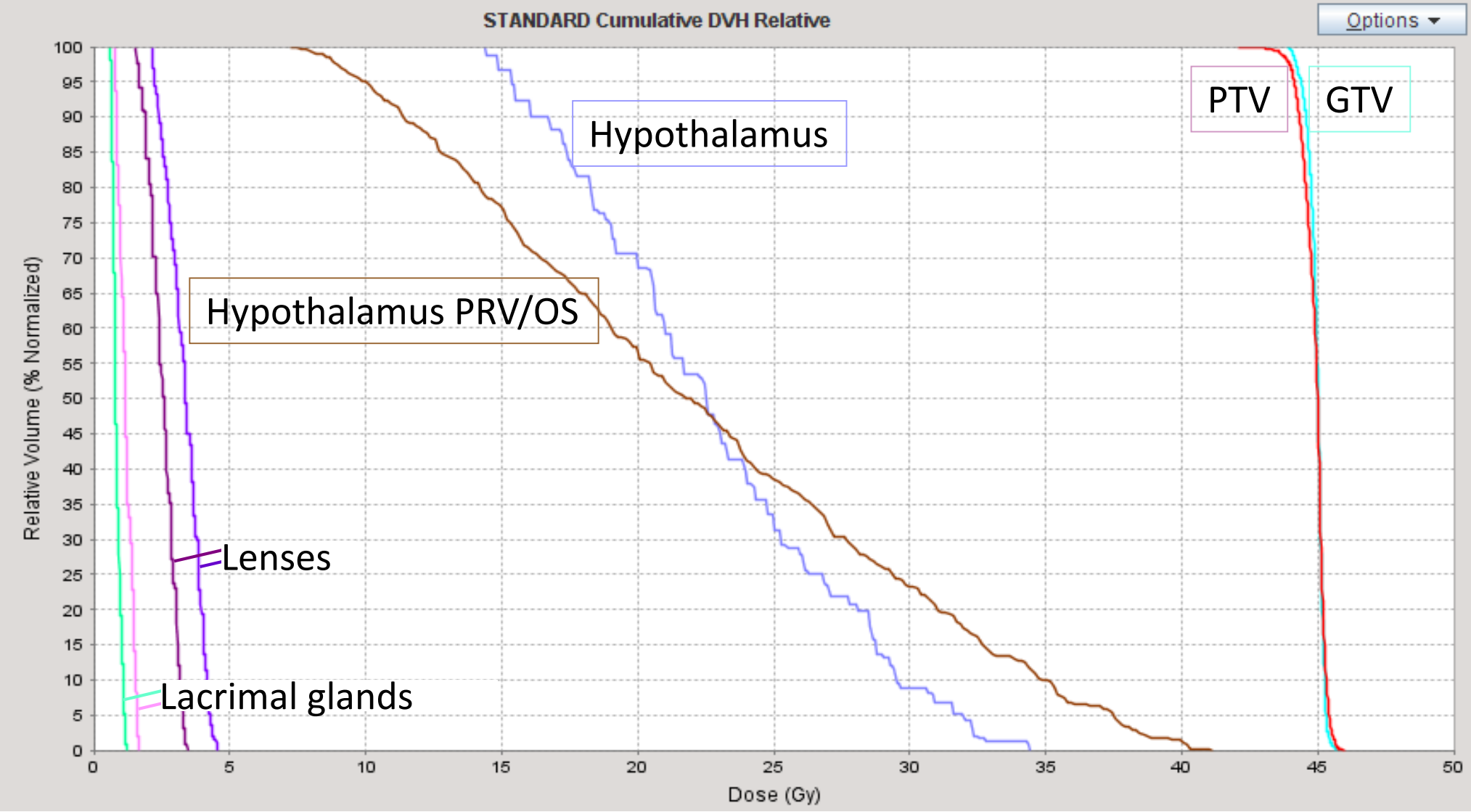
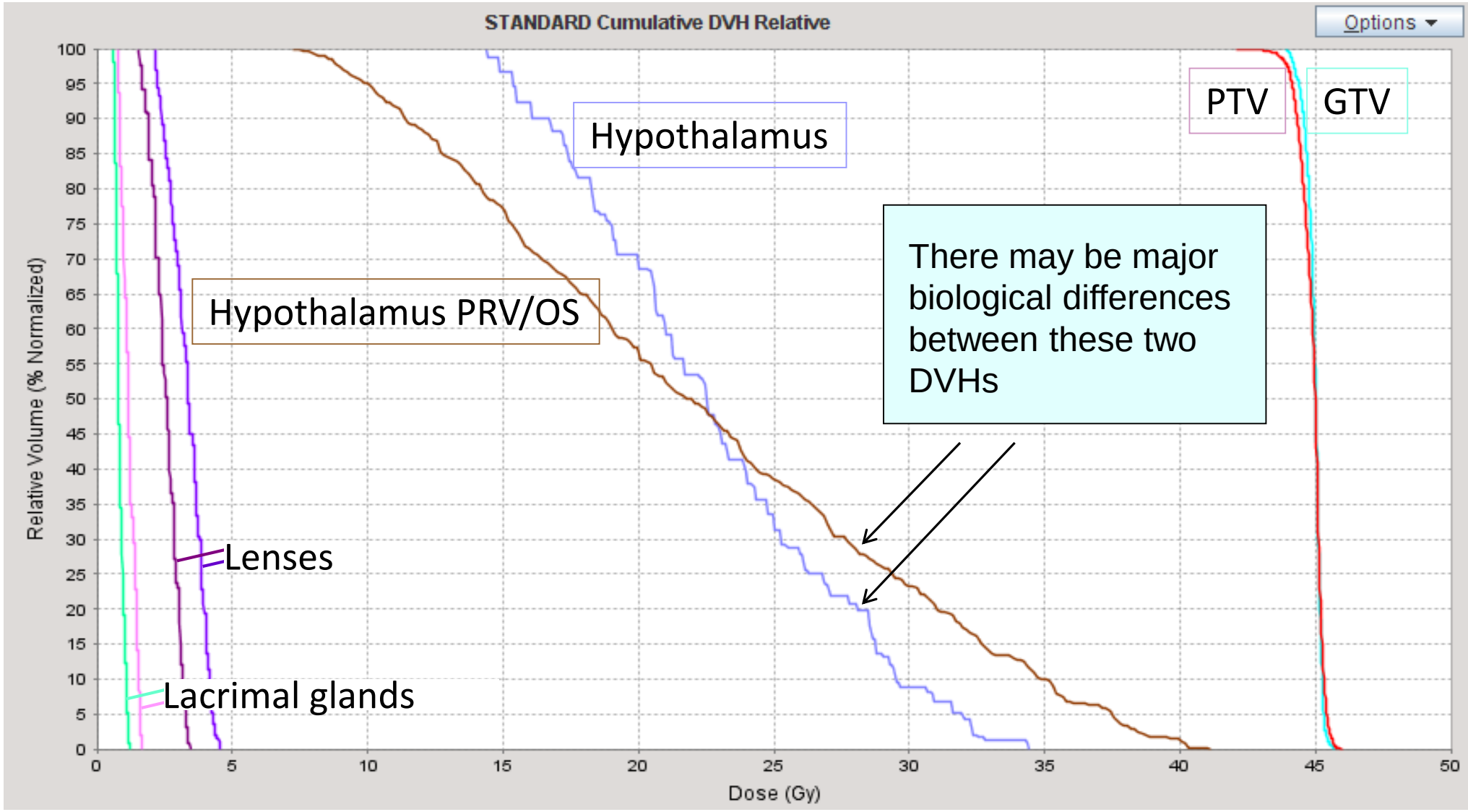
Hypothalamus DVHs



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 fails 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

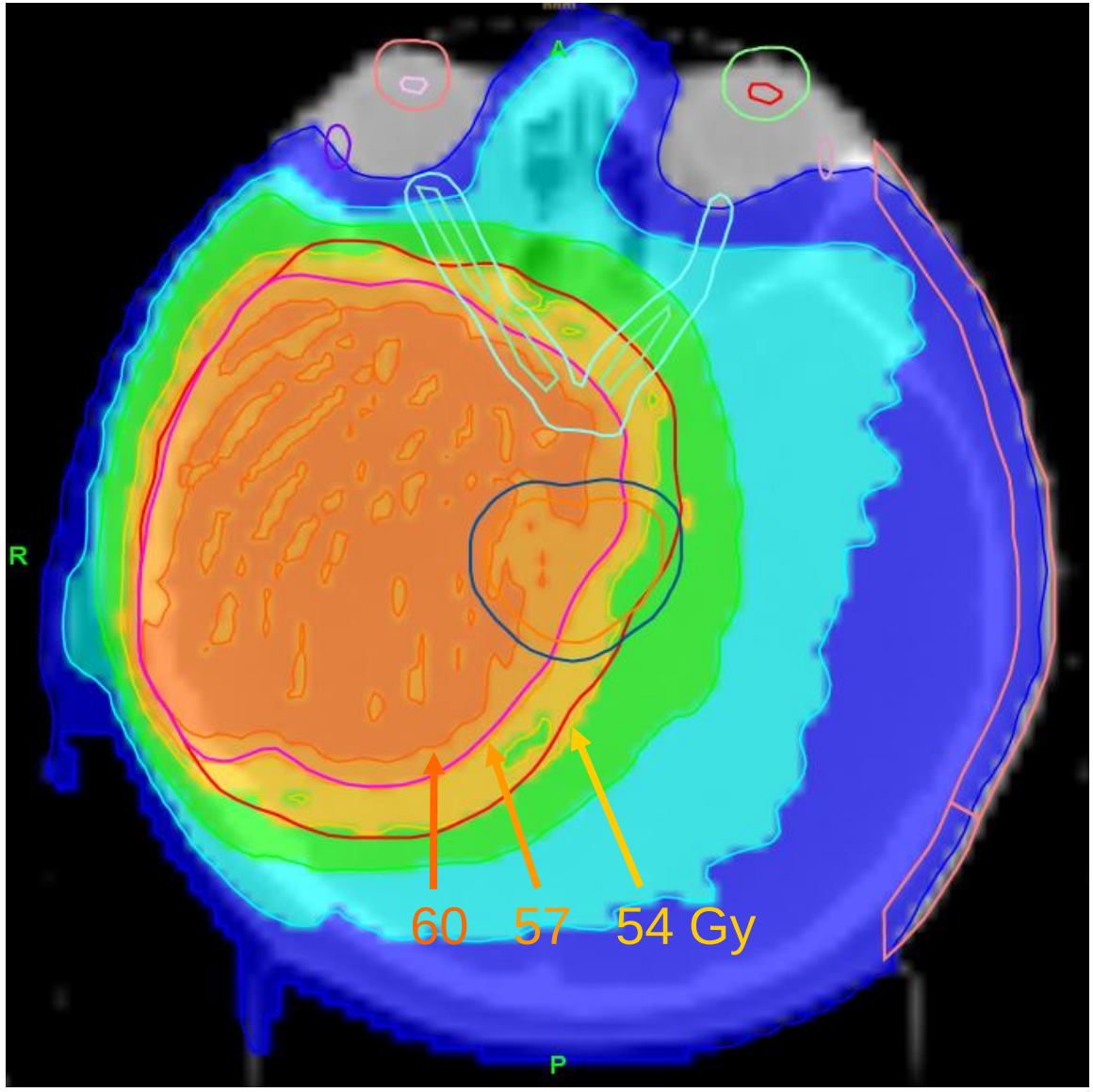
SP		ProSoma Comment	

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

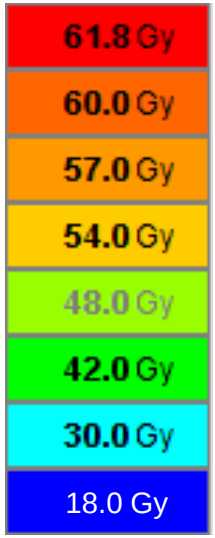
Use?	Organ	Objective (Gy)	Absolute (Gy)
☐	PRV Spinal Cord	48	50
☐	PRV Brainstem	50	52
☐	PRV –Optic Chiasm	50	54
☐	PRV Lt Optic Nerve	50	54
☐	PRV Rt Optic Nerve	50	54
☐	Hippocampus / Eloquent cortex (1cc)		
☐	Pituitary		
☐	Lt Globe	40	45
☐	Rt Globe	40	45
☐	Lt Lens	6	
☐	Rt Lens	6	
☐	Lt Cornea	30	
☐	Rt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



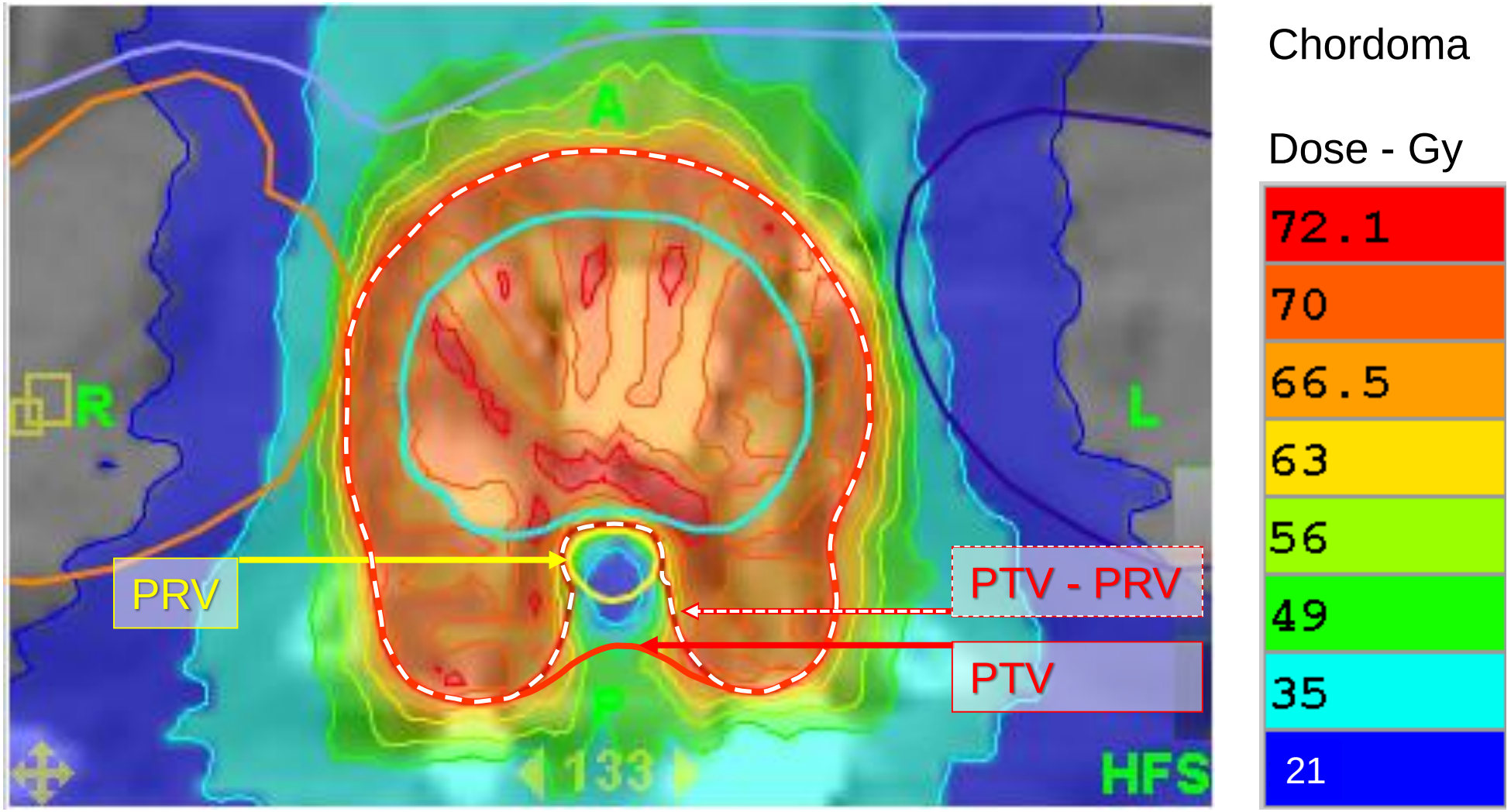
Glioblastoma

Dose - Gy



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

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

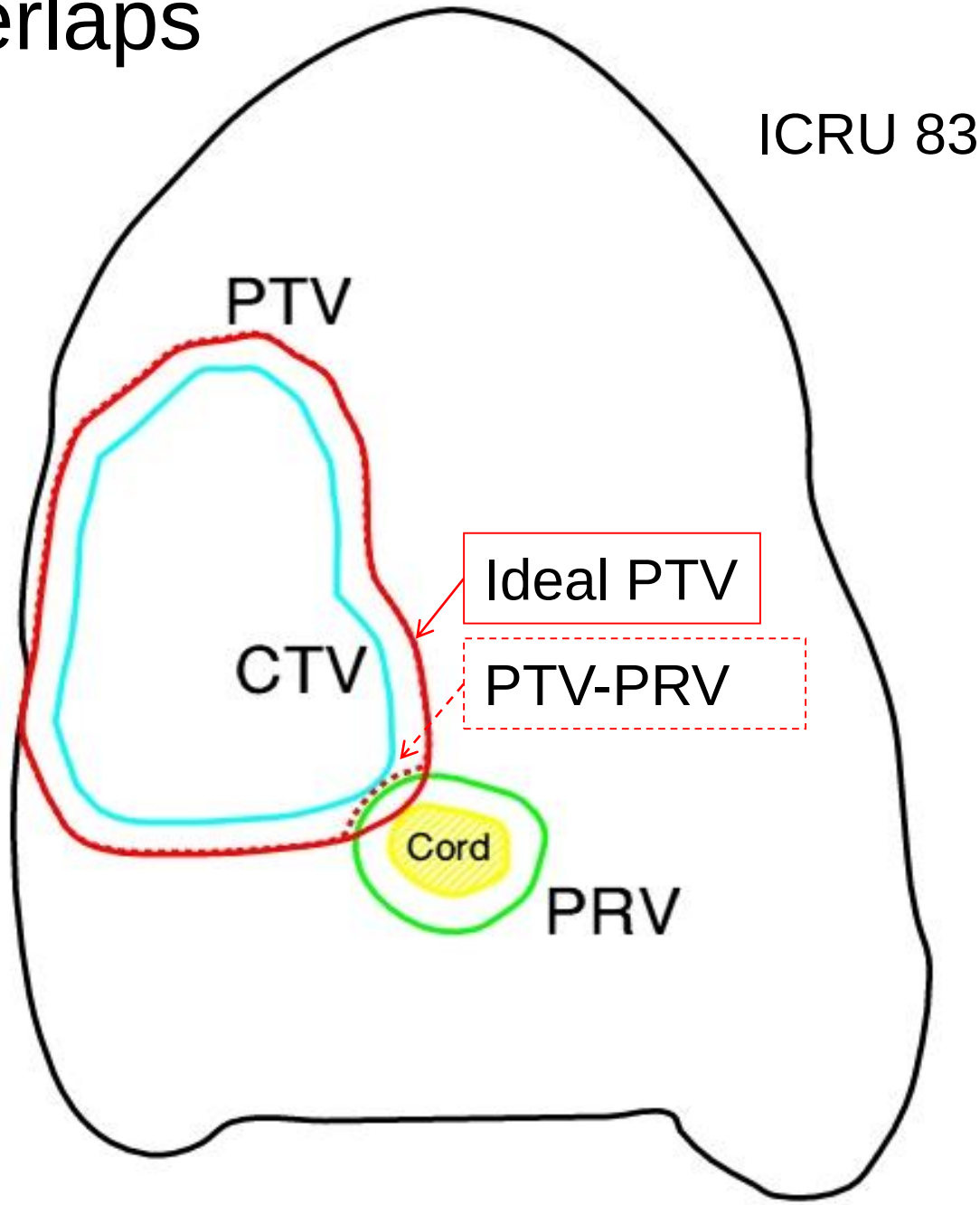
- There are always occasions when the PTV and OARs/PRVs overlap
- What is the best strategy?

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

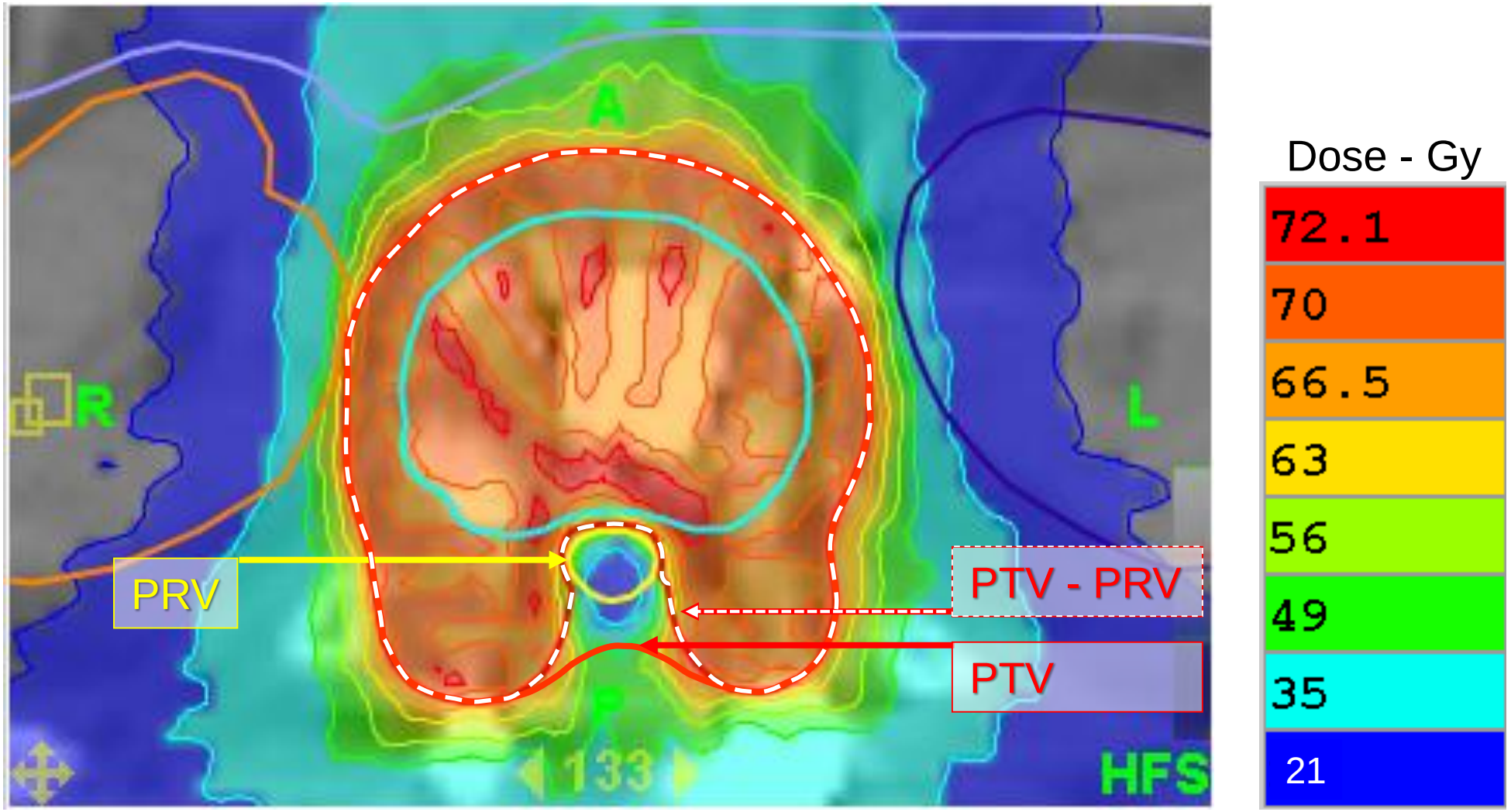
- ICRU 62 – edit PTV (even CTV) – fine for CRT
- ICRU 83 – ***do not*** edit – better for IMRT

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 !

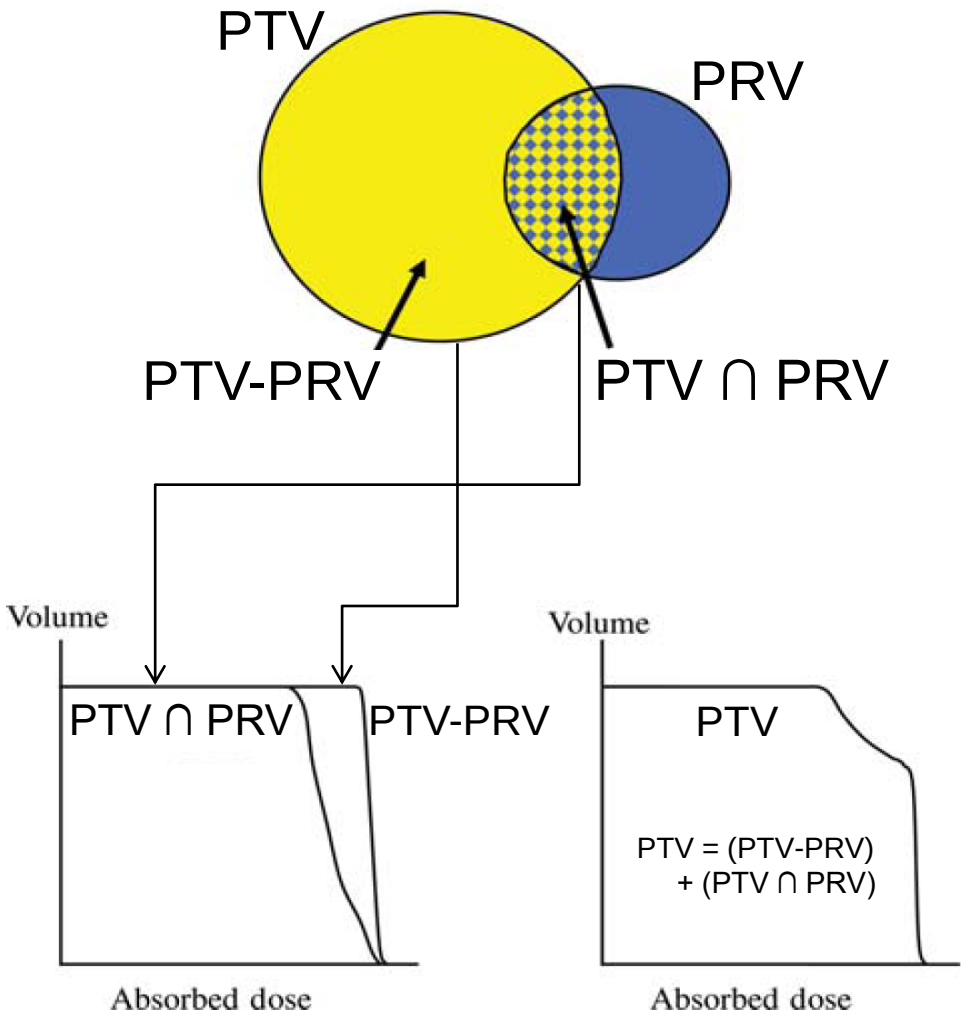
  - Use the optimiser to deliver different doses to different parts of the target

  - 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



Take home messages

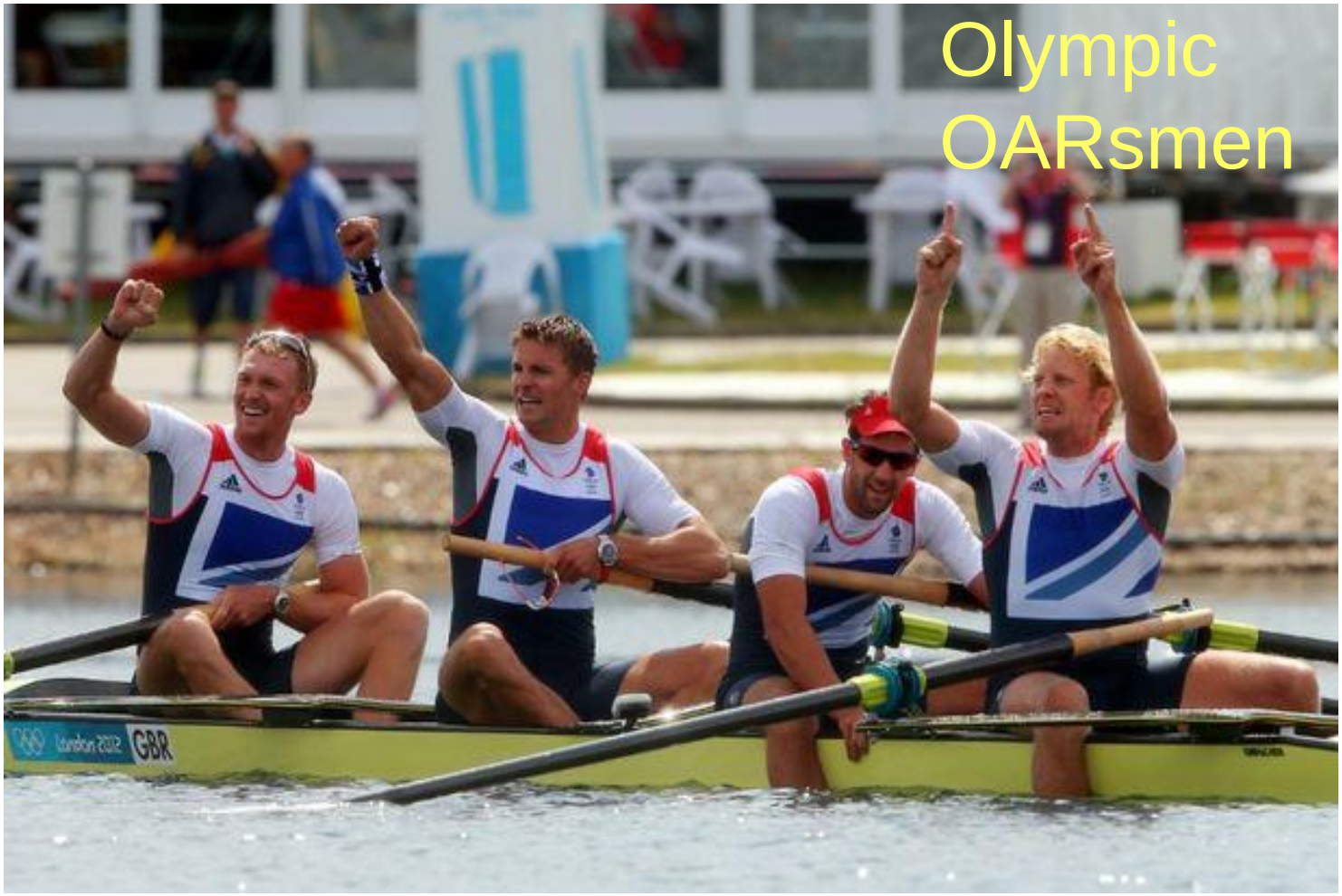
- Median dose closest to ‘old’ ICRU isocentre prescription point

- Use GTV/CTV/PTV volumes carefully
- Contour OARs carefully, with protocol & add PRV if appropriate

- Define
  - Planning objectives and constraints - carefully & interactively
  - Prioritisation

- Overlaps can occur between PTV and OAR (or PRV)
  - Do not edit
  - Construct additional exclusion volumes
  - Use IMRT

Radiation oncology - a team effort



GB men
4-
2016

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Additional resources

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

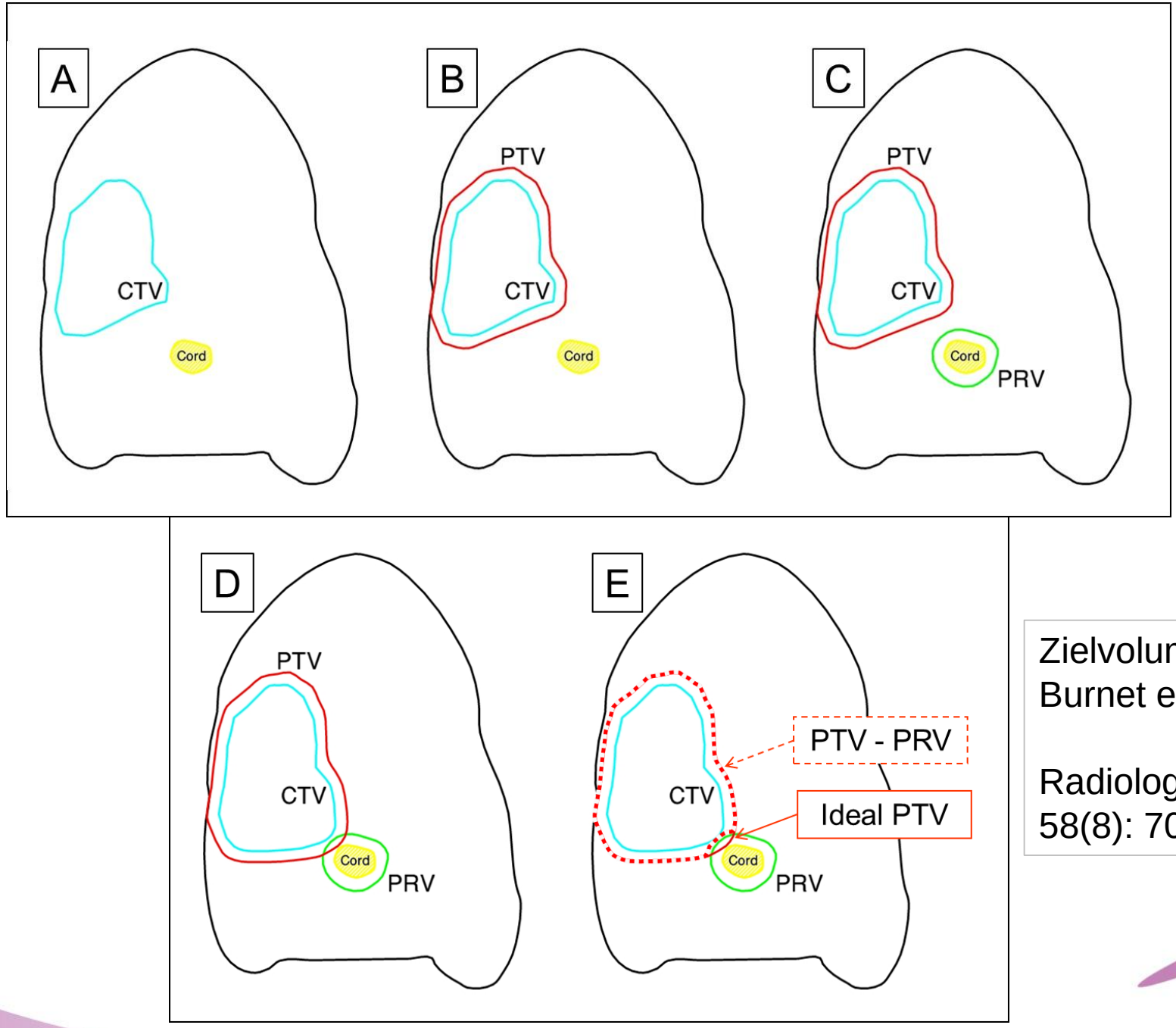
- **Remaining Volume at Risk – RVR**

- 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 - overlaps



Zielvolumenkonzepte Burnet et al.

Radiologe. 2018; 58(8): 708-721

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ICRU guidance

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

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

Homogeneity Index

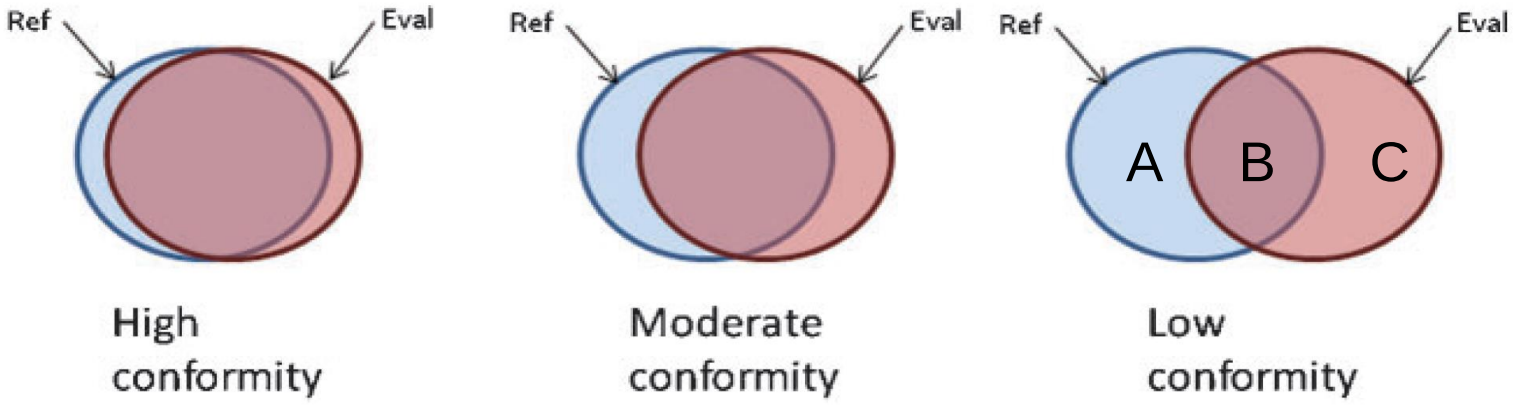
- Designed to show level of homogeneity

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

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

Conformity Index

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



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

Equivalent Uniform Dose - EUD

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

- Useful and worth understanding

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

Equivalent Uniform Dose - EUD

- Depends on 'knowing' the value of the exponent 'a'

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

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

Equivalent Uniform Dose - EUD

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

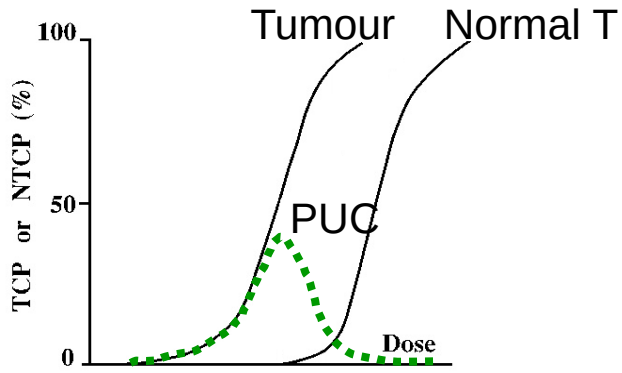
- For normal tissues ‘a’ is positive
  - Parallel - near 1
  - Serial – larger e.g. up to 20 for spinal cord

  - ‘a’ = 1/n in the LKB formulation

TCP, NTCP, PUC

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

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



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Non-IMRT planning
from simple to complex

Advanced Treatment Planning Course
23-27 September 2018 – Athens, Greece

Markus Stock

MedAustron

ESTRO School

Content

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

- advanced treatment planning – how to do it?

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Basics and general planning aspects

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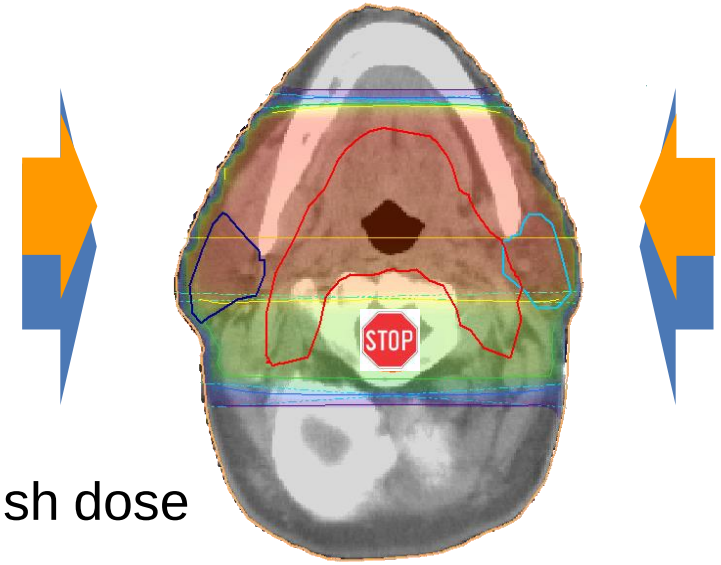
Limitations of 3DCRT



- 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*

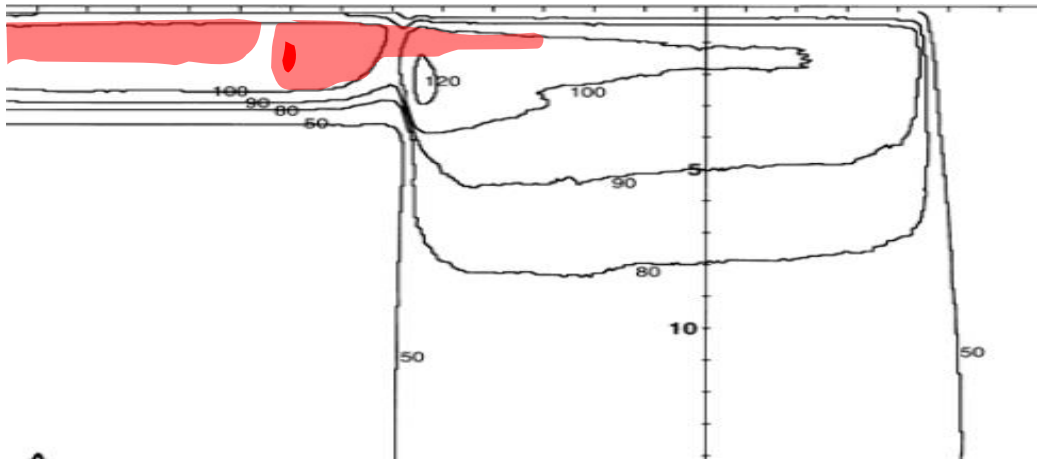
Courtesy Marika Enmark

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

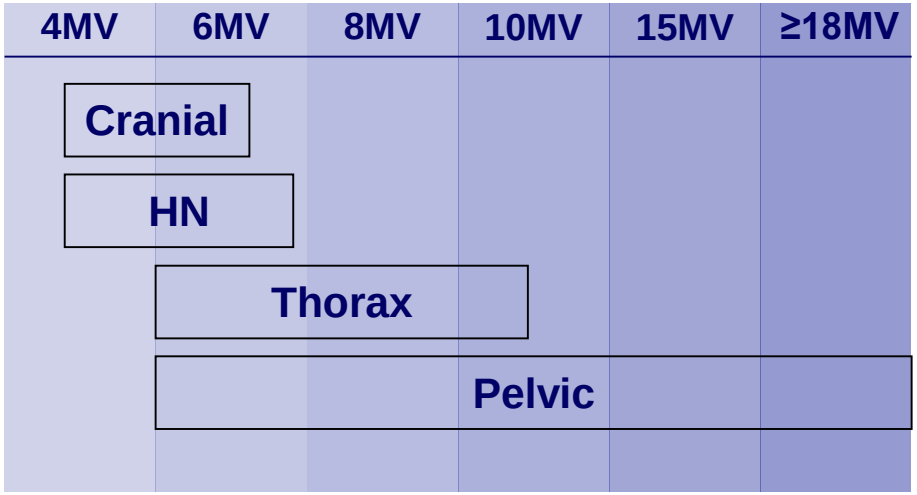
electron **photon**



Choice of optimal beam energy

Aspects

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



Higher energy in low density regions

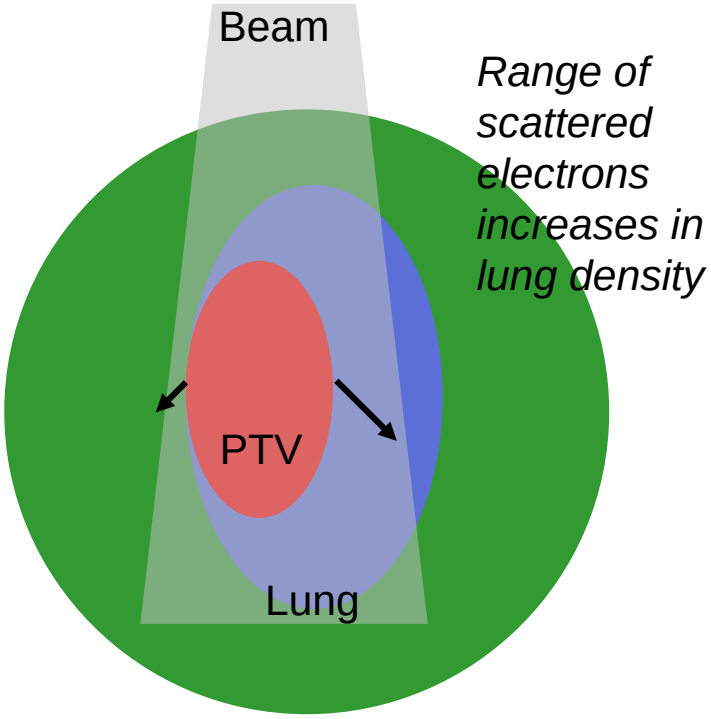
- higher energies means larger penumbra due to increase in lateral electron transport (≥10MV)
- sufficiently accurate planning calculation algorithms are required for decisions on optimal beam energy

Choice of optimal beam energy in the thorax region

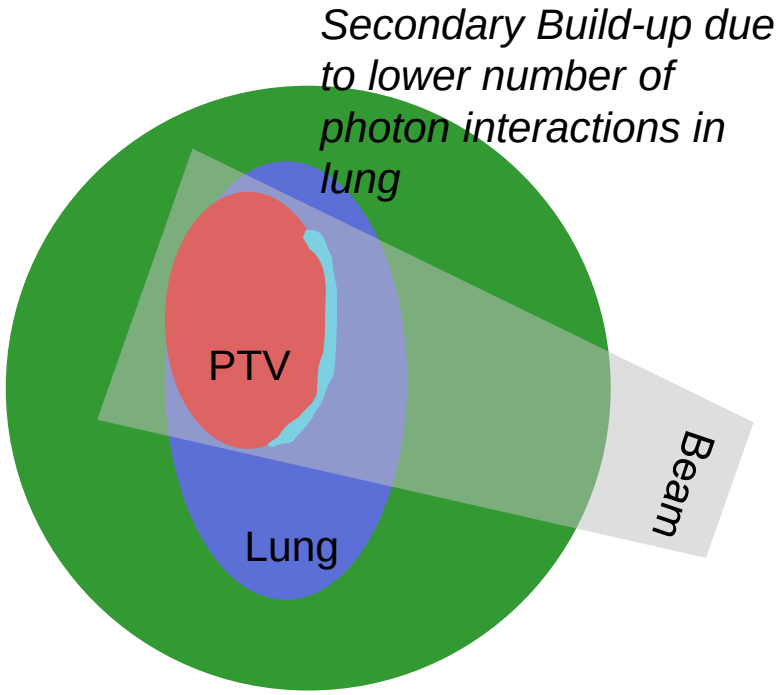
- Low energy beam is preferable
  - tighter margins, sharp dose gradient
  - no significant difference between 6 and 18MV treatment plan (# beams!)
- High energy may be used
  - central tumor location or consolidated lung

Interface effects

- Broadening penumbra in low density area



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



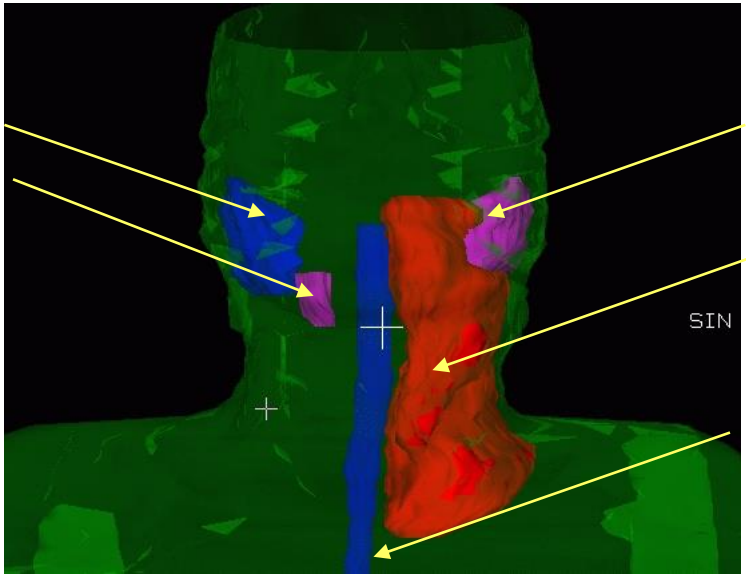
Head & Neck 3D

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



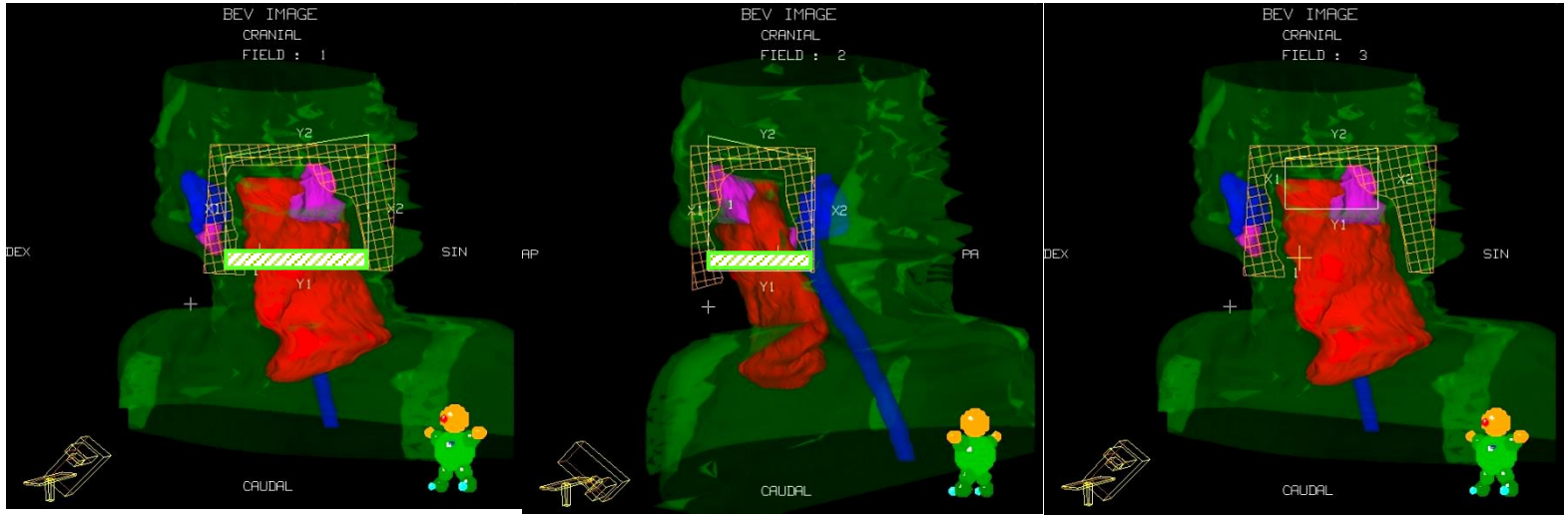
left parotid gland

PTV 0-46 Gy

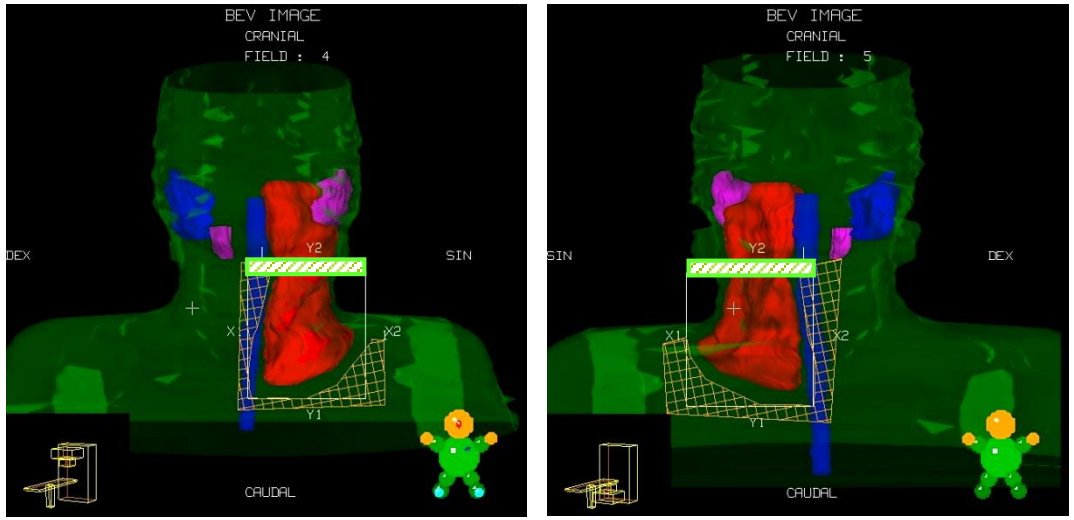
spinal cord

‘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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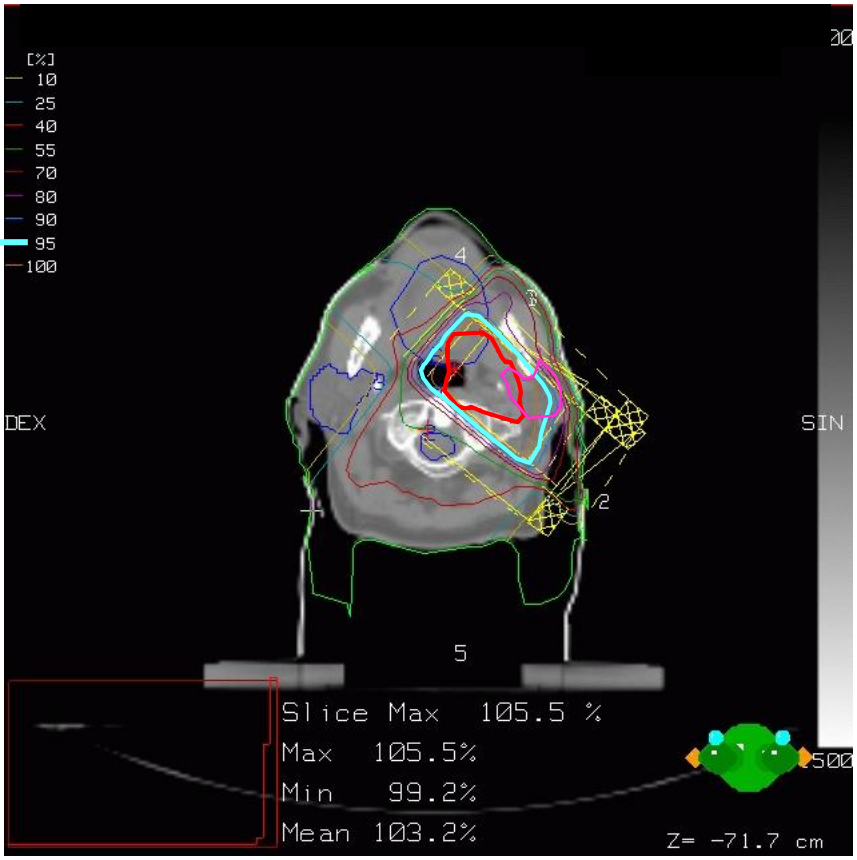
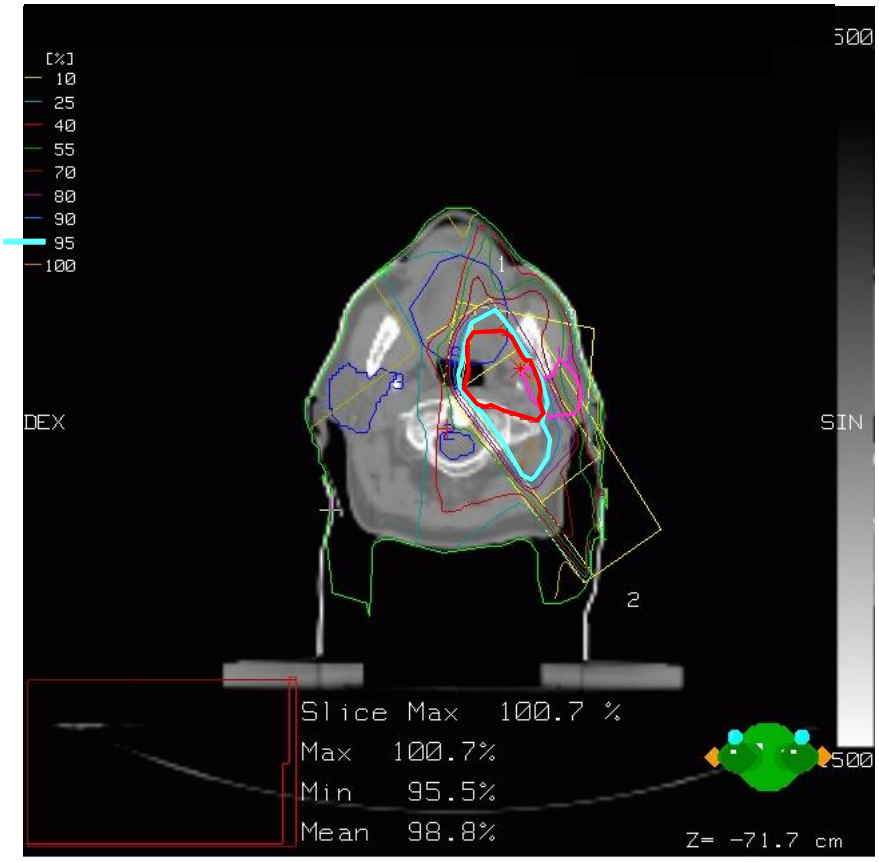
Head and neck: Tonsillar fossa Ca.

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.

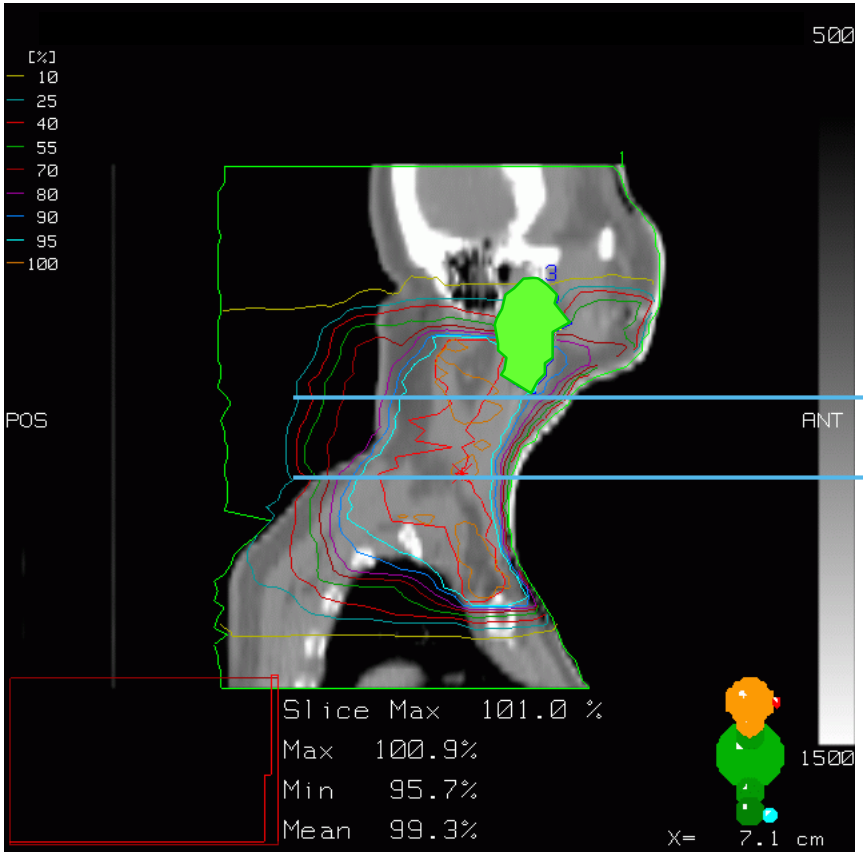
do we <u>really</u> need IMRT for this case?

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

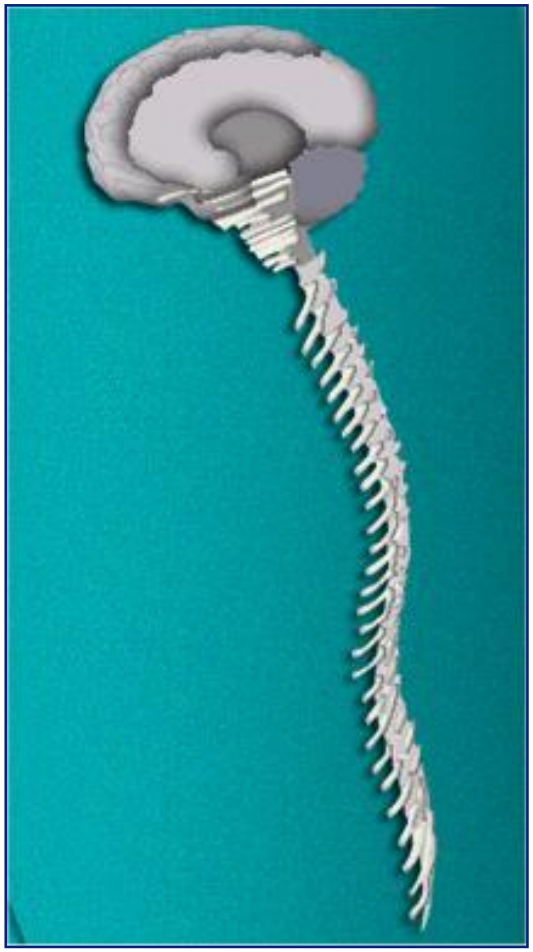
mean dose parotid 27 Gy

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

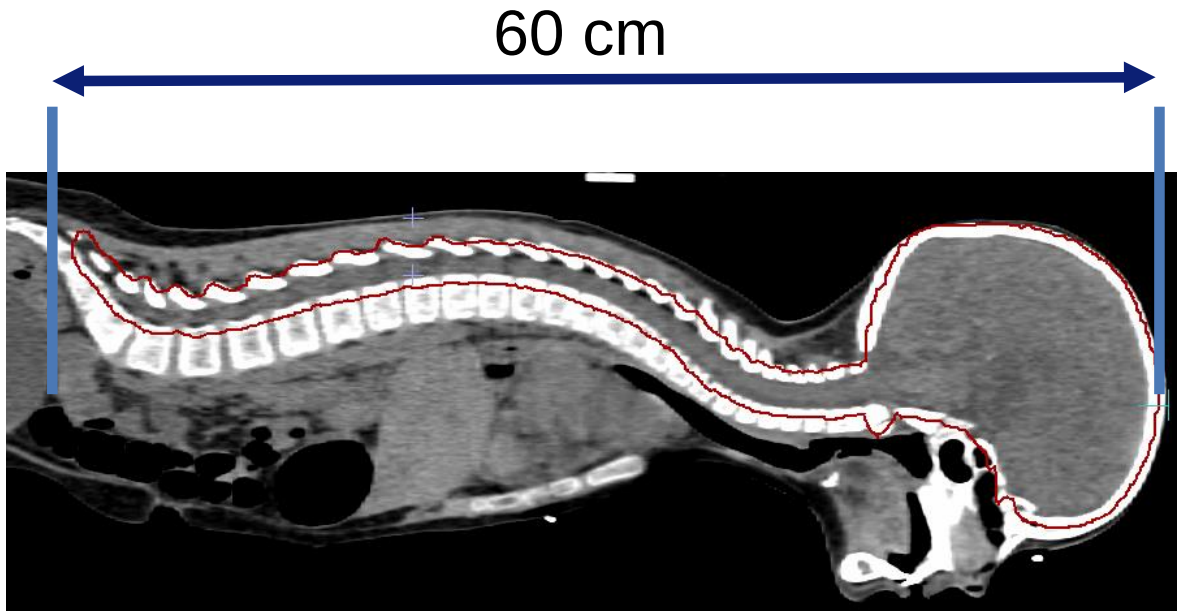
Cranio-spinal lesions

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

Cranio-spinal lesions

Challenges:

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



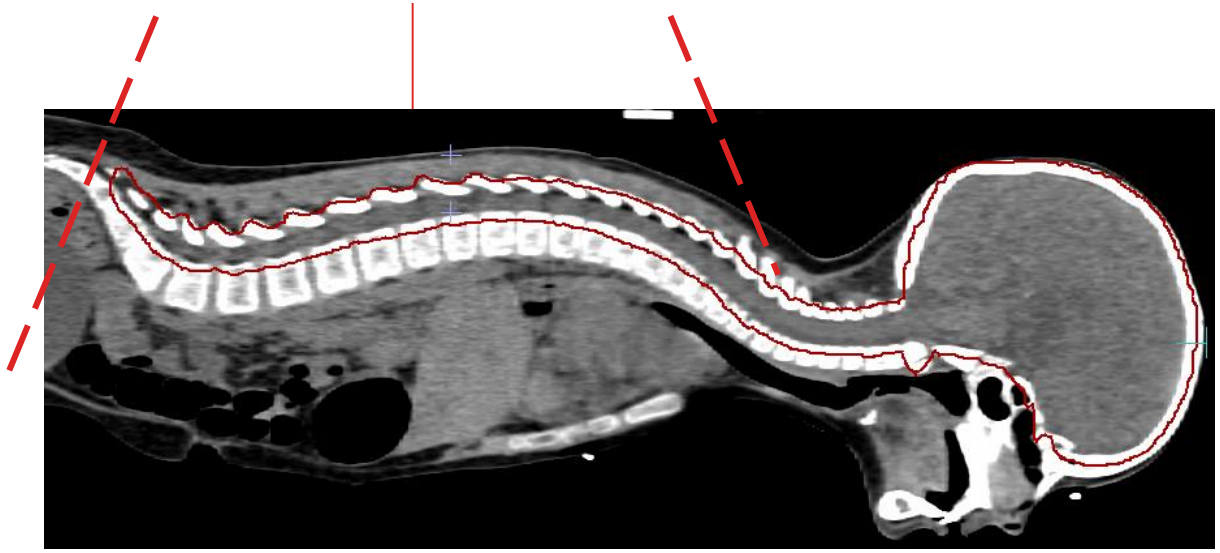
Cranio-spinal lesions

Challenges spinal field:

maximum field size:

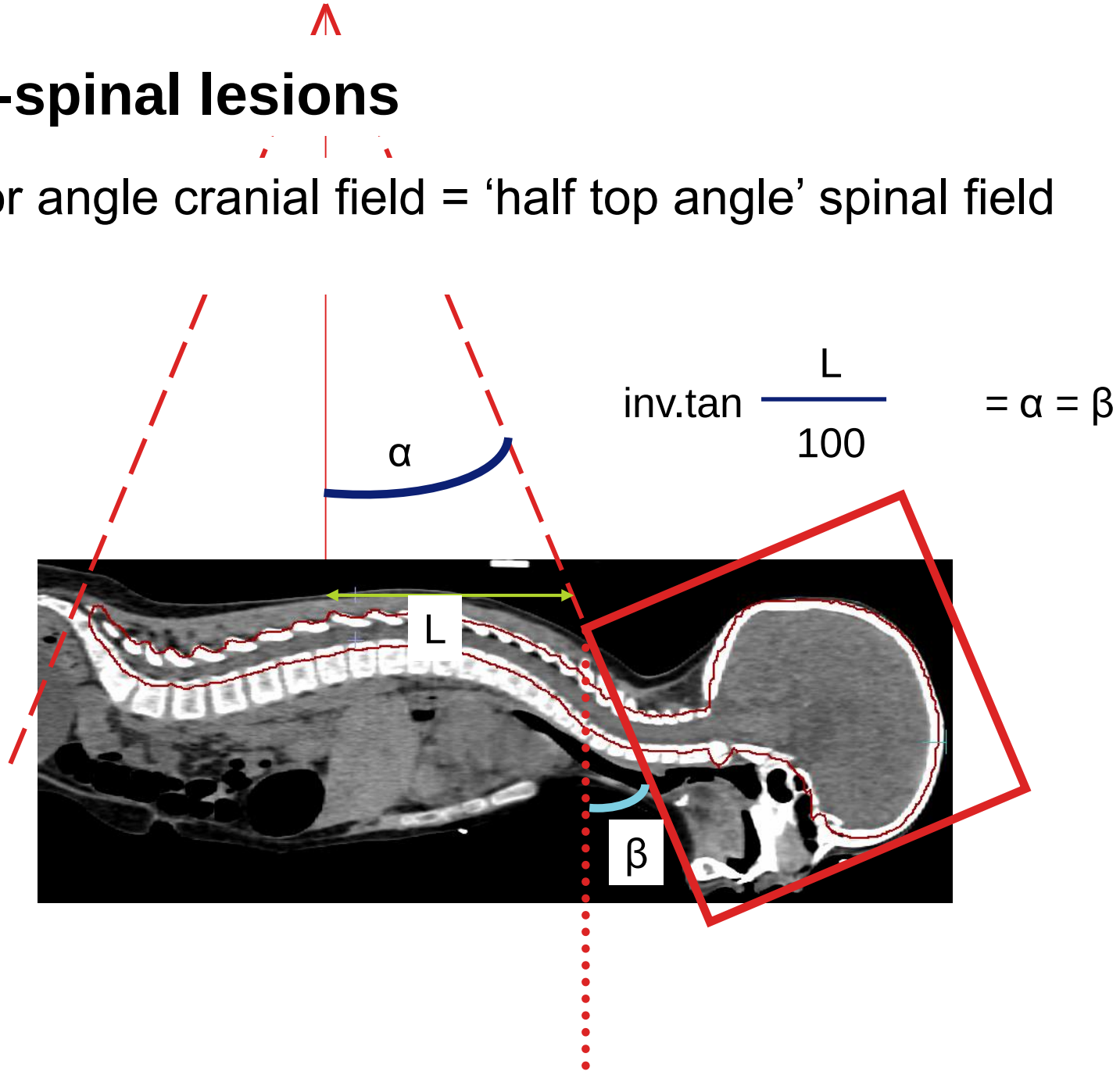
40 cm at focus isocenter distance 100 cm

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



Cranio-spinal lesions

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

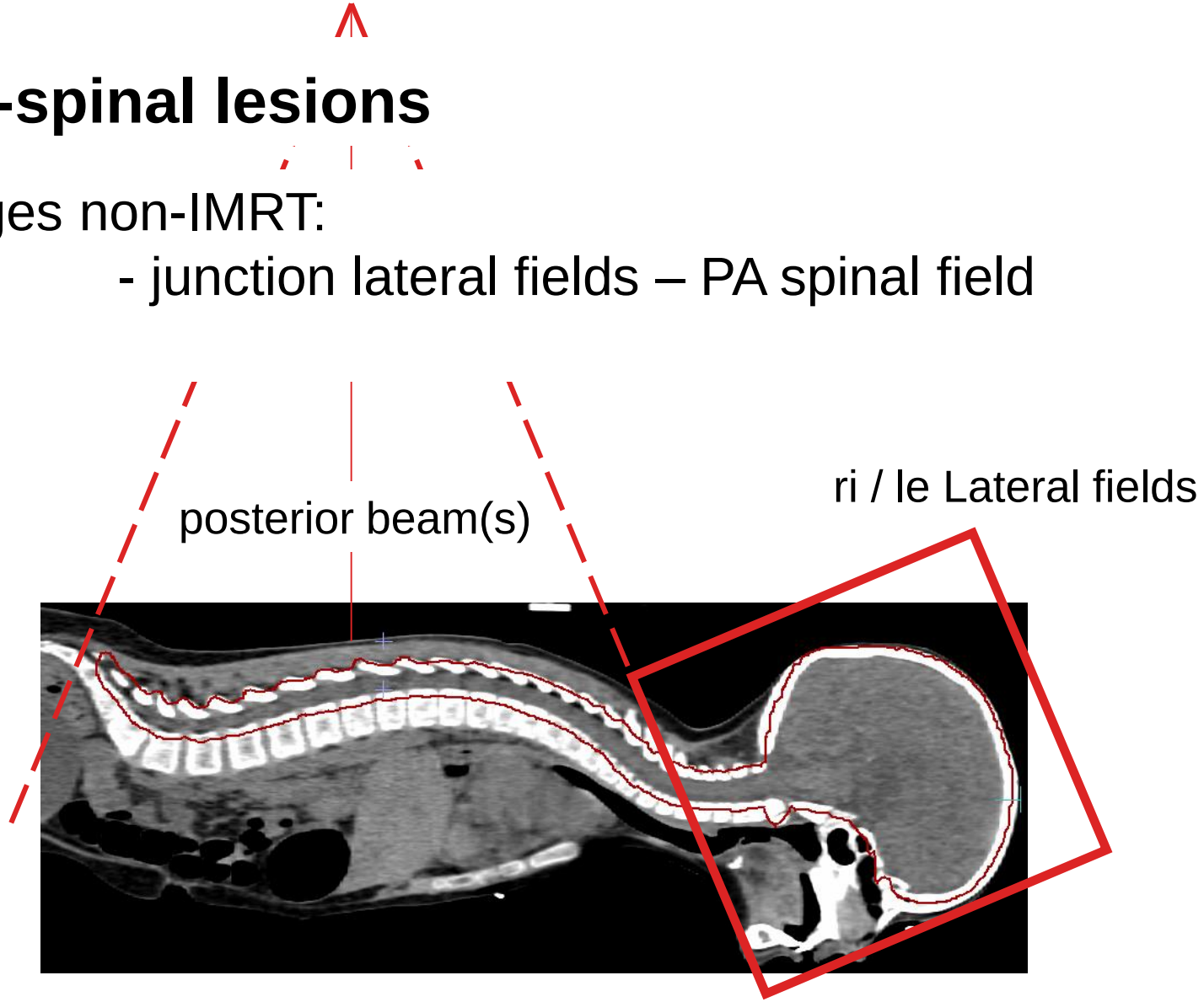


$$\text{inv.tan}\ \frac{L}{100} = \alpha = \beta$$

Cranio-spinal lesions

Challenges non-IMRT:

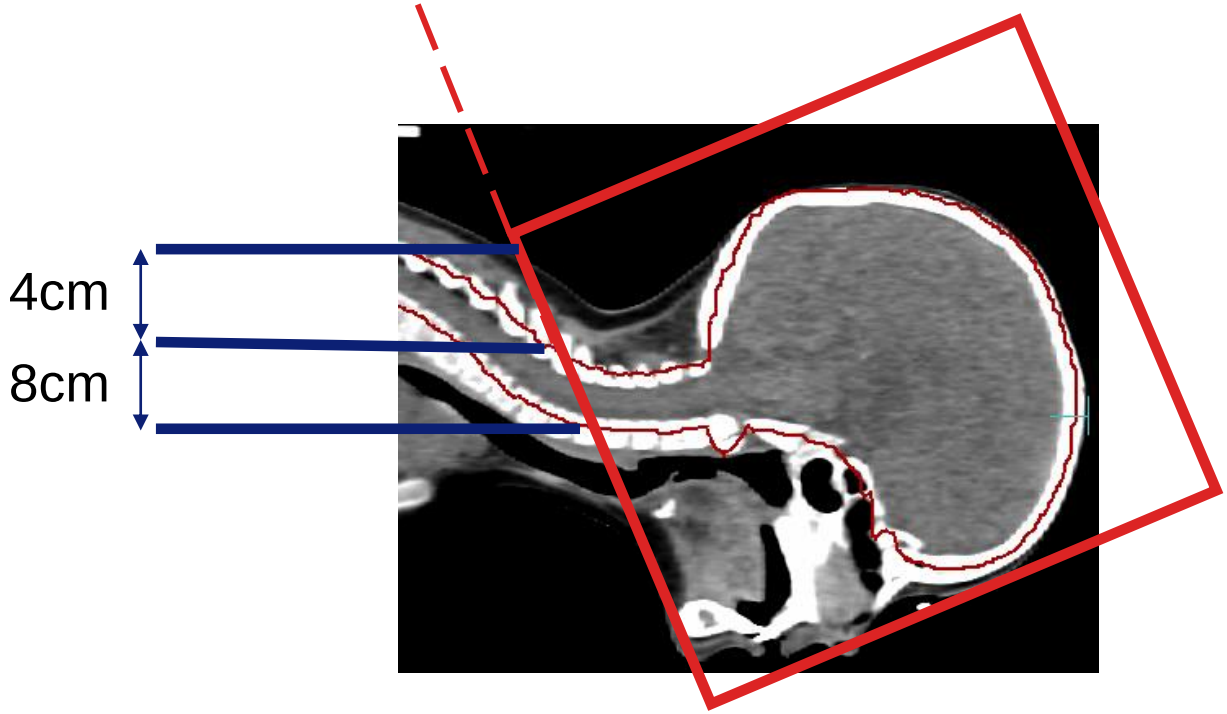
- junction lateral fields – PA spinal field



Cranio-spinal lesions

Challenges non-IMRT:

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



additional sub-fields , multiple energies?

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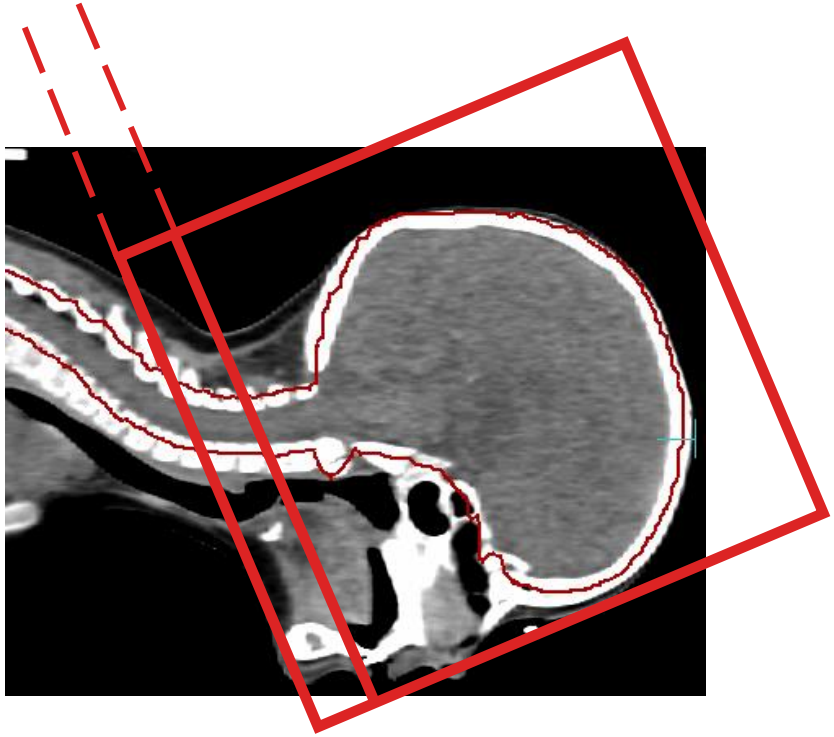
Cranio-spinal lesions: cranial fields

Challenges non-IMRT:

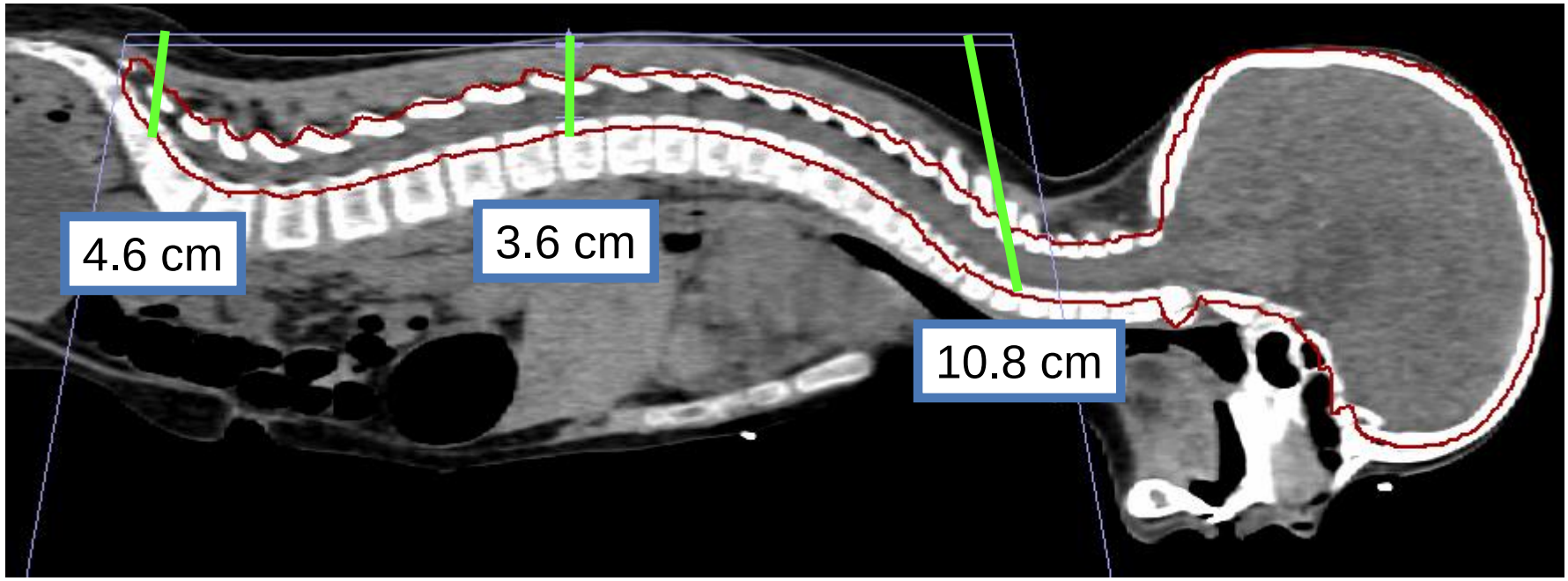
- junction lateral fields – PA spinal field
  better dose-distribution in junction, broader penumbra
  → sliding junction



Cranio-spinal lesions: spinal field

Challenges Non-IMRT:

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

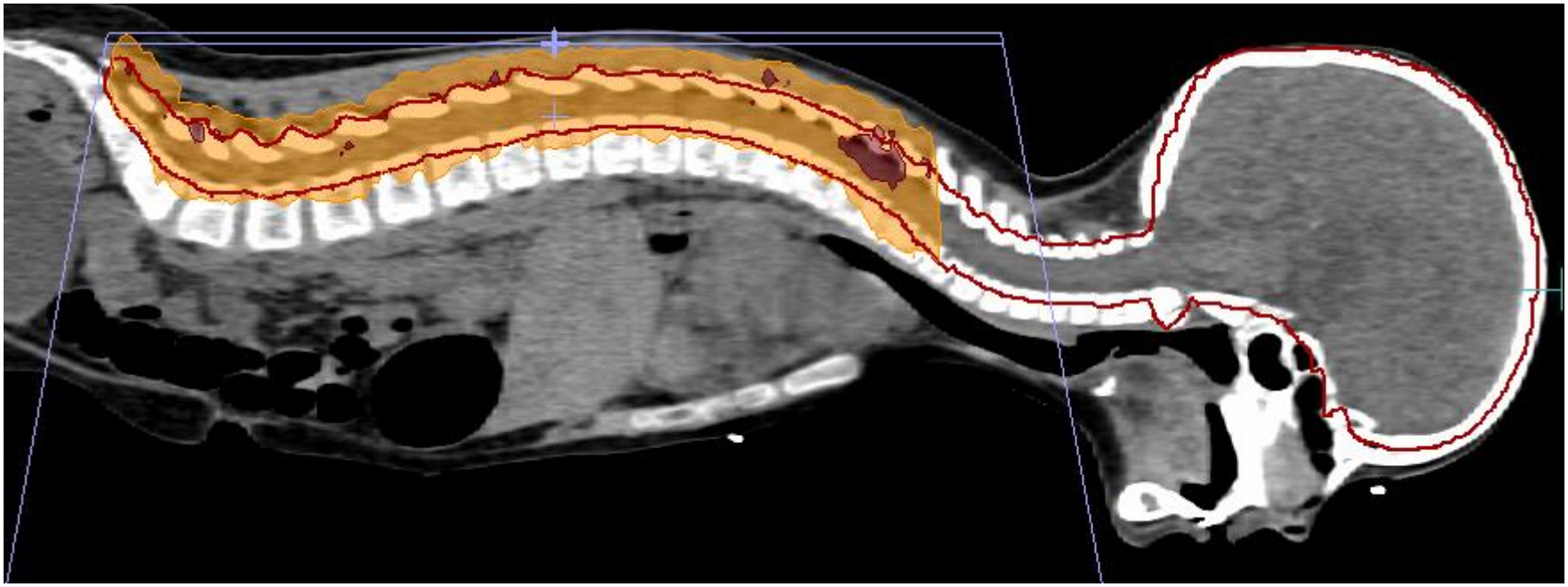


prescribing dose at mean depth, or additional sub-fields needed
multiple energy fields

Cranio-spinal lesions: need for IMRT??

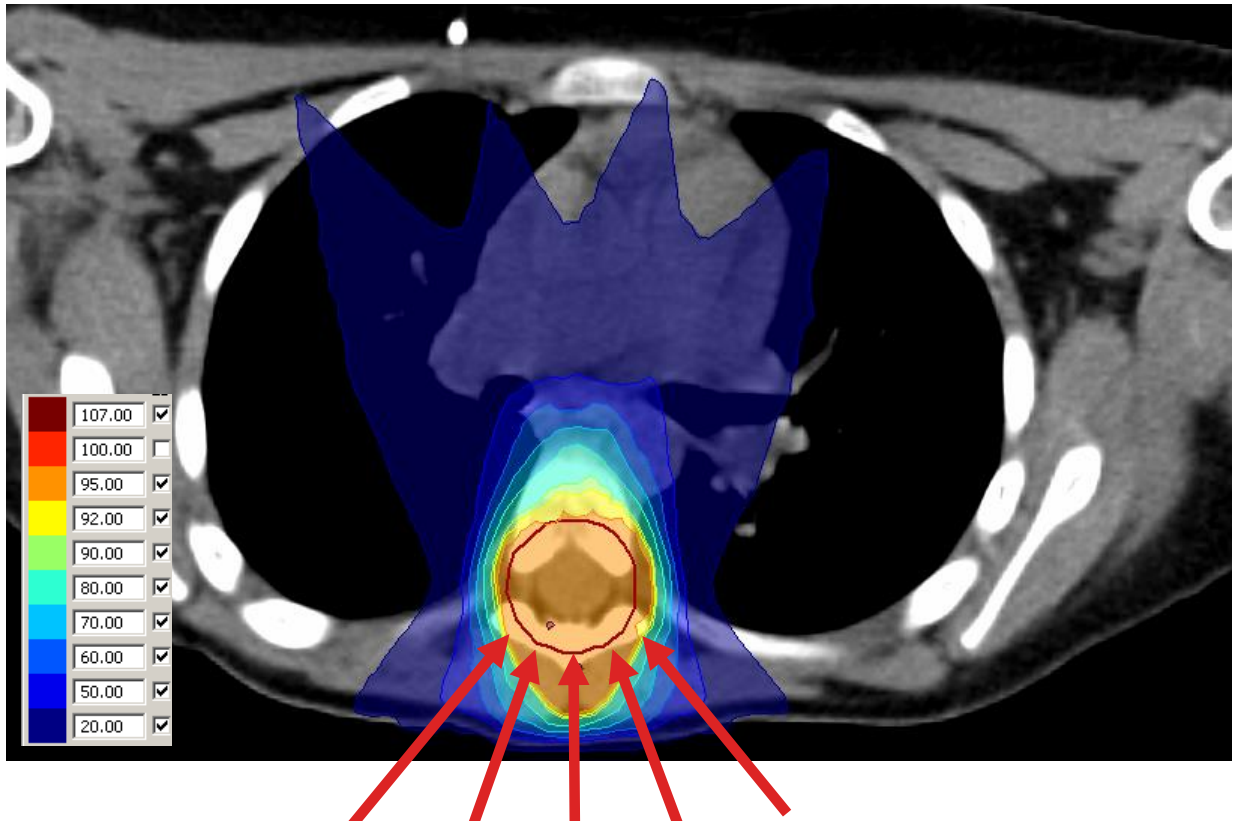
IMRT planning:

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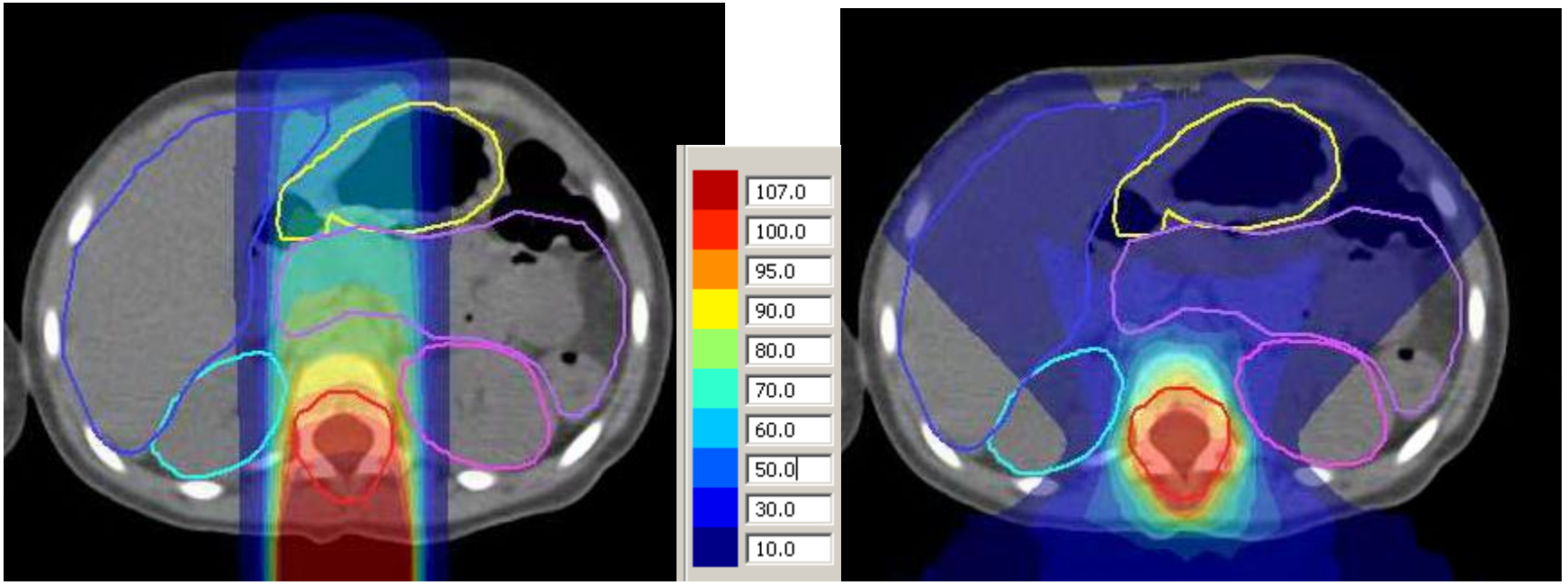
Cranio-spinal lesions: 3D-CRT vs IMRT

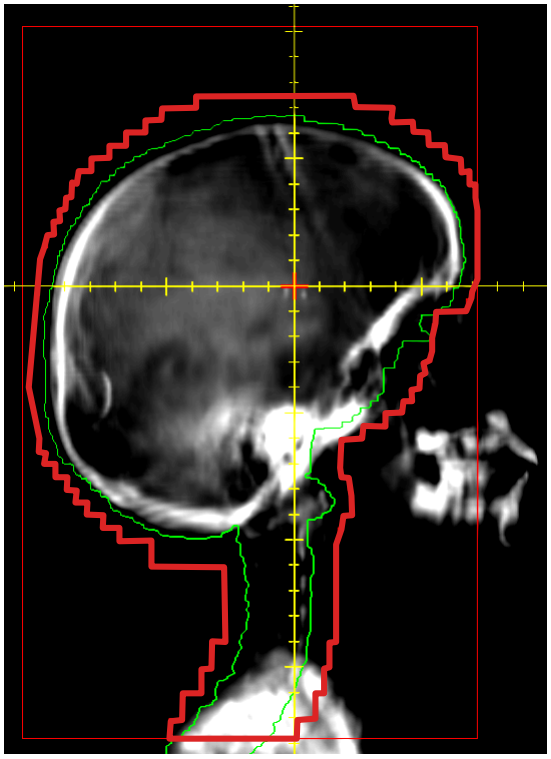
‘simple’ 3D-CRT

5 field IMRT / 3D-CRT

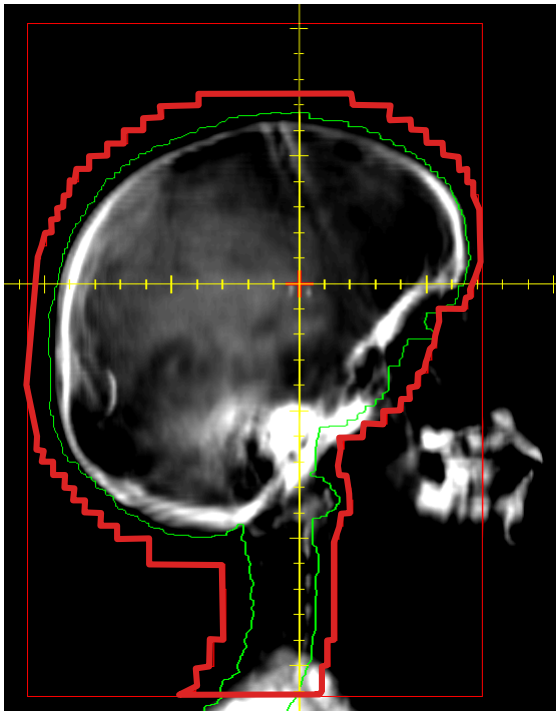


Cranio-spinal lesions: junction with lateral cranial beams

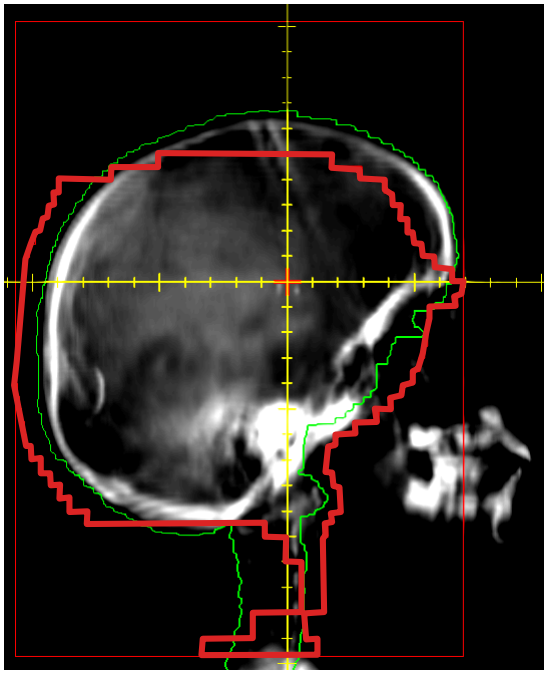
3D-CRT cranial plan with a broad caudal penumbra



ri lat: 1a

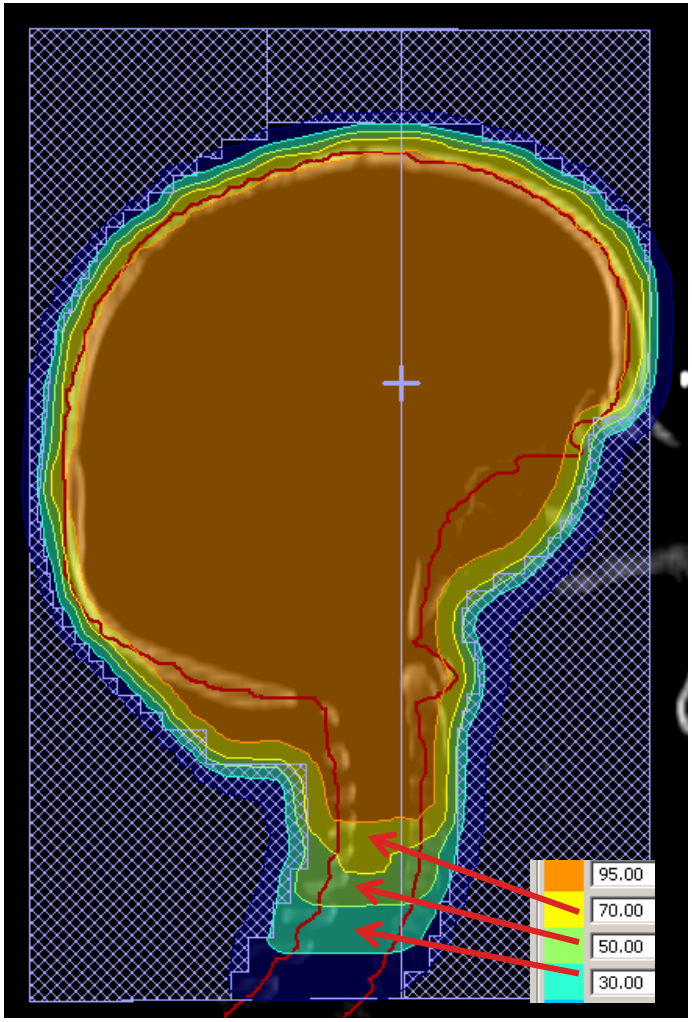


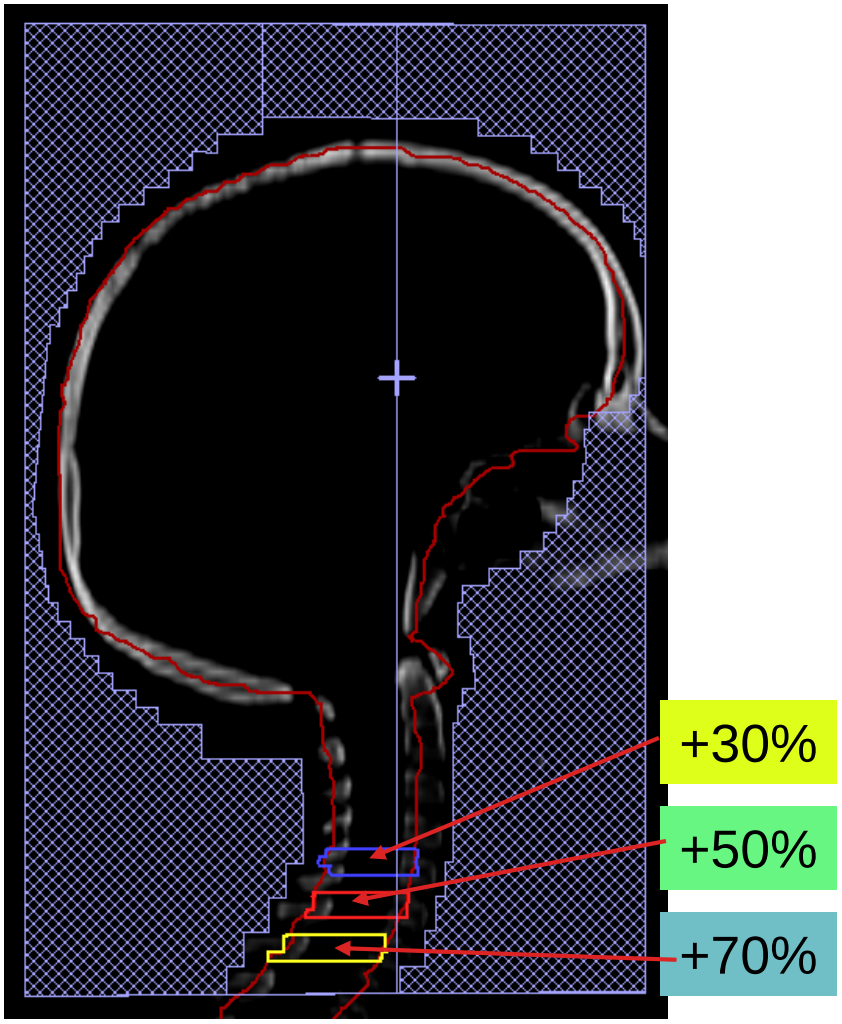
ri lat: 1b



ri lat: 1c

Cranio-spinal lesions: junction with lateral cranial beams





‘dose modulation volumes’

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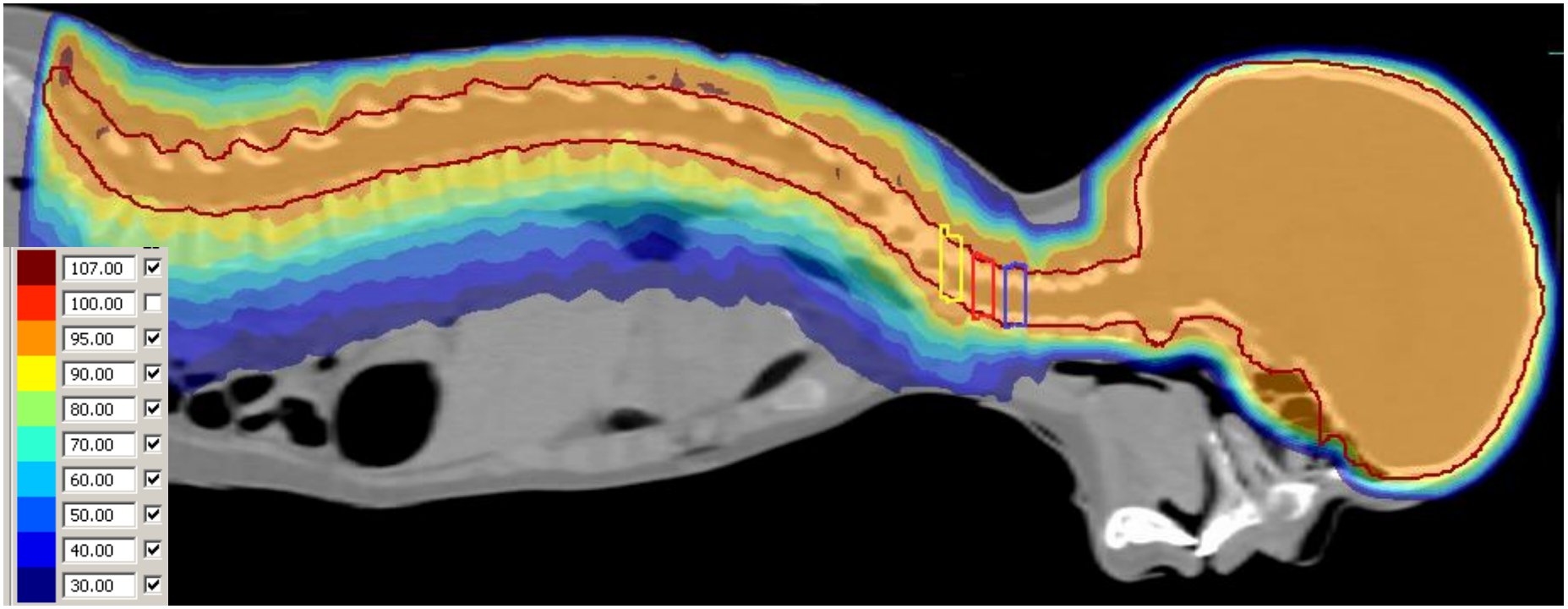
Cranio-spinal lesions: 3D-CRT solution

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



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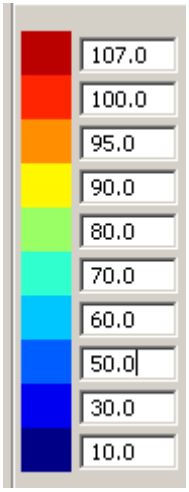
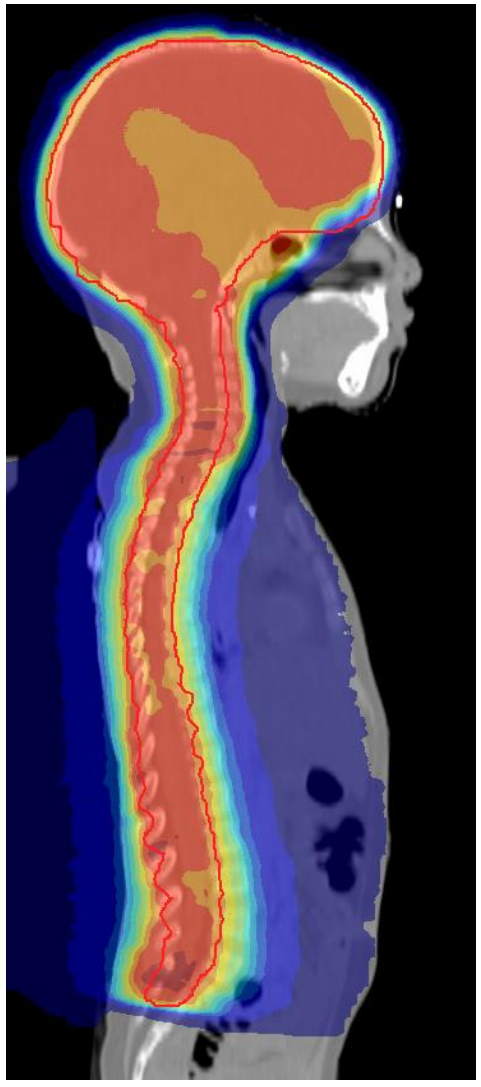
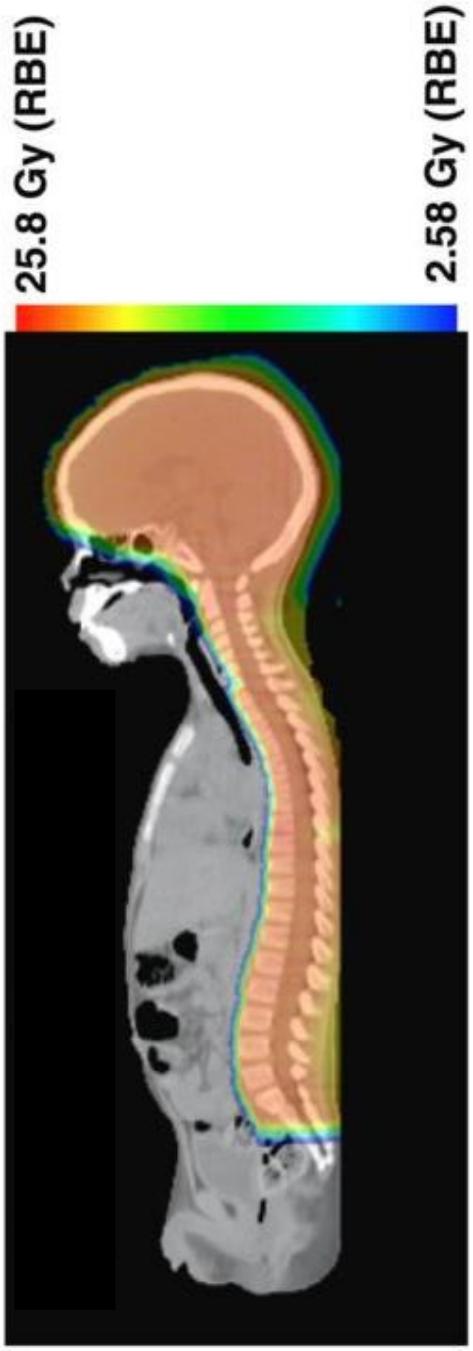
Cranio-spinal lesions: 3D-CRT old vs new

3D-CRT old (single PA)



3D-CRT new





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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?
- type of collimation?

Where to place the isocenter?

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

  (and normally it is a very good choice!)

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

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

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

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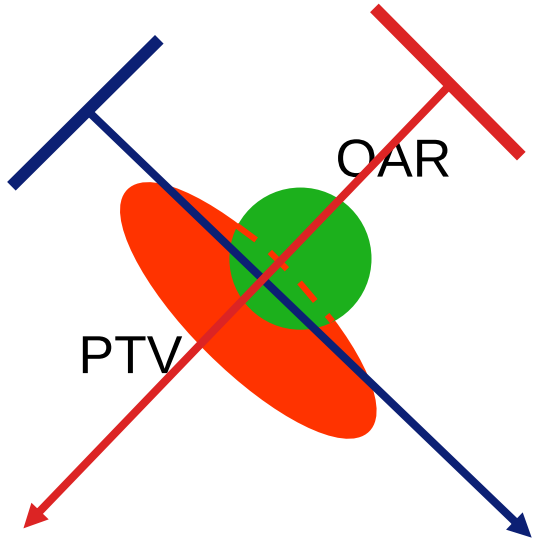
How to select the proper beam angles?

- think about the dose distribution you want to achieve

- geometrical avoidance



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

How to select the proper beam angles? Single lung:

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Radiotherapy and Oncology 62 (2002) 21–25

RADIOTHERAPY & ONCOLOGY
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

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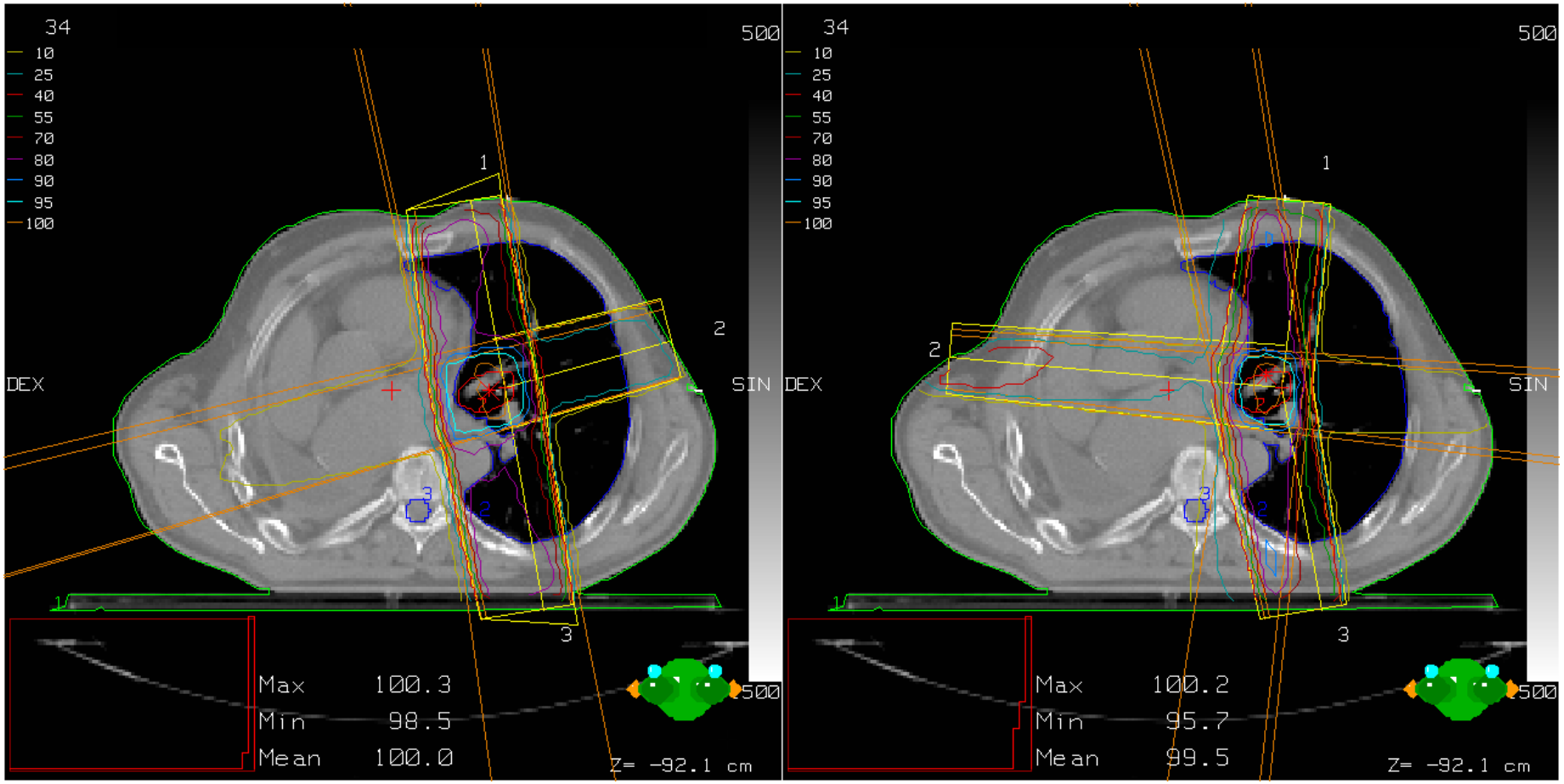

V_{20} = 25 %

V_{20} = 19 %

Lagerwaard et al: R&O, 2001

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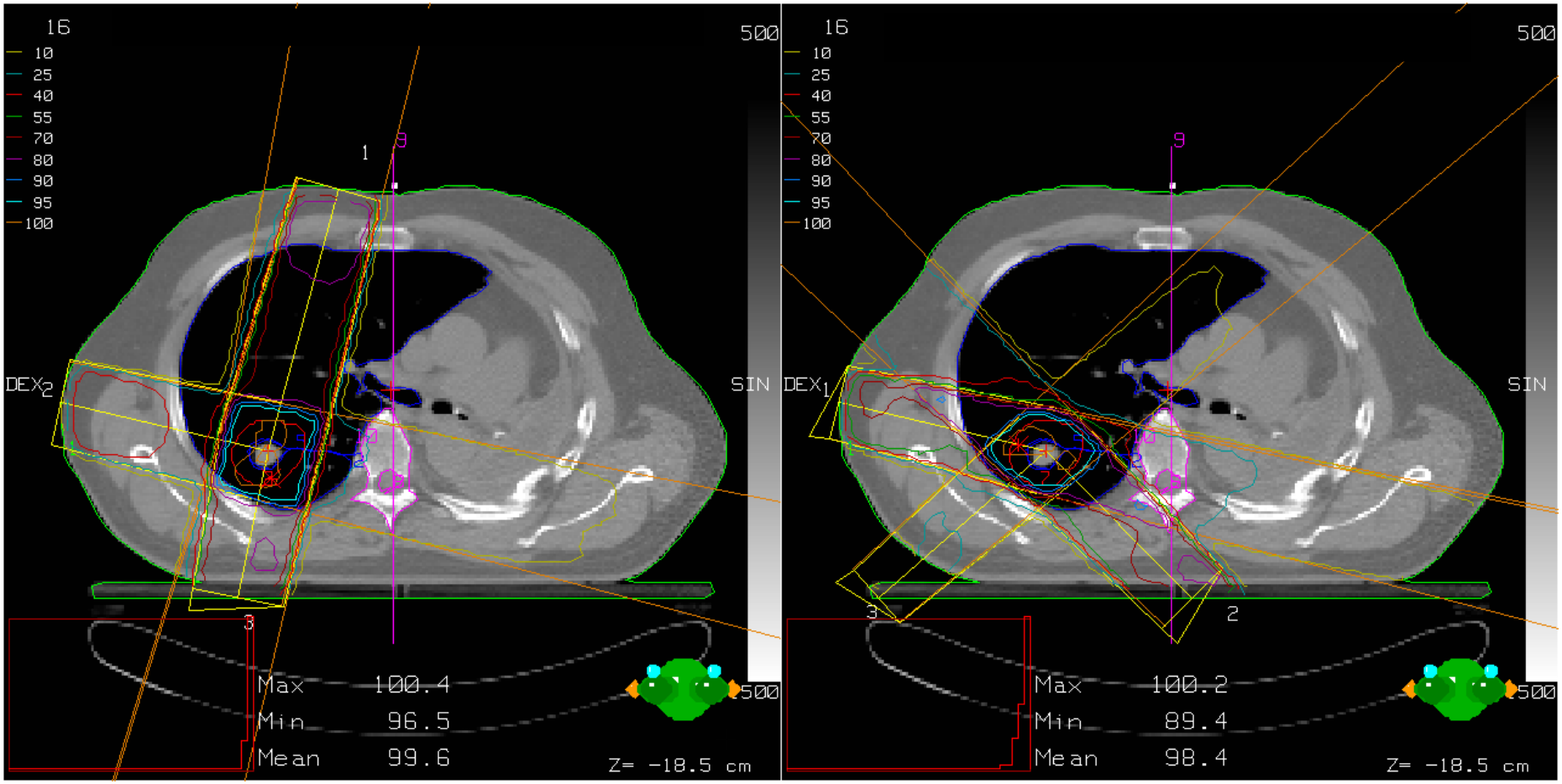

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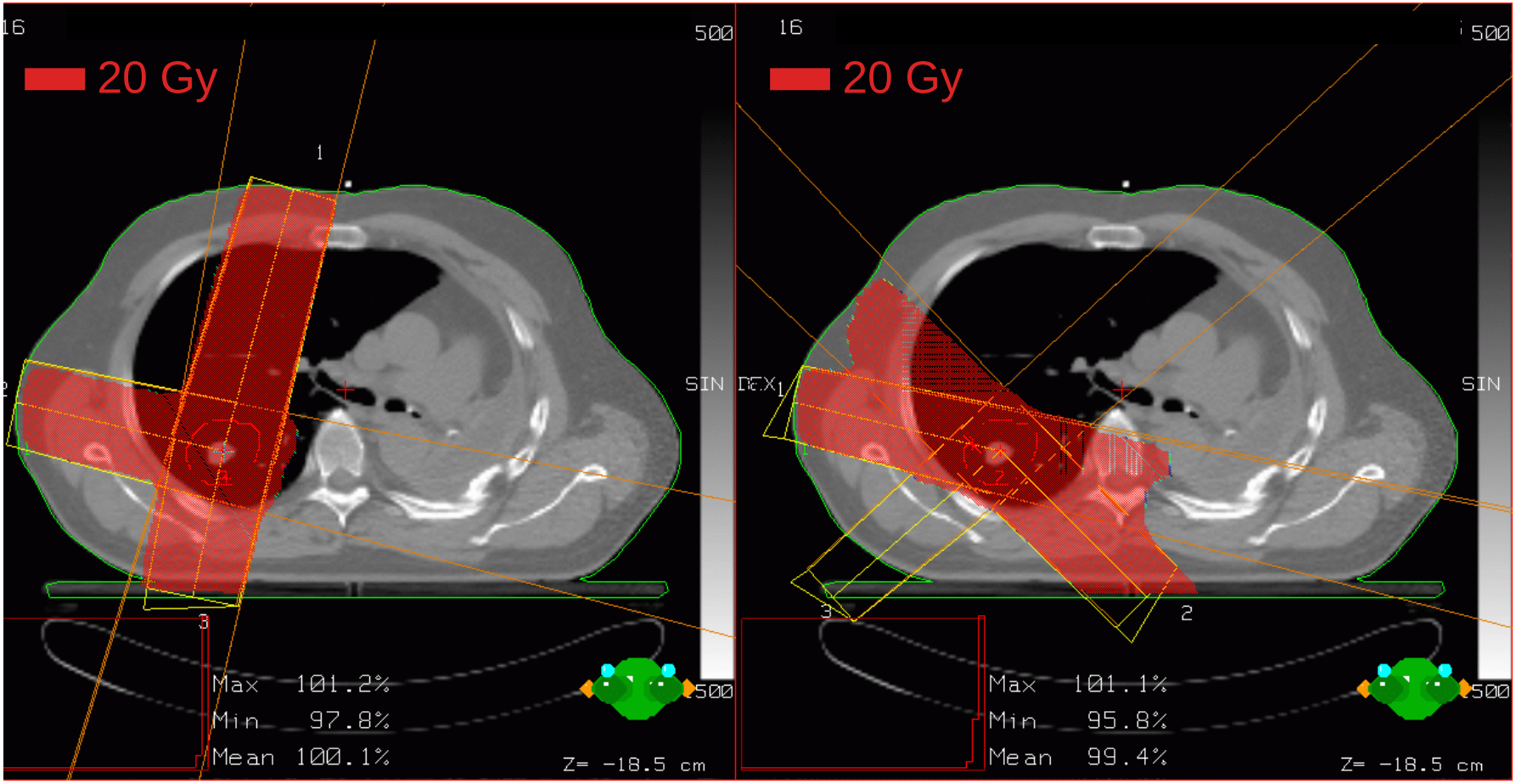

$V_{20} = 27\ \%$

$V_{20} = 15\ \%$

Lagerwaard et al: R&O, 2001

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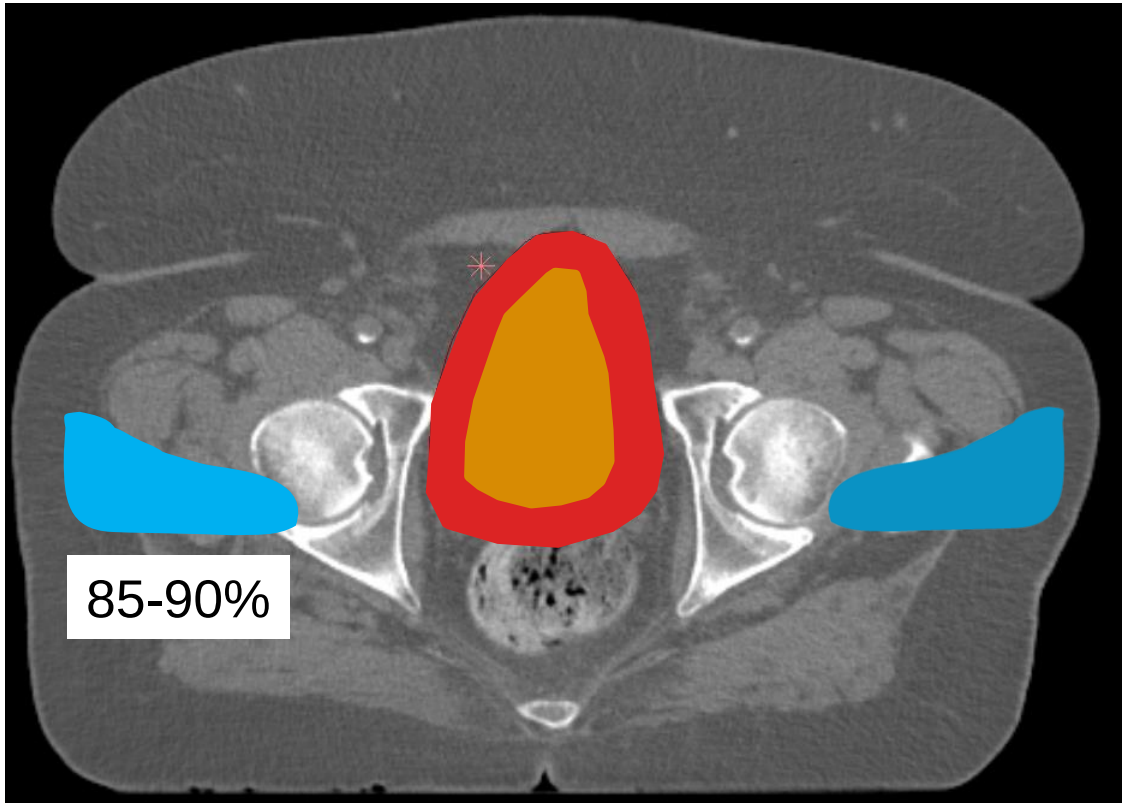
How many fields?

- 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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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…*

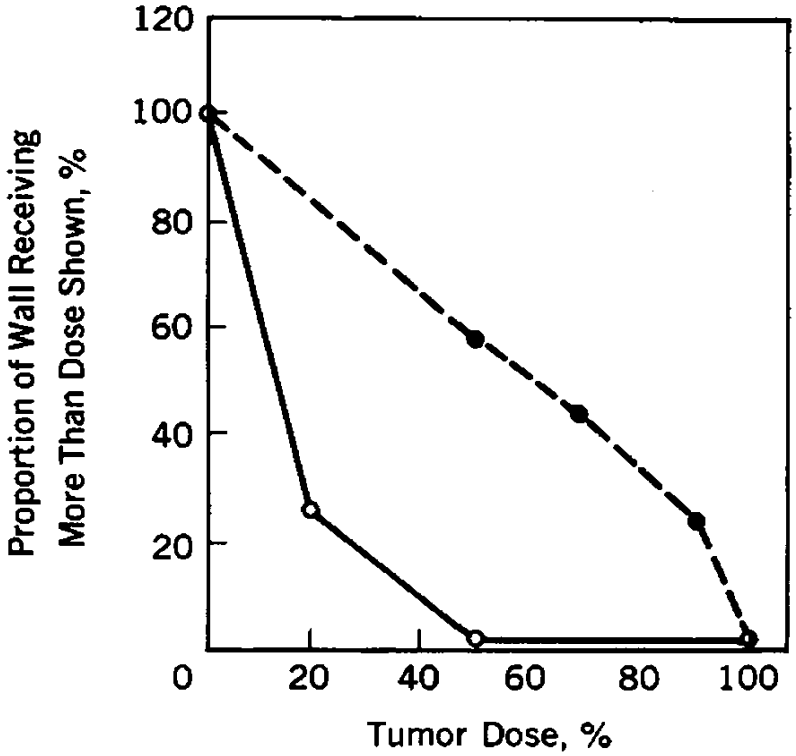

Fig 3.—Comparison of radiation dose to posterior rectal wall by 10-MV x-rays and 160-MV protons. Proportion of the wall is plotted vs dose it received. Dose is expressed as percentage of tumor dose. Solid line indicates protons; dashed line, 10-MV x-rays.

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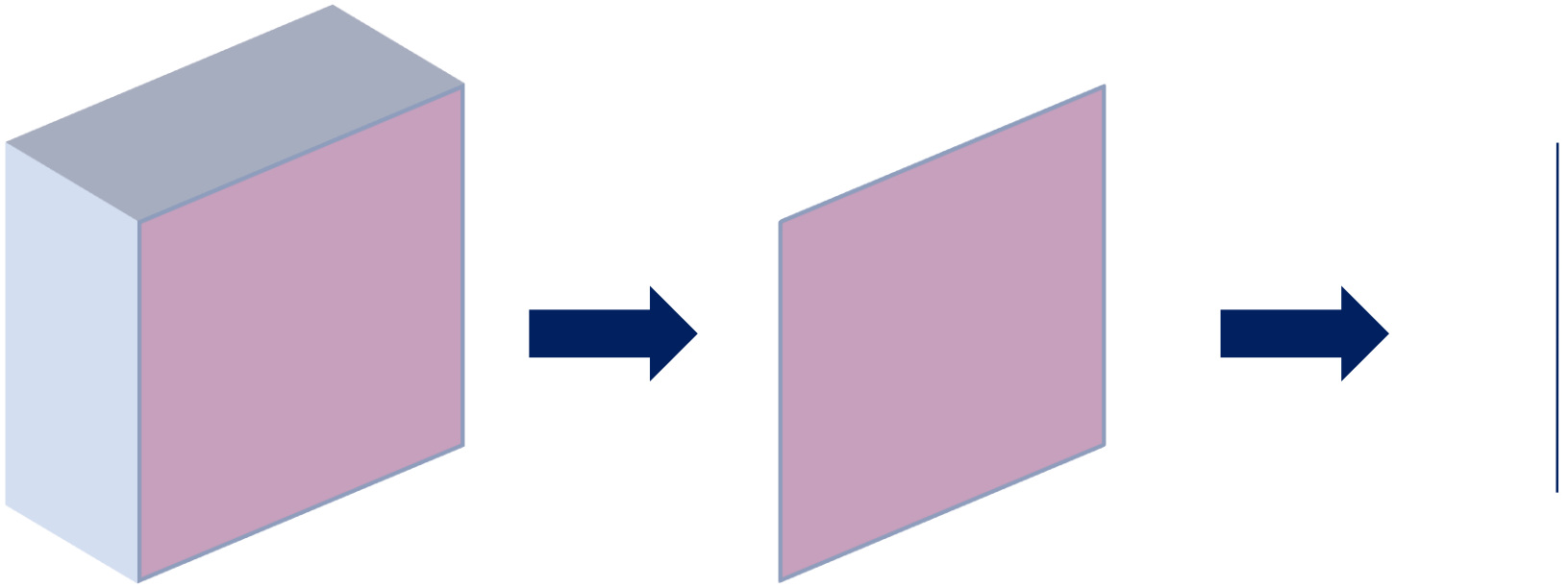
DVH related indicators



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

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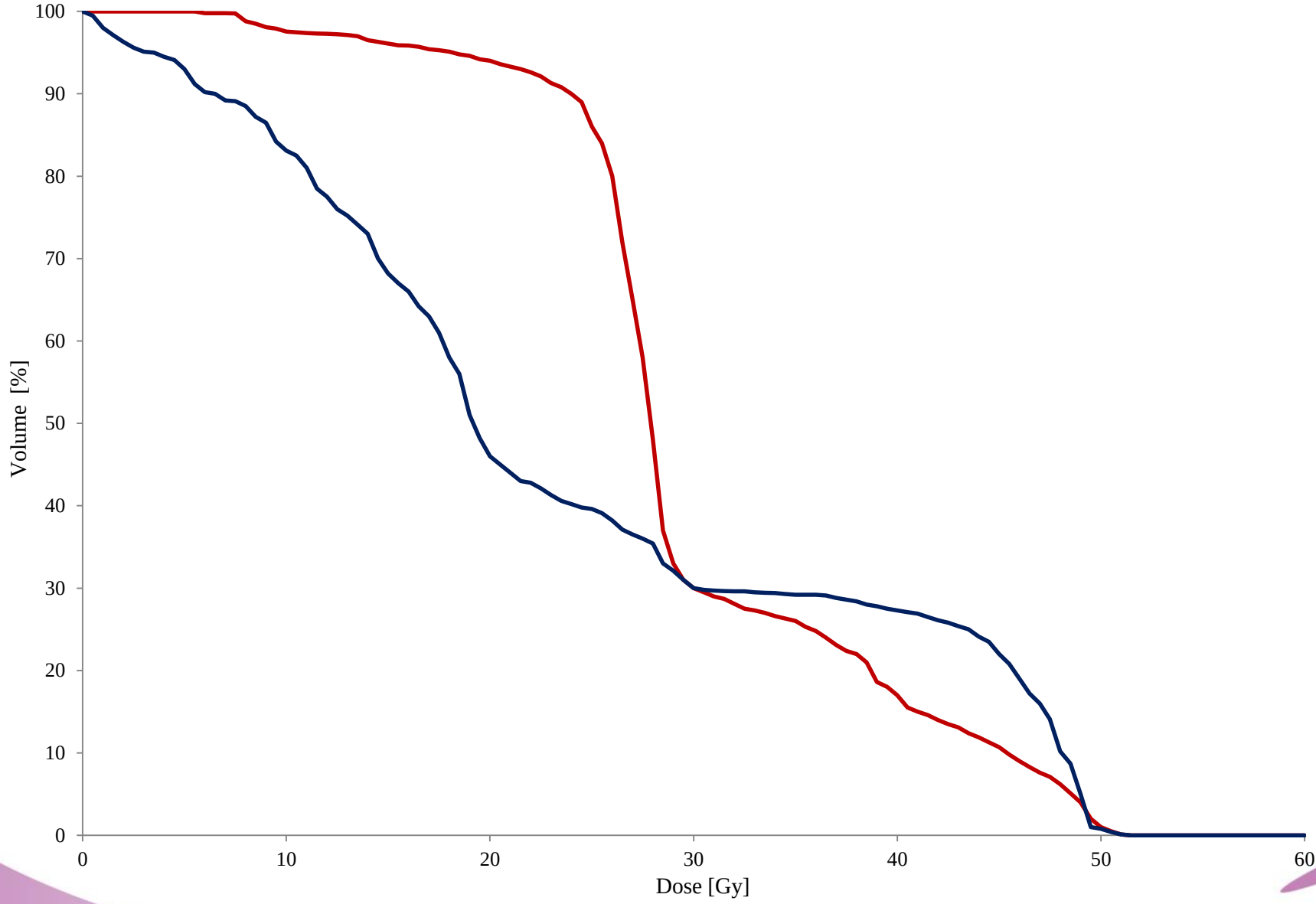
Be careful using single point indicators…



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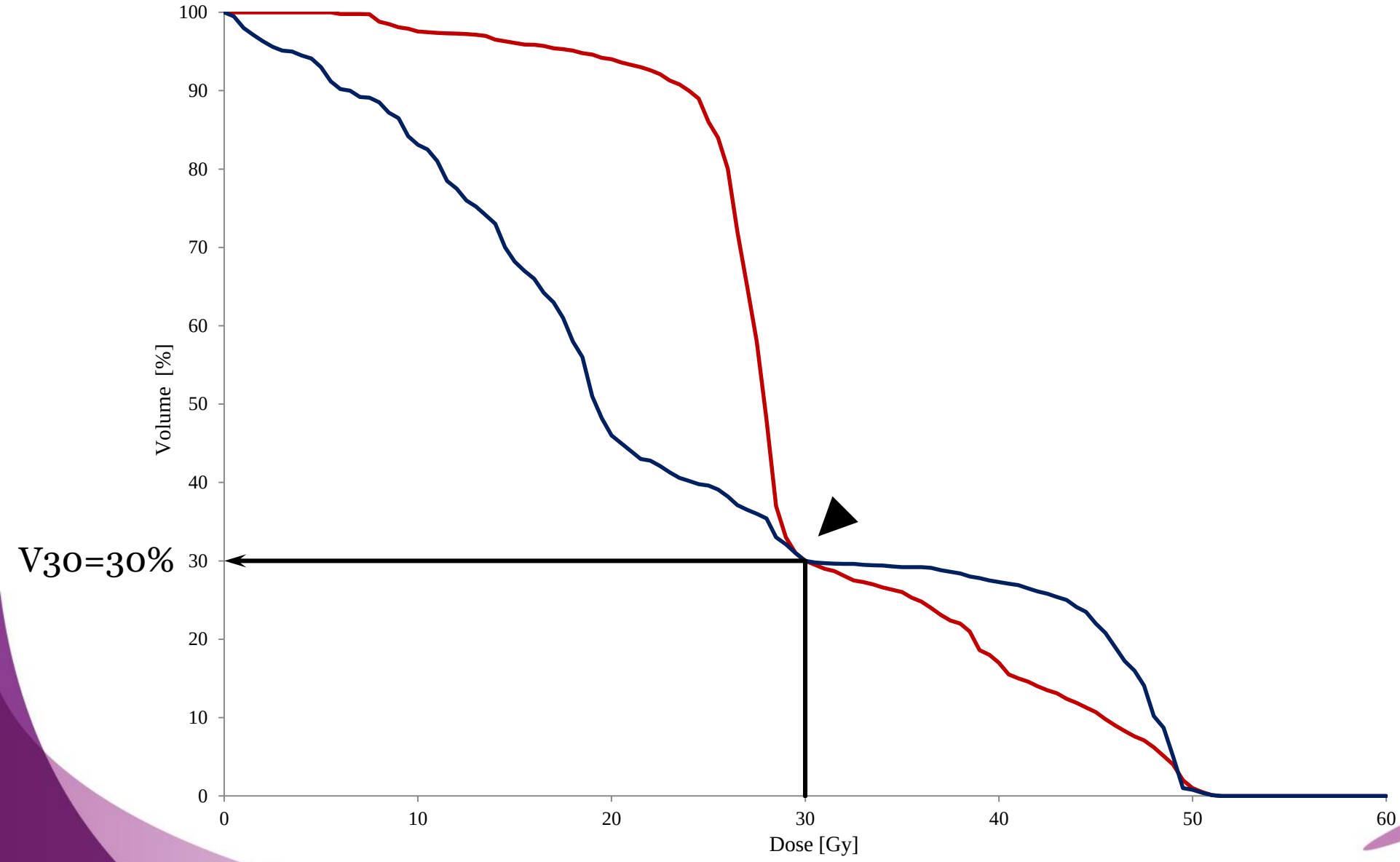

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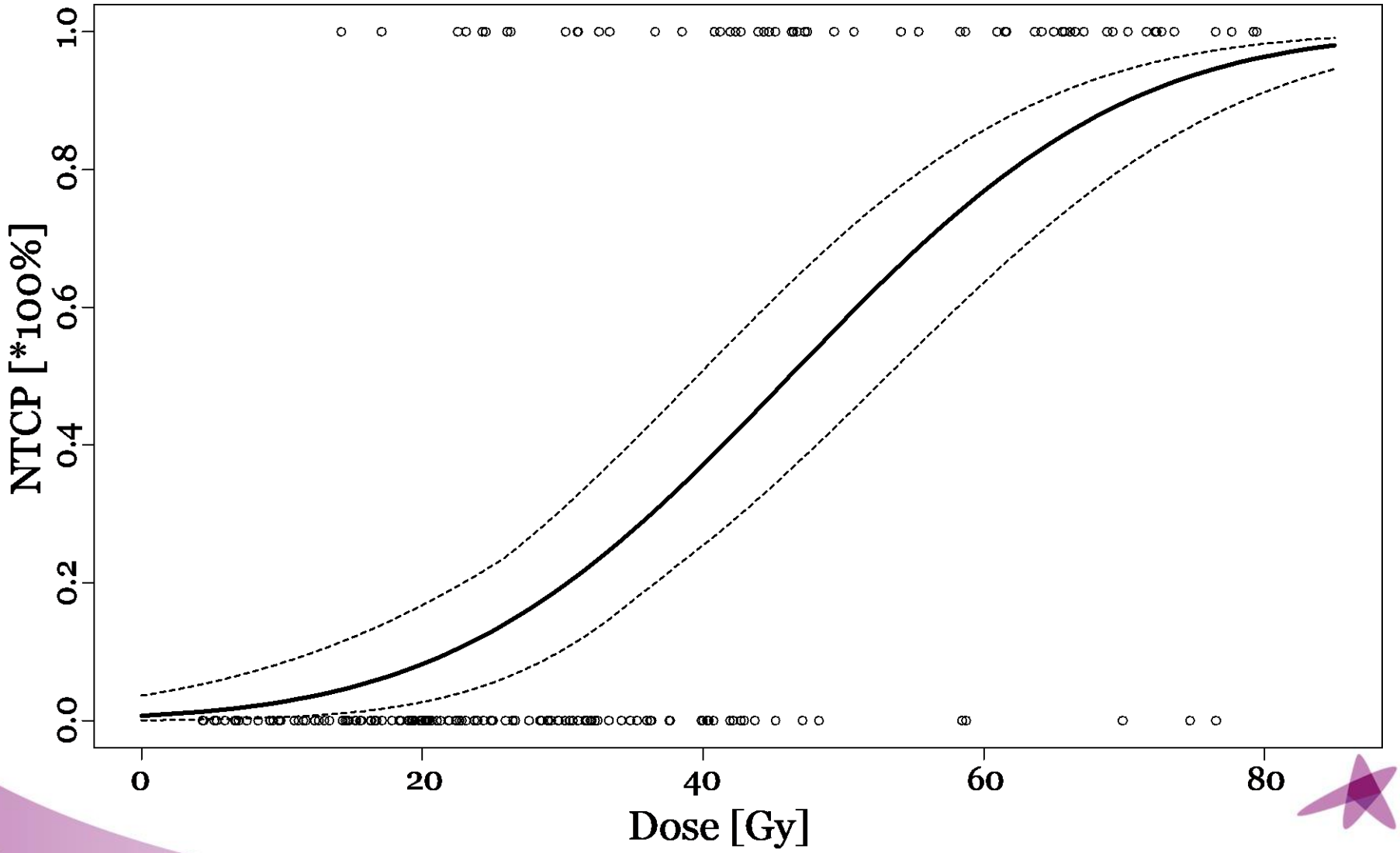
Dose/response models

- Dose-response models are tools for calculating the **probability** of a given outcome related to the delivered «**dose**»



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NTCP models formalisms

- *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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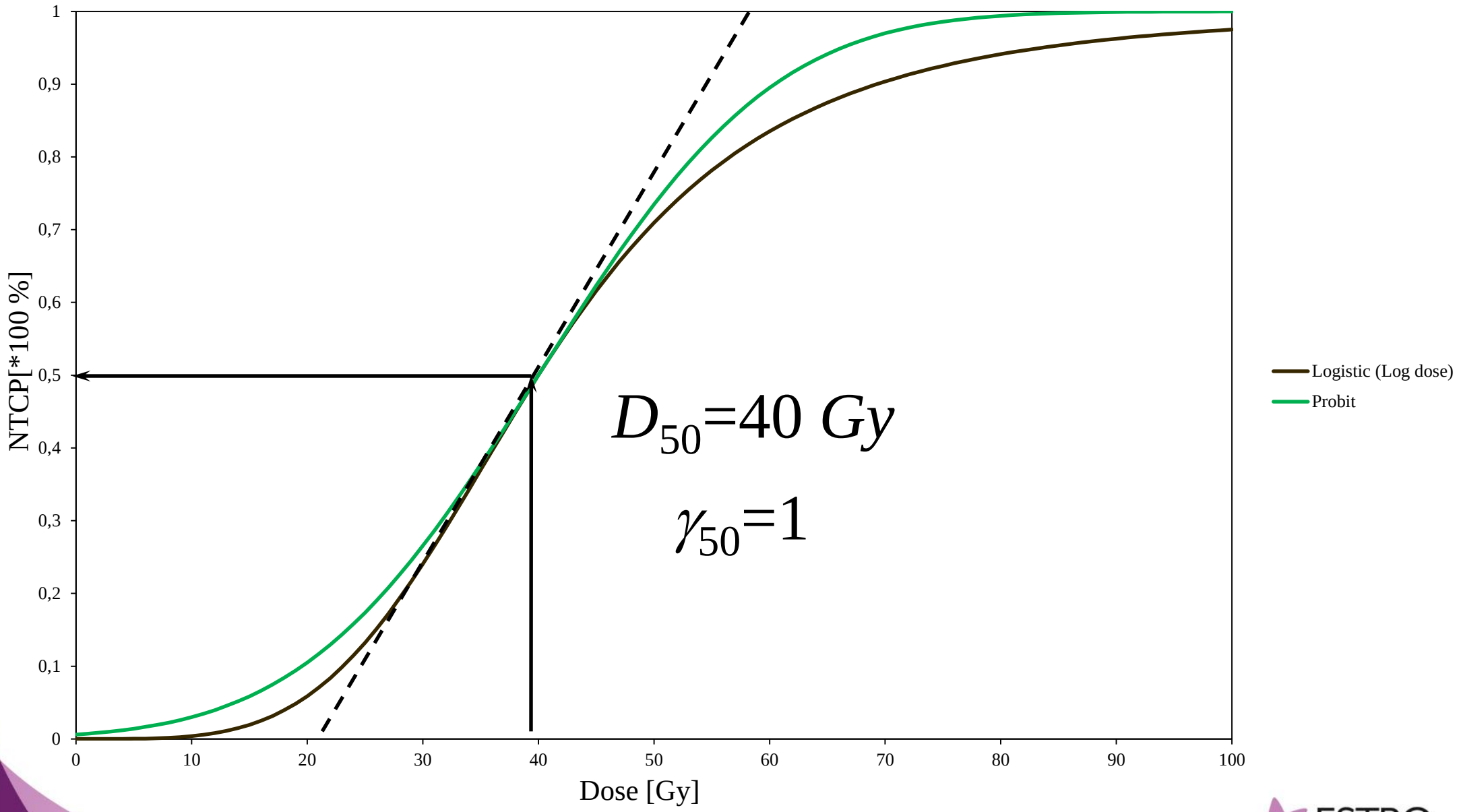
NTCP models



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Which dose should be used within NTCP models?

- Dose extracted from DVH
  - Maximum (D_{vol})
  - D_{volume}
  - Mean dose

But…

- 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

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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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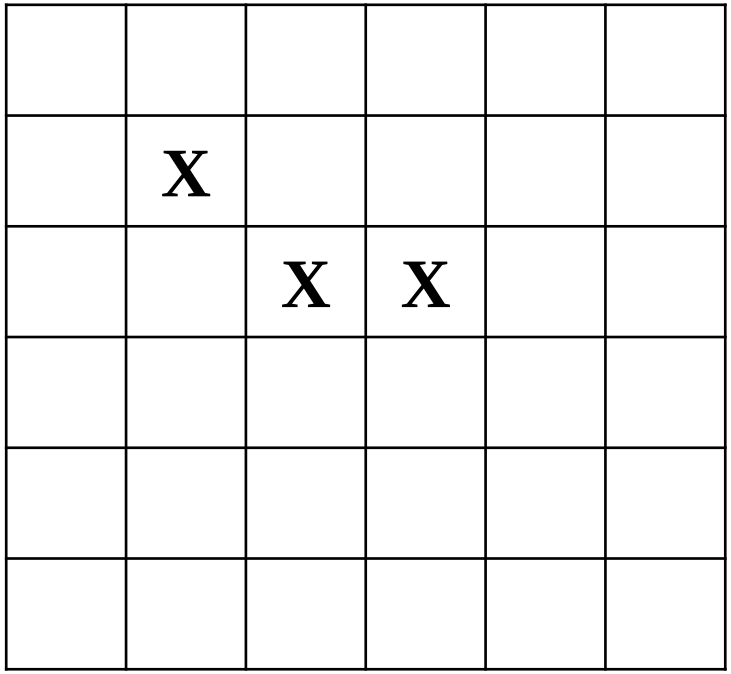
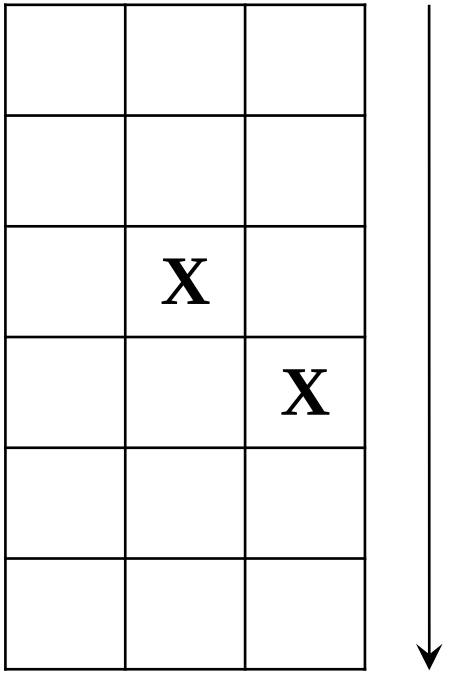
The Volume Effect in OAR

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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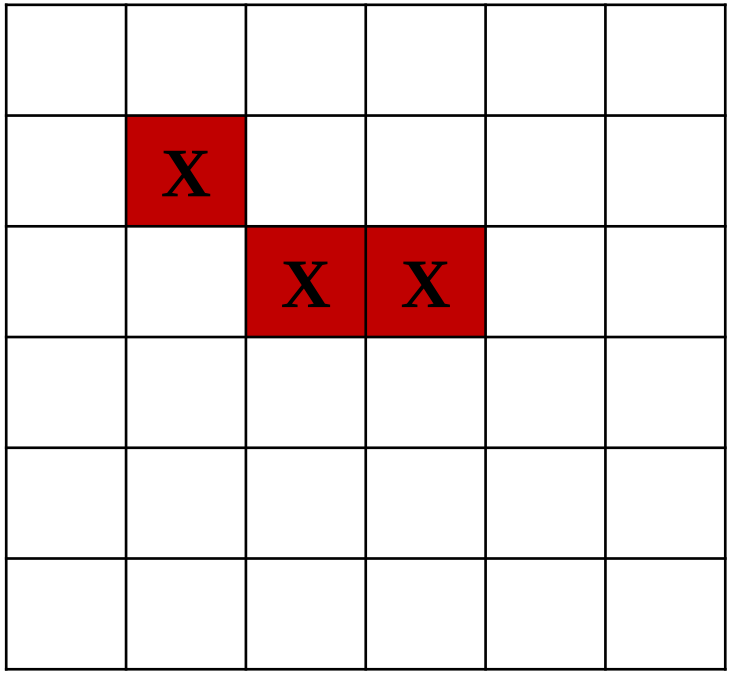
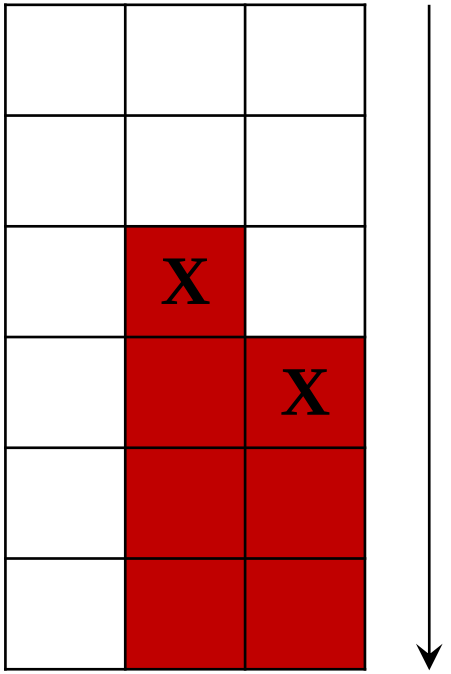


Lung, liver, kidney

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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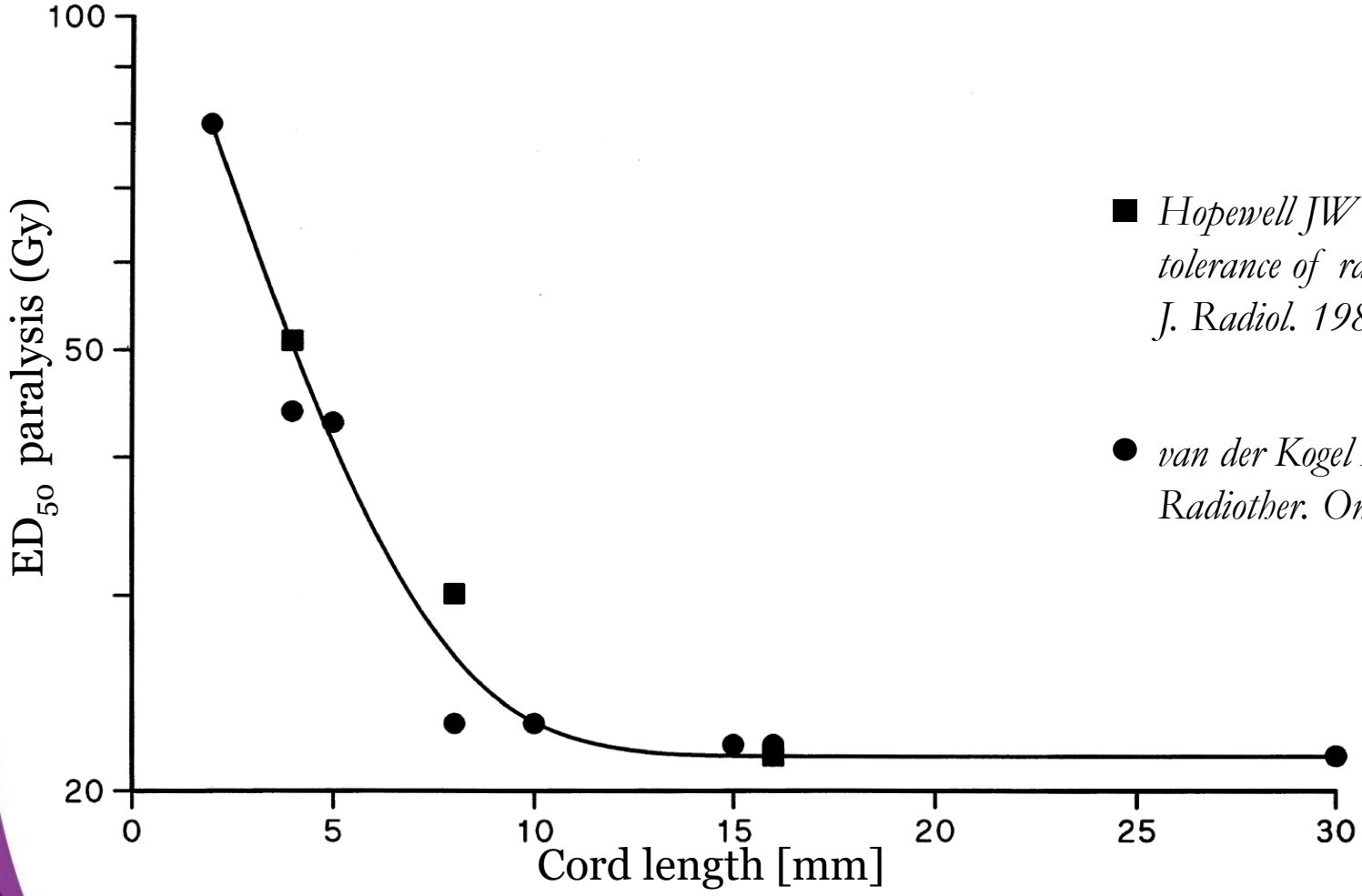
The Volume Effect in OAR

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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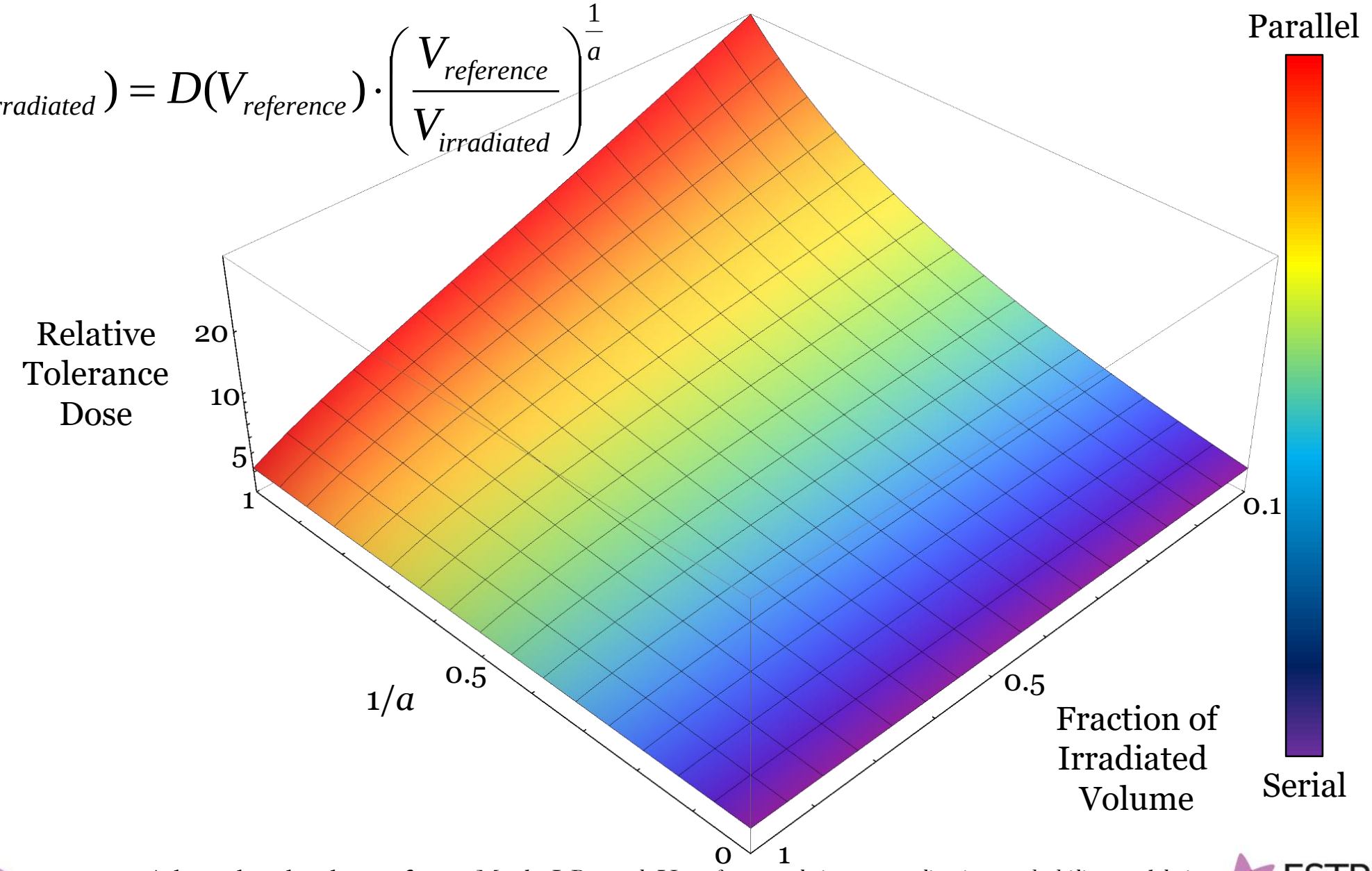
The Volume Effect in OAR

$$D(V_{irradiated}) = D(V_{reference}) \cdot \left(\frac{V_{reference}}{V_{irradiated}} \right)^{\frac{1}{a}}$$



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

$$D(V_{irradiated}) = D(V_{reference}) \cdot \left(\frac{V_{reference}}{V_{irradiated}} \right)^{\frac{1}{a}}$$

1. *a* value is function of the structure:
   - ▲ Spinal cord (>20)
   - ▼ Lung (≈1)
2. Within a structure *a* can be function of the effect:
   - ▲ Rectal bleeding (Rectum)
   - ▼ Proctitis (Rectum)
   - ▲ Necrosis (Brain)
   - ▼ Cognitive impairment (Brain)
3. Within a structure *a* can be function of the anatomy

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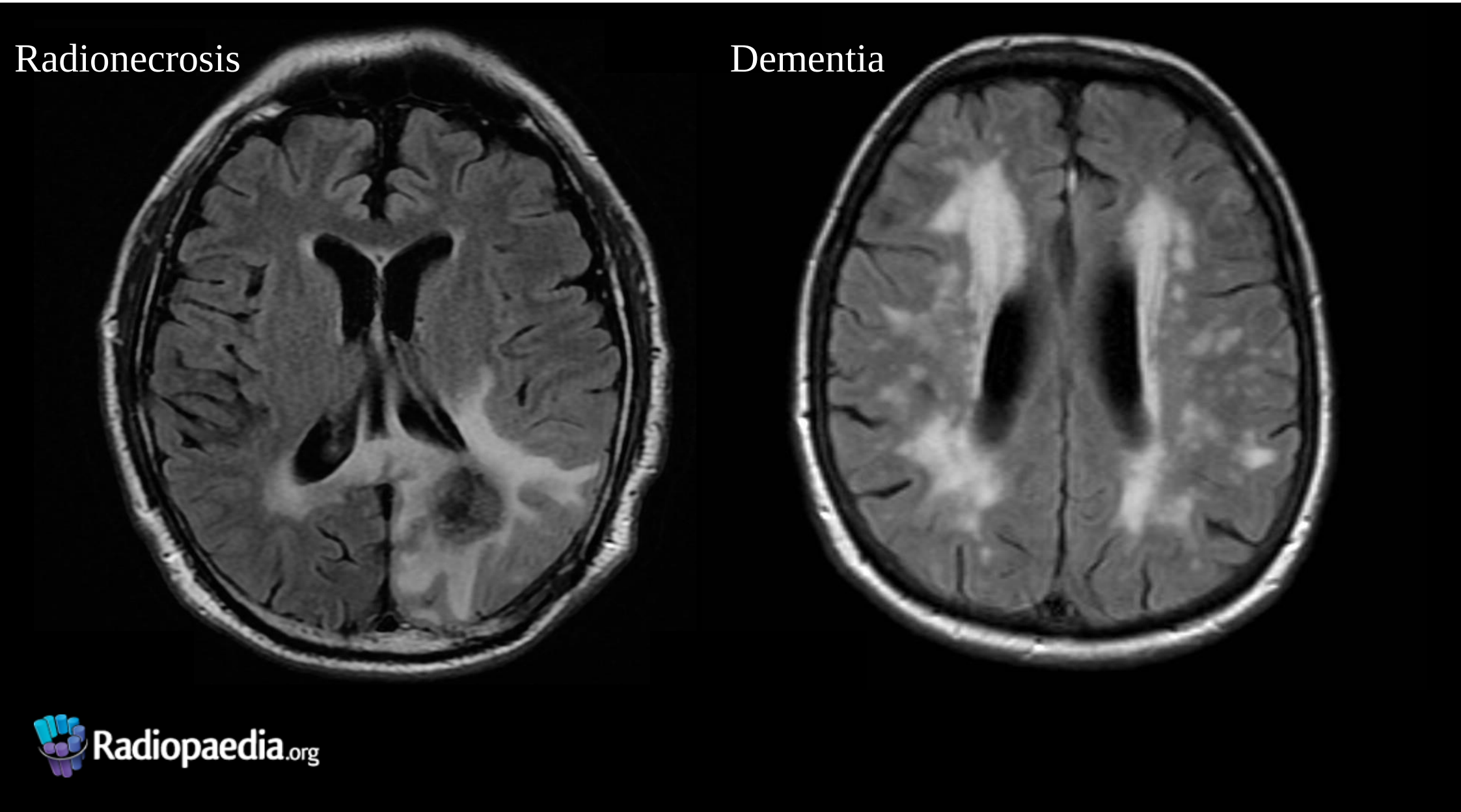

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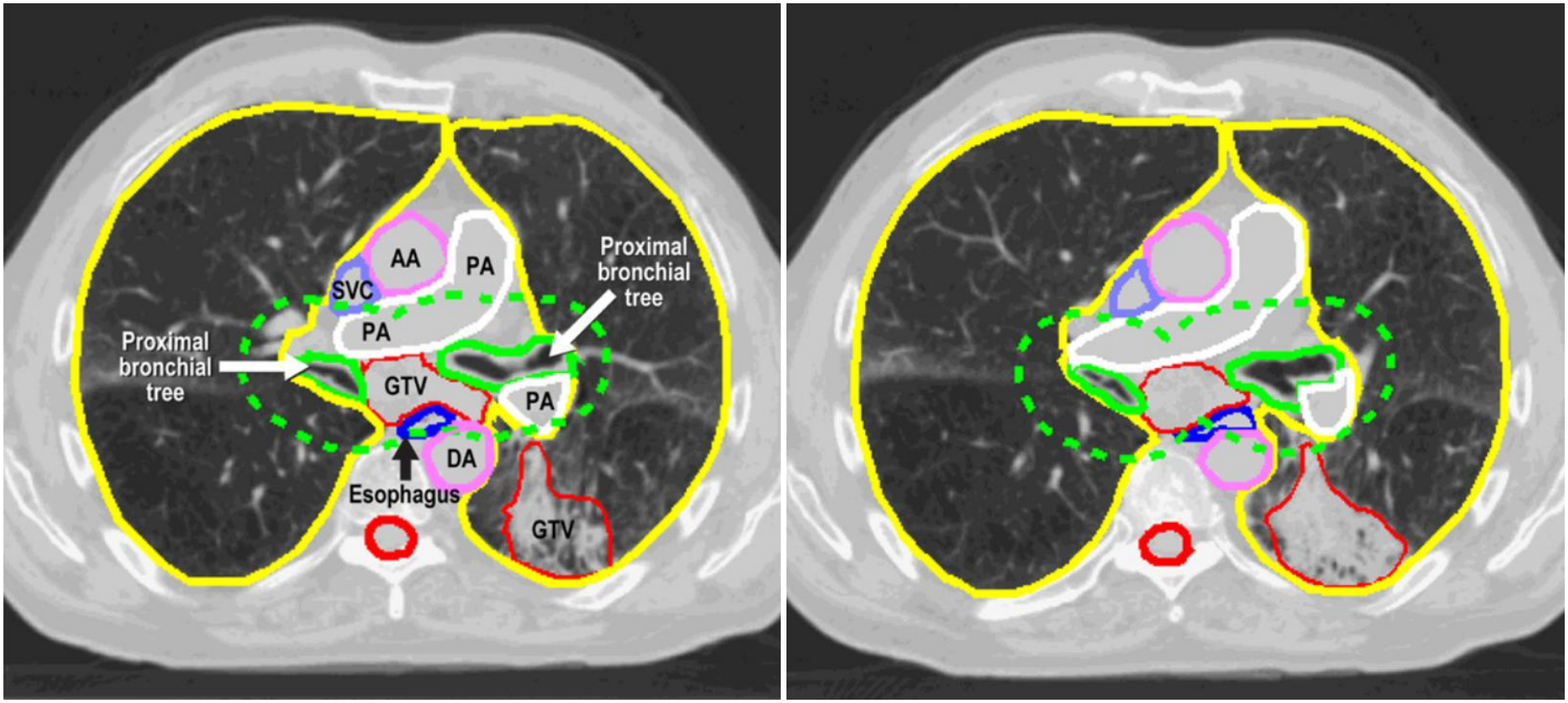

Kong FM et al. Consideration of dose limits for organs at risk of thoracic radiotherapy: Atlas for lung, proximal bronchial tree, esophagus, spinal cord, ribs, and brachial plexus. Int J Radiat Oncol Biol Phys 2011;81:1442–57.

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

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

  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

Beyond the DVHs

I.	Host	Age Comorbid conditions Host response to radiation Smoking KPS
II	Organ	Pre-radiation organ condition (Poor PFTs; LFTs; COPD) Regional variation of radiosensitivity with the organ Impact of other organs Hierarchal organization of the organ: Serial: dose effect: spinal cord Parallel: volume effect: lung, liver Both: kidney
III	Natural history of tumor	
IV	Treatment	A—Radiation Dose (max, min, mean) Fractionation (fractional dose): BED Dose rate Overall treatment time Treatment energy Volume (V dose: absolute or relative)
IV	Treatment	B—Nonradiation Chemotherapy (drug type, dose, schedule) Radiation modifiers (type, dose, schedule) Surgery (interval)
V	End points ACUTE	Type: Clinical LATE Radiographical: anatomical, functional Biochemical (blood test, functional test) Degree of severity Degree of frequency Impact on quality of life (QOL)
VI	Issues on reporting of toxicity	

Emami B. Tolerance of Normal Tissue to Therapeutic Radiation. Reports Radiother Oncol. 2013; 1:36–48.

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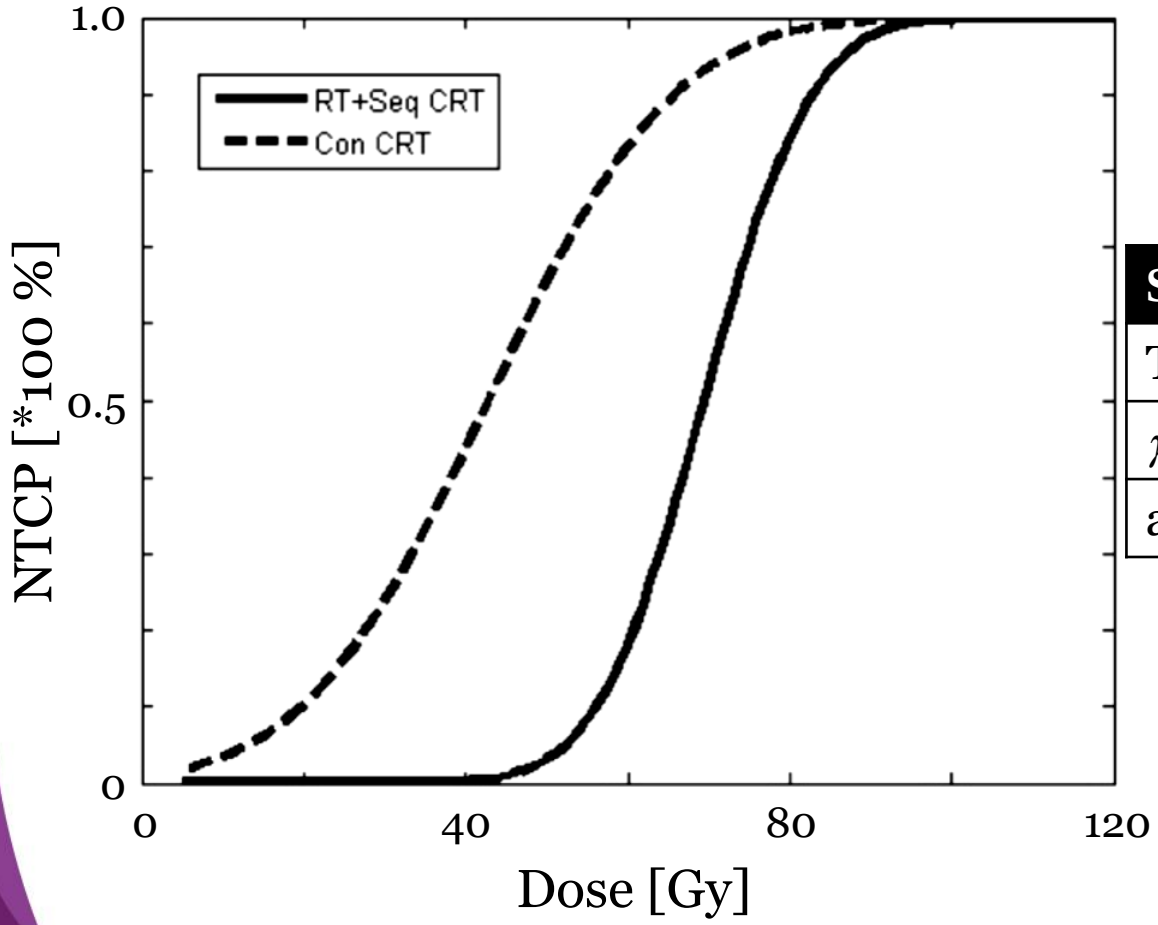
Reliability of radiobiological evaluation

- 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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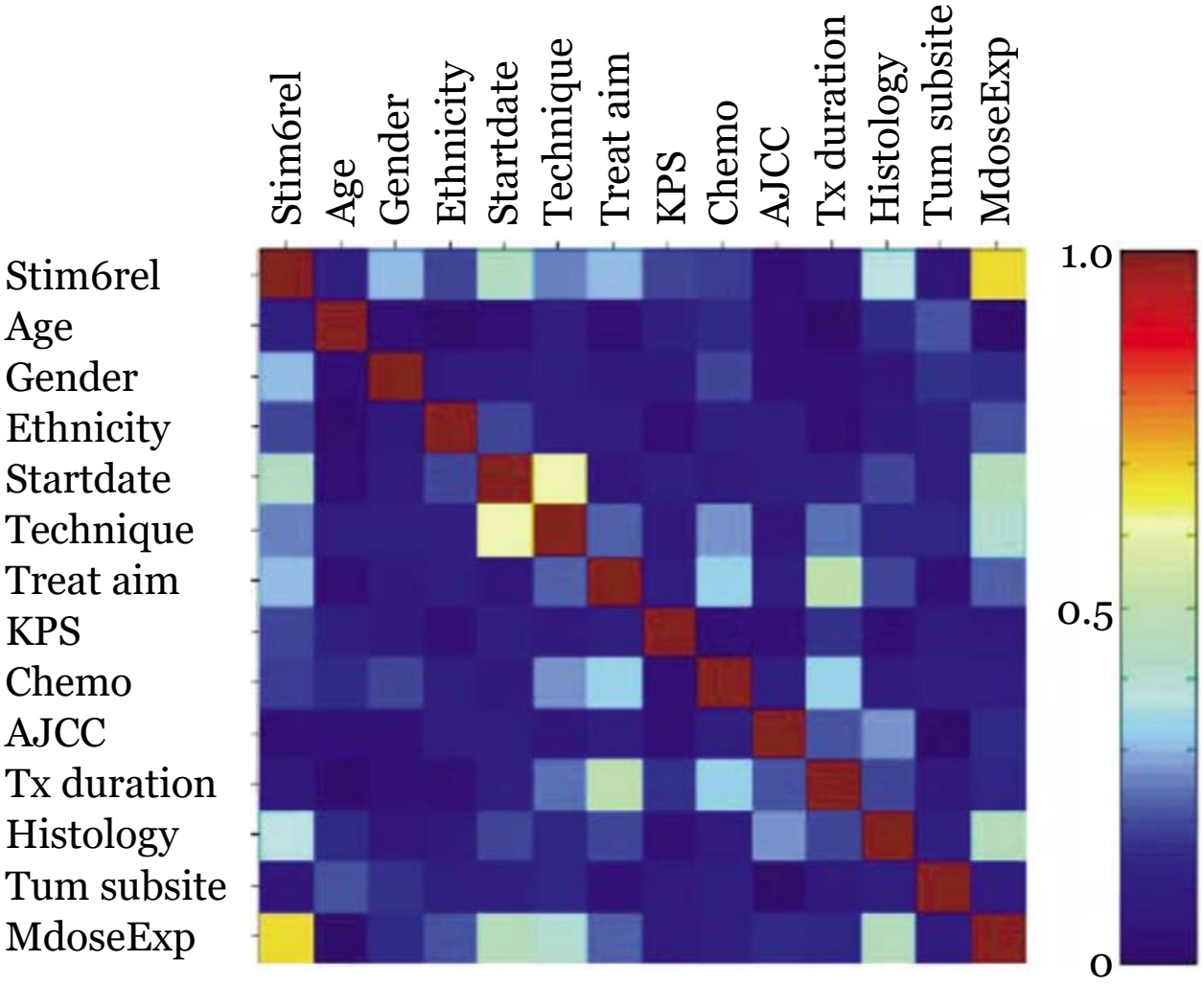
Reliability of radiobiological evaluation

- 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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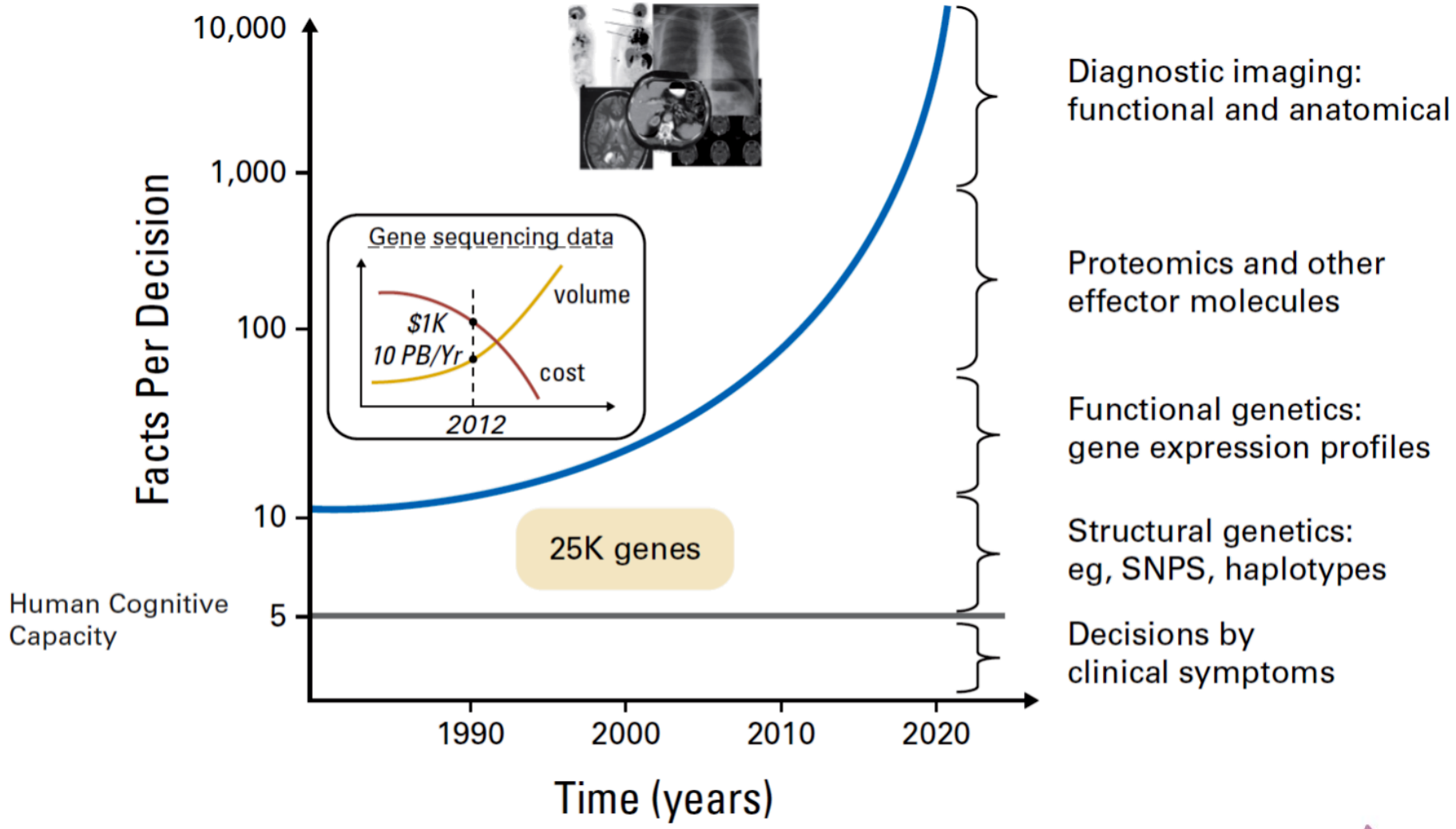
Reliability of radiobiological evaluation

- 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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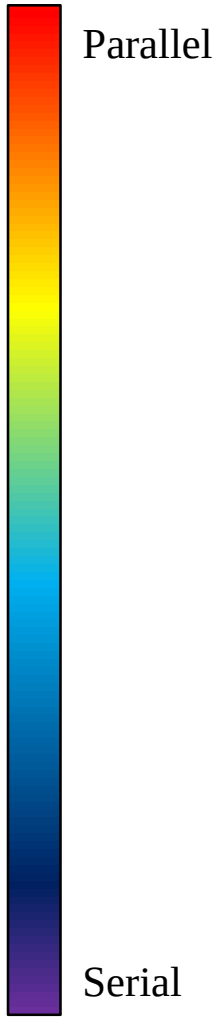
ATP: treatment planning evaluation summary

- Yes
  1. Standard fractionation
  2. Combined modality data
  3. QUANTEC
  4. QUANTEC updates
- No
  1. SBRT
  2. Hypofractionation
  3. Protons/Heavy particles
  4. BRT

ATP: treatment planning evaluation summary

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



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Beyond the theory: QUANTEC and more…

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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Beyond the theory: QUANTEC and more…

Tolerance of Normal Tissue to Therapeutic Radiation

Dr Emami B
Department of Radiation Oncology, Loyola University Medical Center, Maywood, Illinois, USA

Reports Radiother Oncol. 2013; 1:36–48.

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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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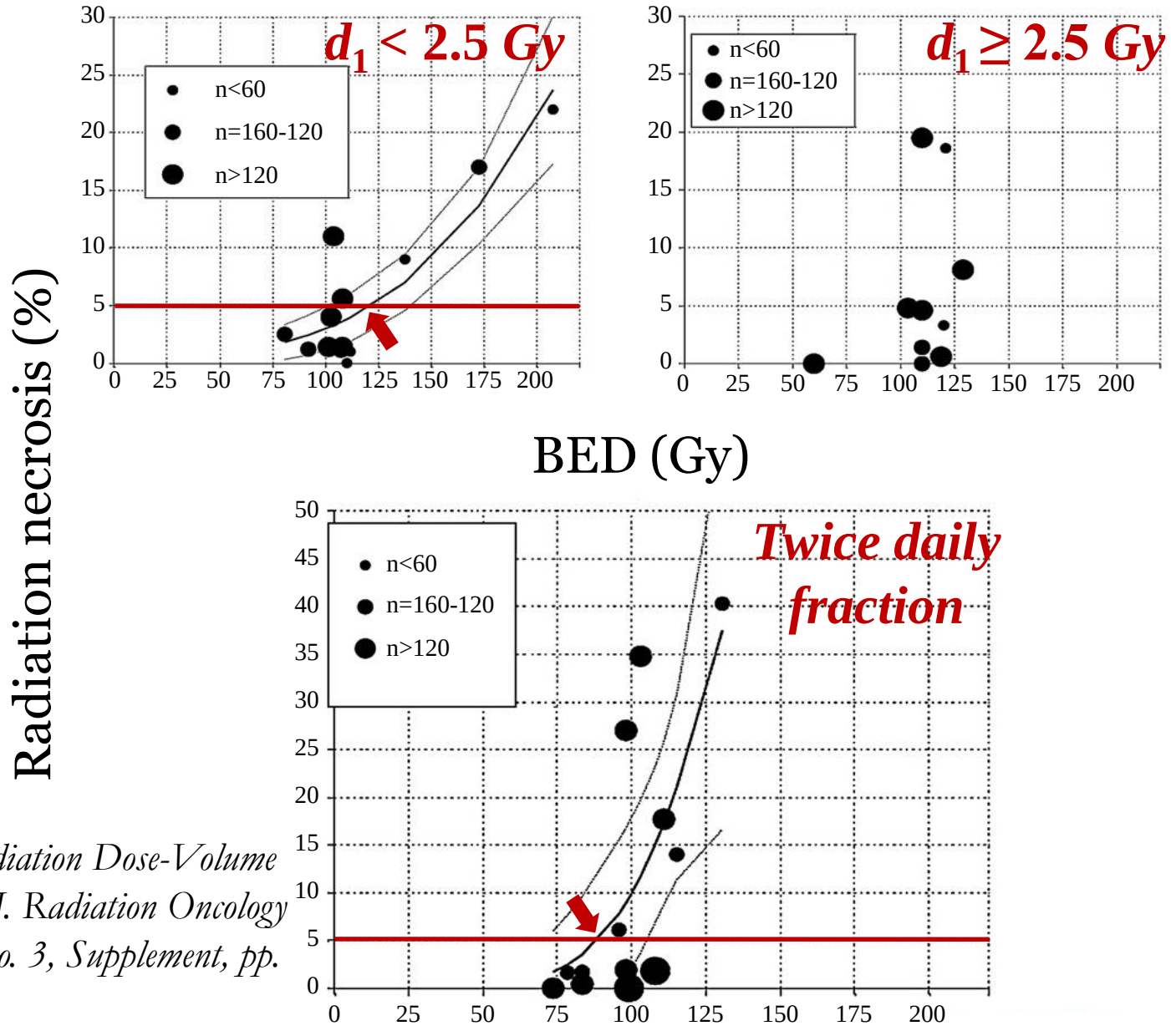
Parameters for clinical outcome: Brain



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

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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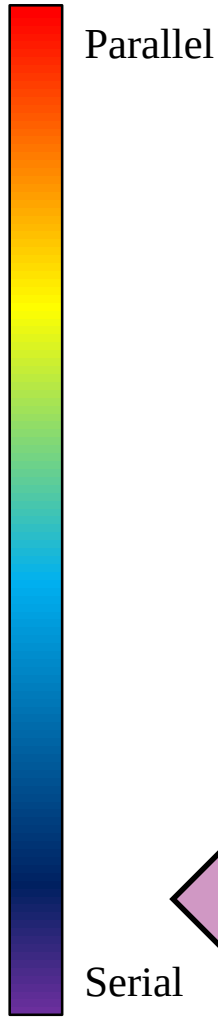
ATP: brain summary

Dose (Gy), or dose/volume parameters	Rate (%)
D_{max} <60	<3
D_{max} = 72	5
D_{max} = 90	10

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



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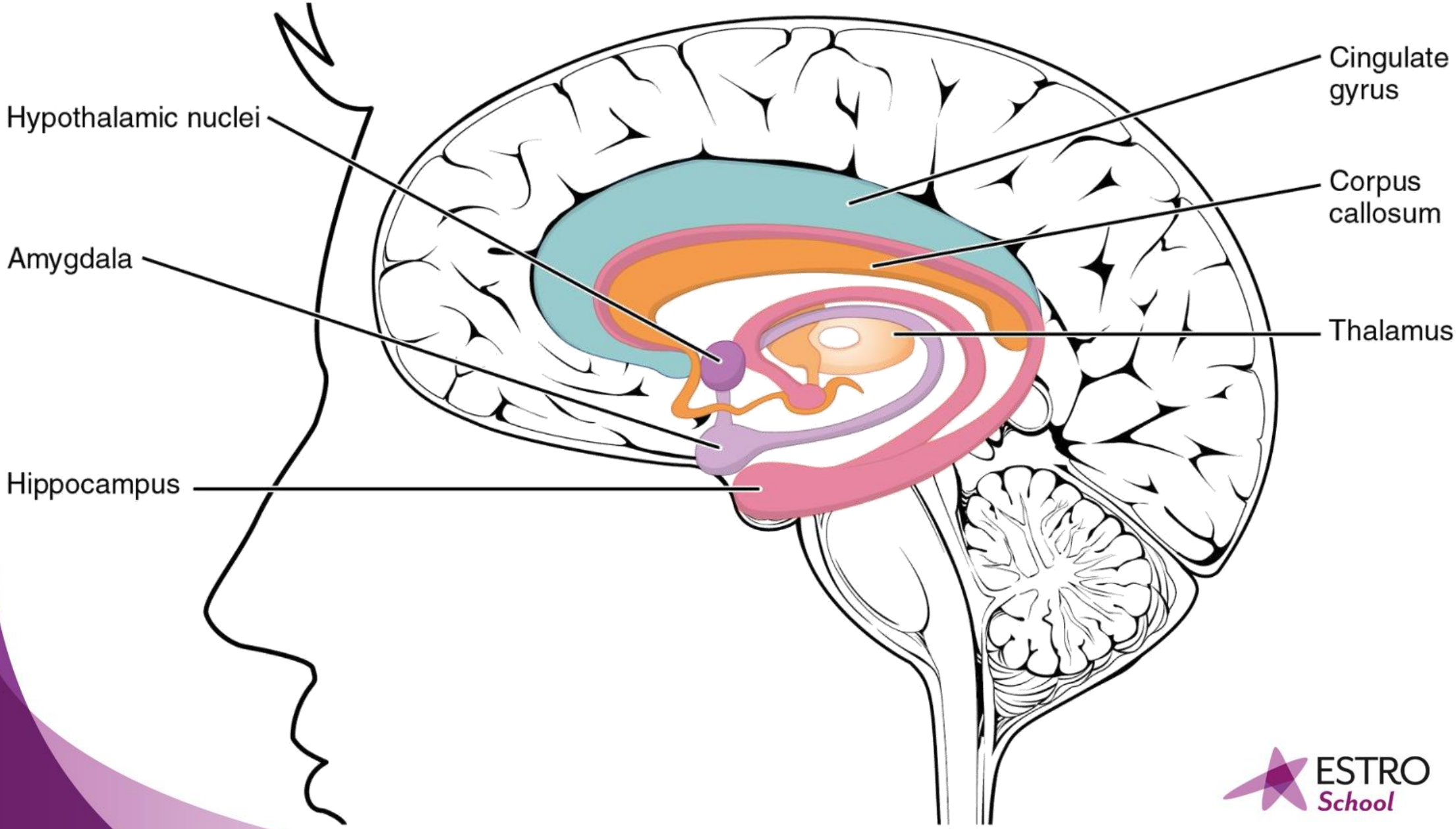
Parameters for clinical outcome: hippocampus



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Parameters for clinical outcome: hippocampus

Main cognitive test results in patients treated with in Intensity Modulated Radiotherapy using hippocampal avoidance approaches.

Authors	Number of patients	Prescribed total dose	Hippocampi dose constraints	Delivered dose to the hippocampi	Hippocampus α/β	Median follow-up (months)	Main cognitive test results
Gondi et al. [53]	113	WBRT for BM: 30 Gy in 10 fractions	D_{max} < 16 Gy $D_{100\%}$ < 9 Gy	/	/	/	Significant reduction in HVLT-R Delayed Recall (verbal learning and memory) decline at 4 months compared to historical control Over time: significant decline in HVLT-R Delayed Recall; No significant decline in HVLT-R Total Recall and Immediate Recognition; D100% predictive of decline in HVLT-R Delayed Recall (univariate analysis)
Redmond et al. [54]	20	PCI: 25 Gy in 10 fractions	D_{mean} < 8 Gy	Hippocampi: D_{mean}: 7.4 Gy Avoidance structure: D_{mean}: 10.25 Gy	/	16.7	At 6 and 12 months following the completion of IMRT: No significant decline in HVLT-R Delayed Recall, Trail Making Test (information processing speed, executive function), Controlled Oral Word Association Test (verbal fluency) compared to baseline
Ma et al. [55]	60	PCI: 25 Gy in 10 fractions (n = 21) GBM: 60 Gy in 30 fractions (n = 39; 30 treated using HAA)	PCI: D_{mean} < 8 Gy GBM: Dose reduced as much as possible to the NPC (patients treated using HAA)	PCI: Mean D50%: 5.1 Gy Mean D100%: 4.2 Gy Mean D_{max}: 7.6 Gy GBM HAA: Mean D50%: 23.6 Gy Mean D100%: 12.0 Gy Mean D_{max}: 42.8 Gy GBM without HAA: Mean D50%: 54.5 Gy Mean D100%: 44.7 Gy Mean D_{max}: 61.7 Gy	2 Gy	/	D50% of 22.1 Gy and 62.9 Gy (EUD) exposed to 20% and 50% probabilities of HVLT-R Delayed Recall decline, respectively D100% of 10.9 Gy and 59.3 Gy (EUD) exposed to 20% and 50% probabilities of HVLT-R Delayed Recall decline, respectively GBM: Dmax associated to HVLT-R Delayed Recall results' change (univariate and multivariate analyses)

BM: Brain metastases, D50%: Dose delivered to 50% of the hippocampi, D100%: Dose delivered to 100% of the hippocampi, D_{max}: Maximal dose, D_{mean}: Mean dose, EUD: Equivalent Uniform Dose, GBM: Glioblastoma Multiforme, HAA: Hippocampal avoidance approach, HVLT-R: Hopkins Verbal Learning Test-Revised, NPC: Neural Progenitor Cells, PCI: Prophylactic Cranial Irradiation, WBRT: Whole Brain Radiotherapy.

Jacob J, Durand T, Feuvret L, et al. Cognitive impairment and morphological changes after radiation therapy in brain tumors: A review. Radiother Oncol. Elsevier B.V.; 2018;128:221–228.

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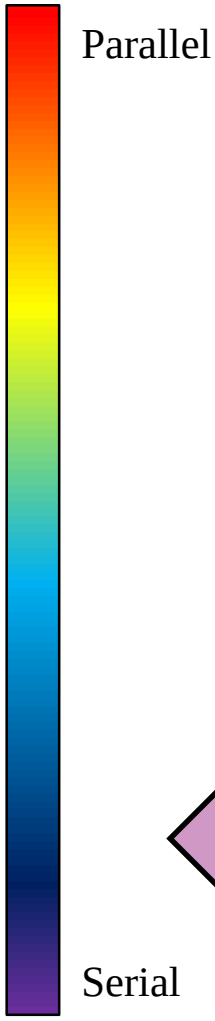
ATP: hippocampus summary

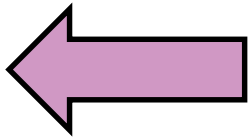
WB-RT 30 Gy @ 3 Gy/fr

Dose (Gy), or dose/volume parameters	**Outcome**
D_{max} < 16 $D_{100\%}$ < 9	Decrease of cognitive impairment at 4 months

Gondi et al.

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





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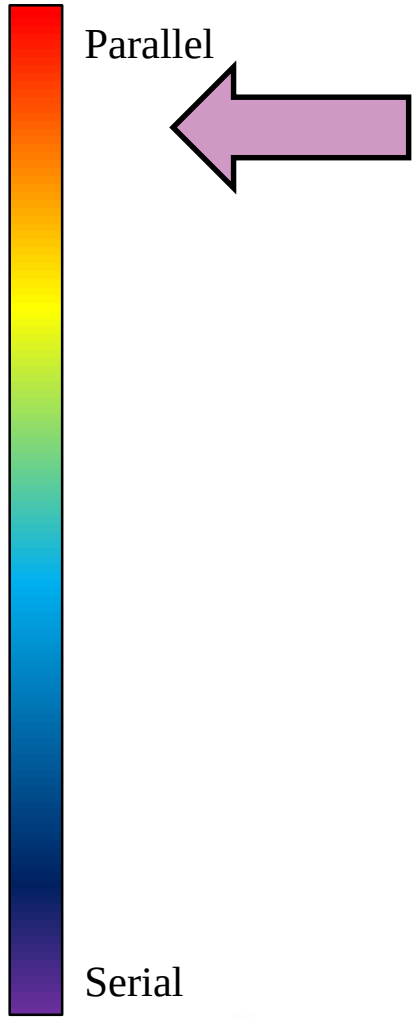
ATP: brain summary

WB-RT 25 Gy @ 2.5 Gy/fr

Dose (Gy), or dose/volume parameters	**Outcome**
D_{mean} < 9	No cognitive impairment at 12 months

Redmond et al.

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



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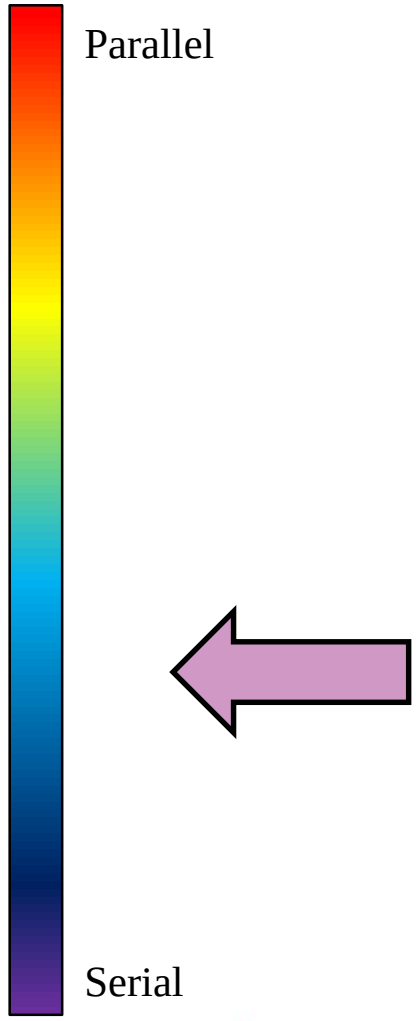
ATP: hippocampus summary

WB-RT 25 Gy @ 2.5 Gy/fr
3D CRT (GBM) 60 Gy @ 2 Gy/fr

Dose (Gy), or dose/volume parameters (EUD)	**Outcome**
$D_{50\%}$ < 22,1	20%
$D_{50\%}$ < 62,9	50%

Report of cognitive impairment
Ma et al.

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



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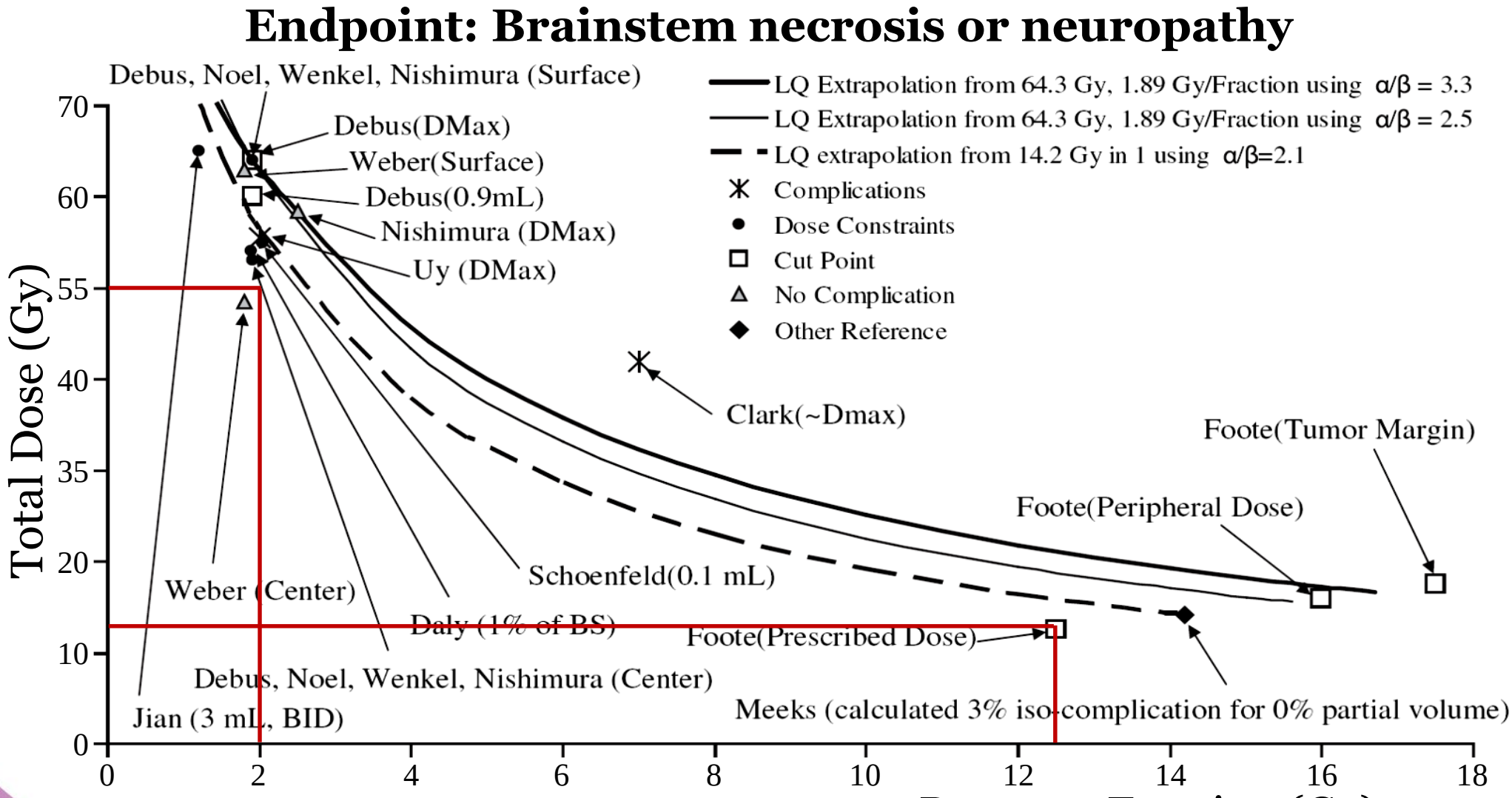
Parameters for clinical outcome: Brainstem



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.

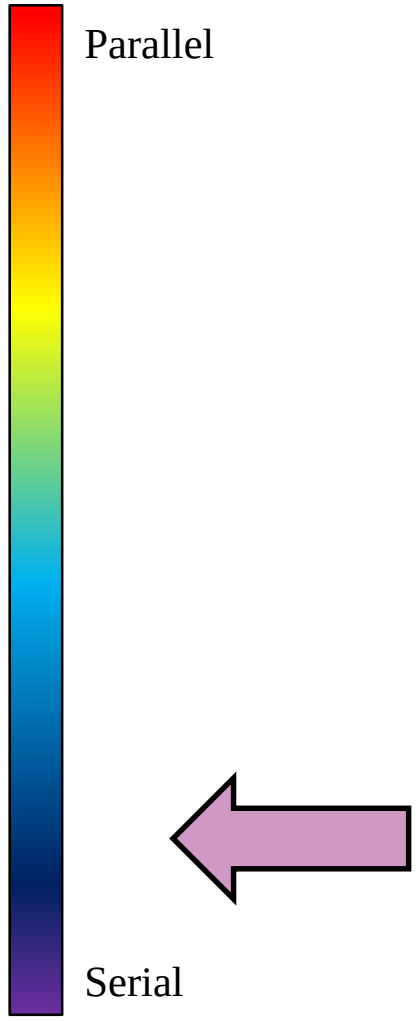
ATP: brainstem summary

WB-RT 25 Gy @ 2.5 Gy/fr
3D CRT (GBM) 60 Gy @ 2 Gy/fr

Dose (Gy), or dose/volume parameters (EUD)	**Outcome**
D_{max} < 54	<5%
$D_{1\text{-}10cc}$ < 59	<5%

Permanent cranial neuropathy or necrosis

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



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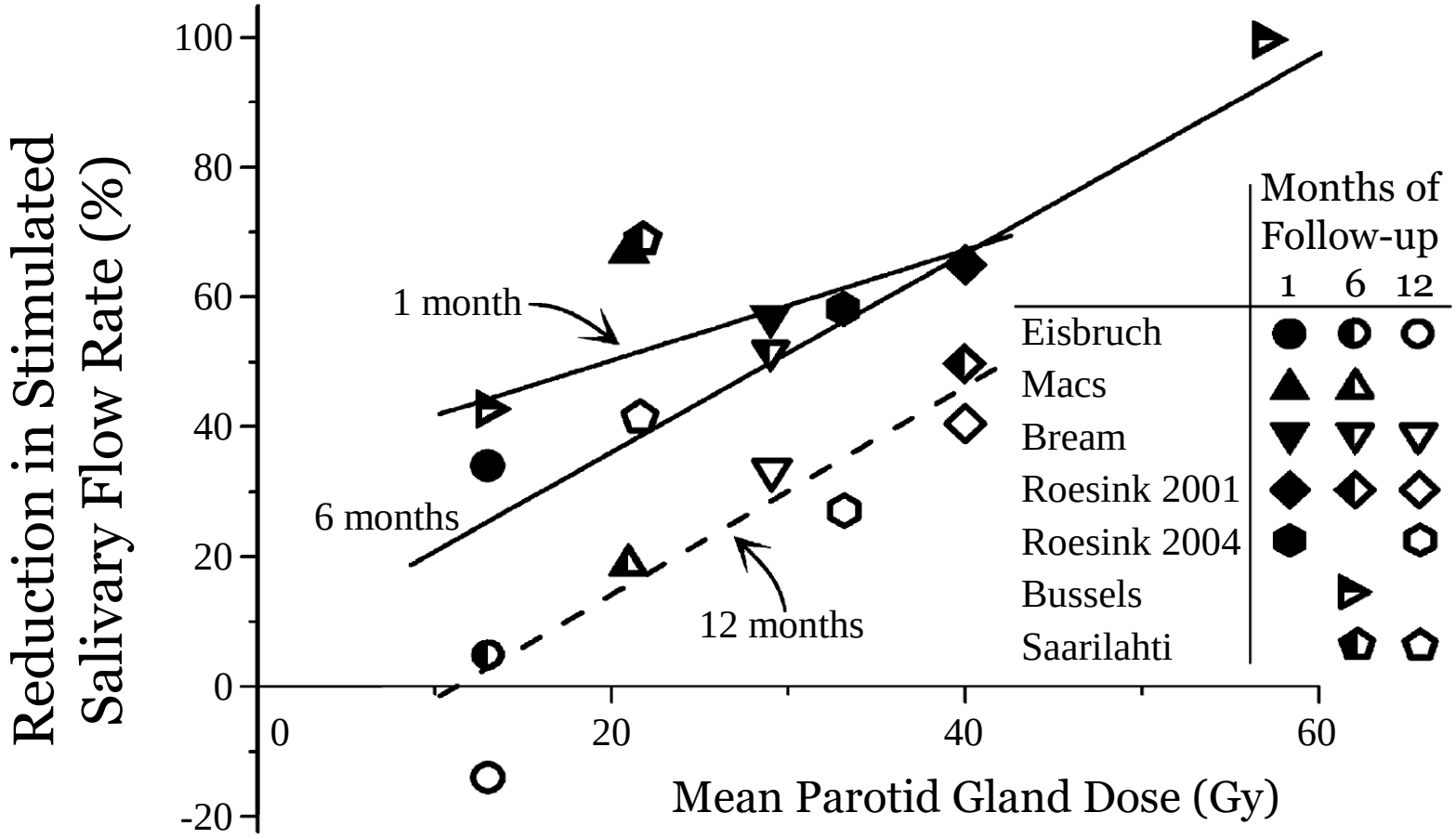
Parameters for clinical outcome: Salivary glands

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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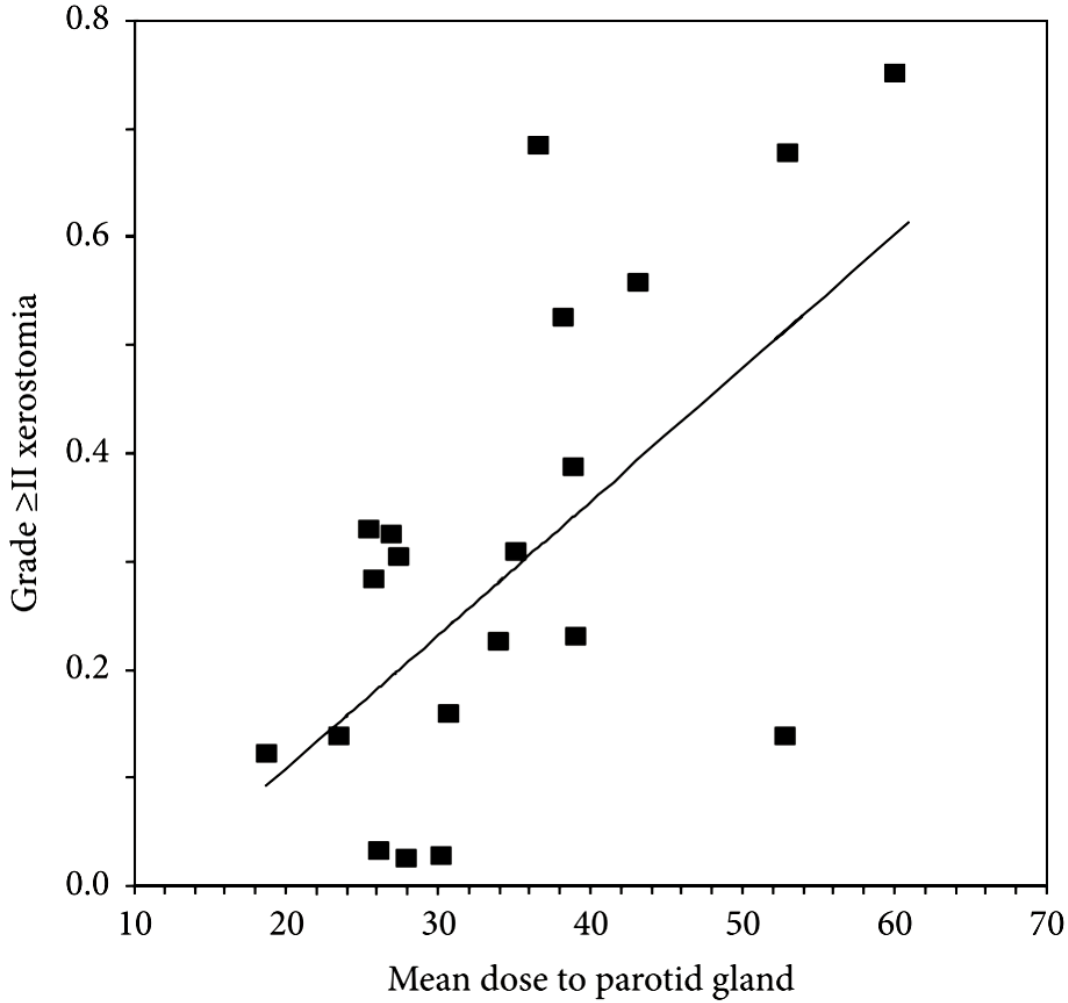
Parameters for clinical outcome: Salivary glands

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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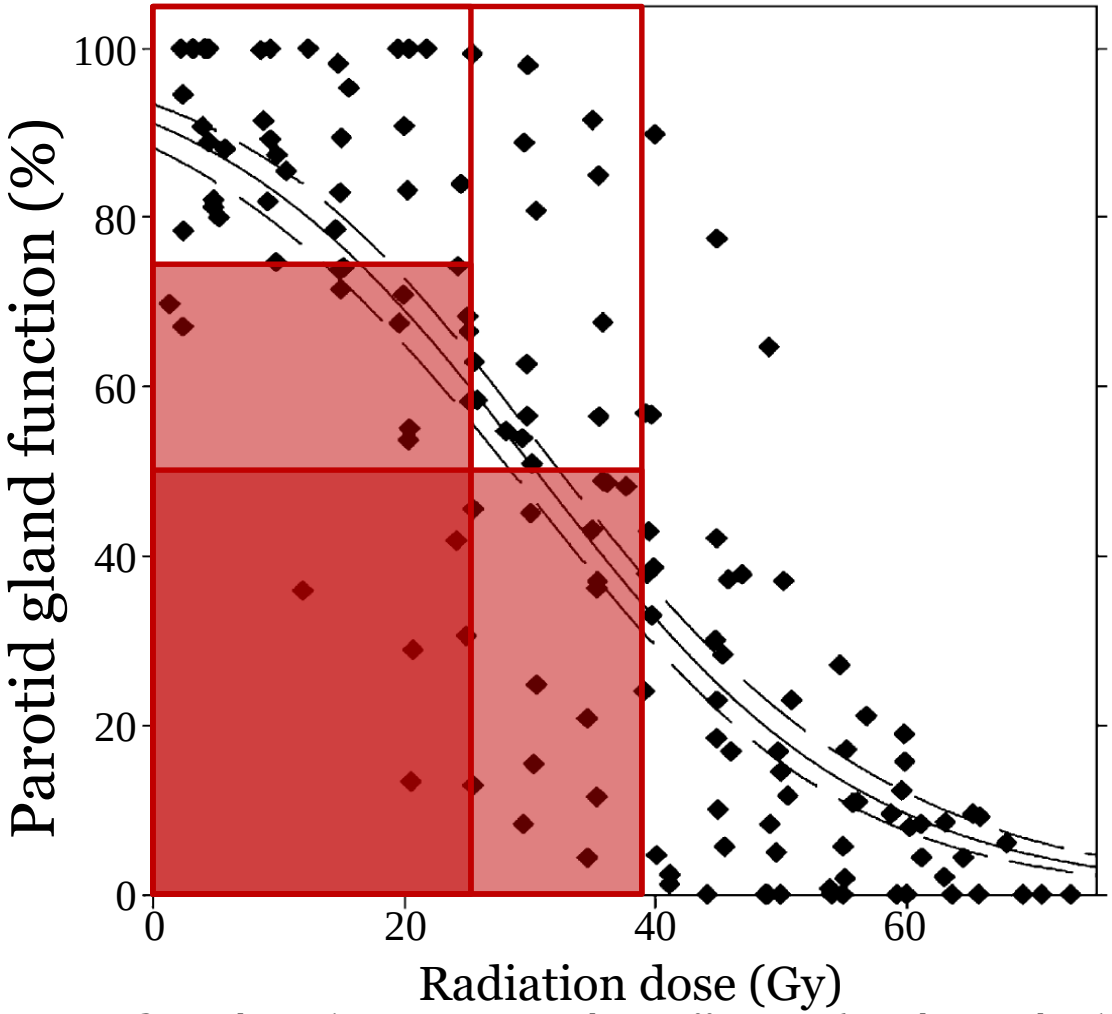
Parameters for clinical outcome: Salivary glands

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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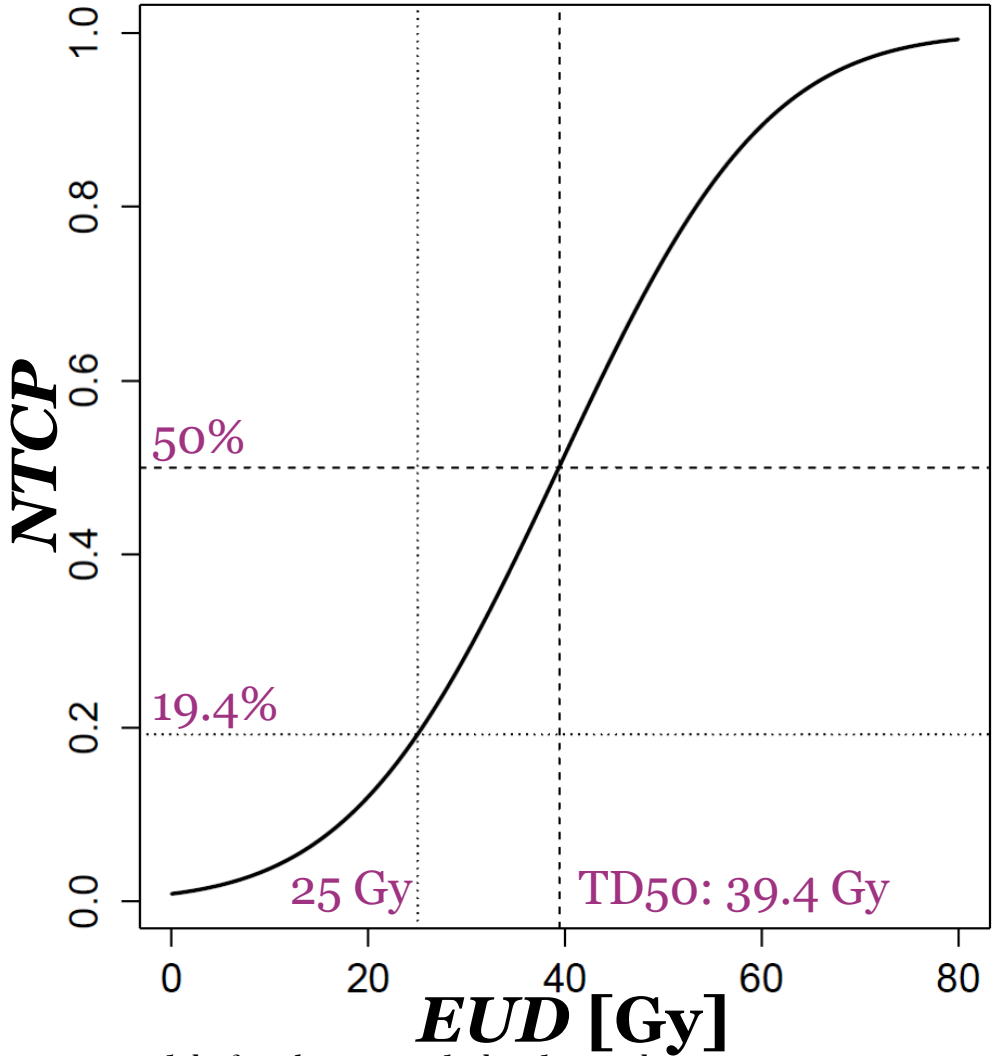
Parameters for clinical outcome: Salivary glands

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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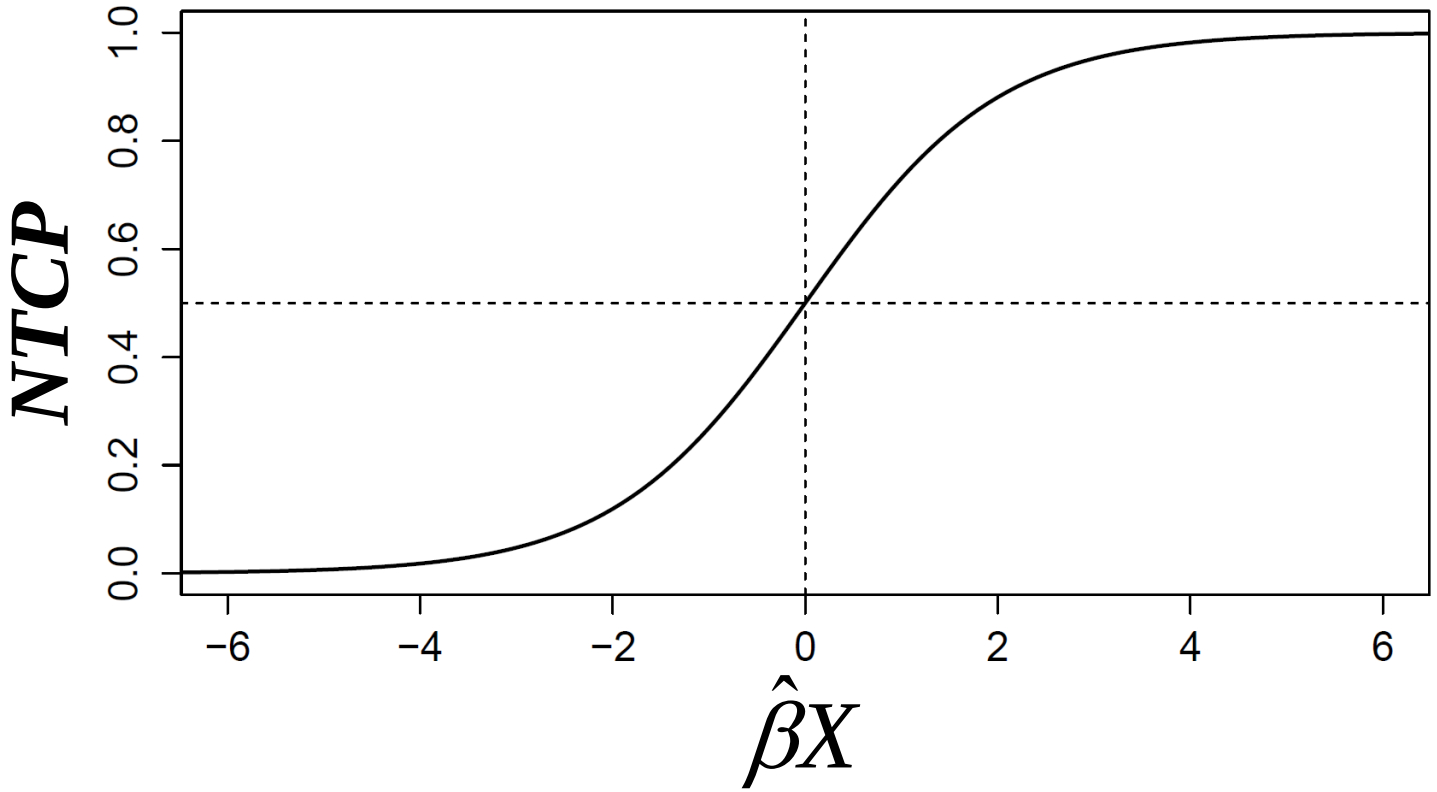
Parameters for clinical outcome: Salivary glands

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

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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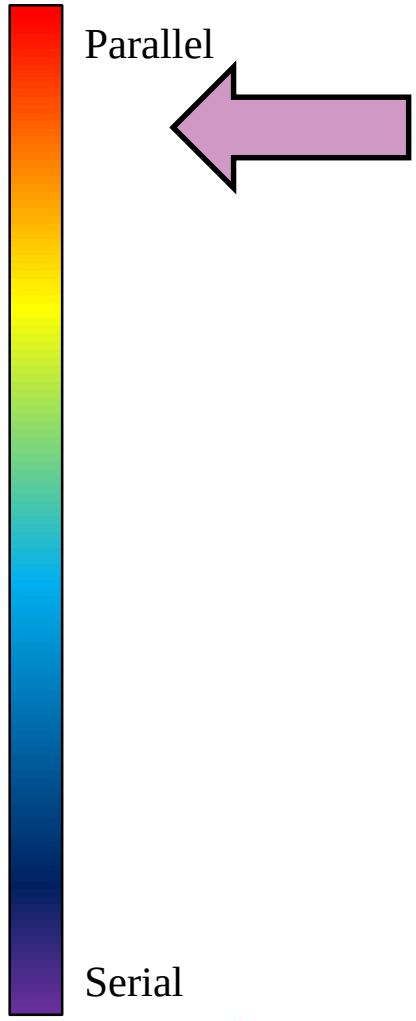
ATP: parotid glands summary

Bilateral parotid irradiation at standard fractionation

Dose (Gy), or dose/volume parameters	**Outcome**
D_{mean} < 25	<20%
D_{mean} < 39	<50%

Long term parotid salivary function reduced to <25% of pre-RT level

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



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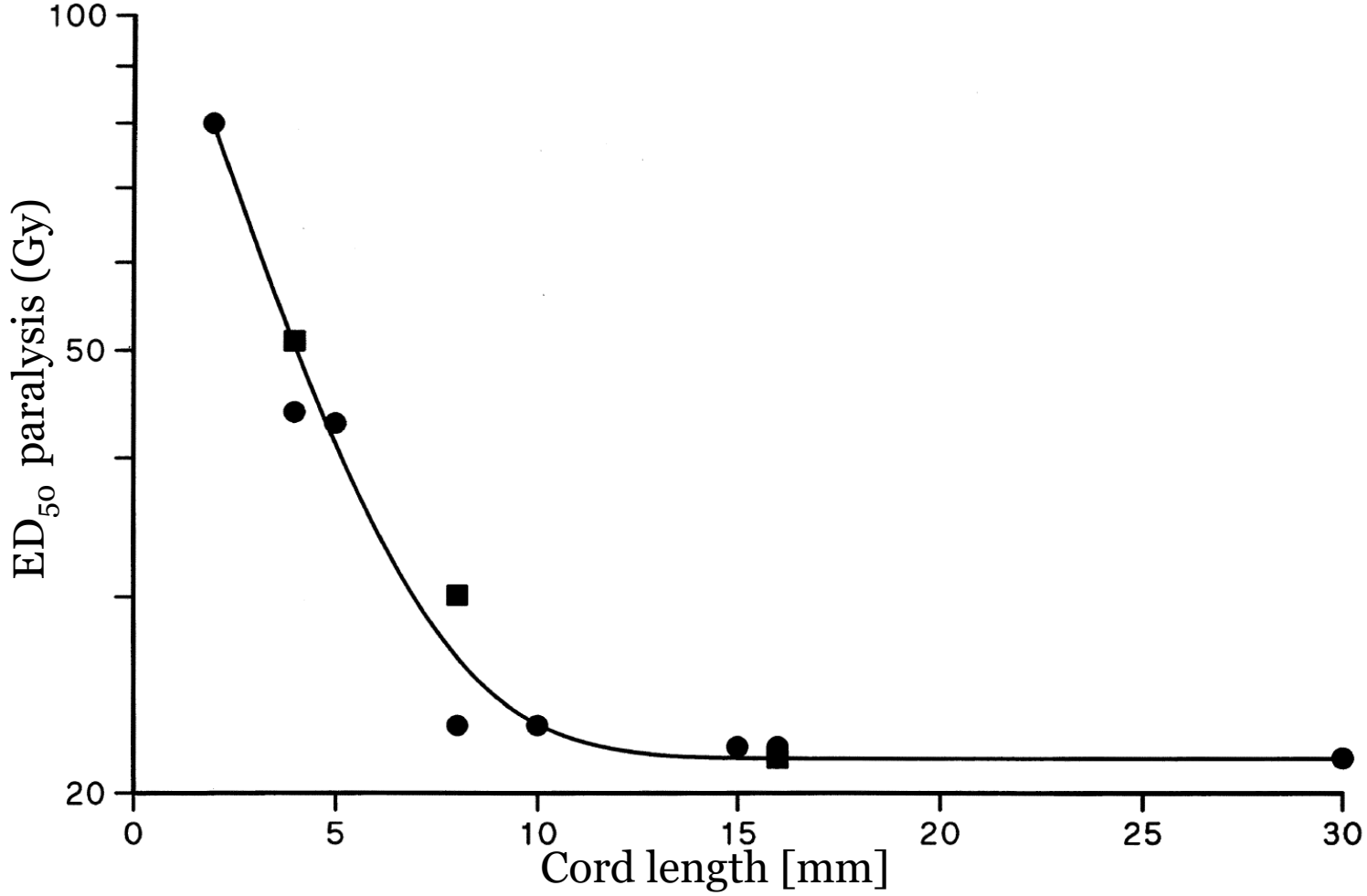
Parameters for clinical outcome: Small bowel

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



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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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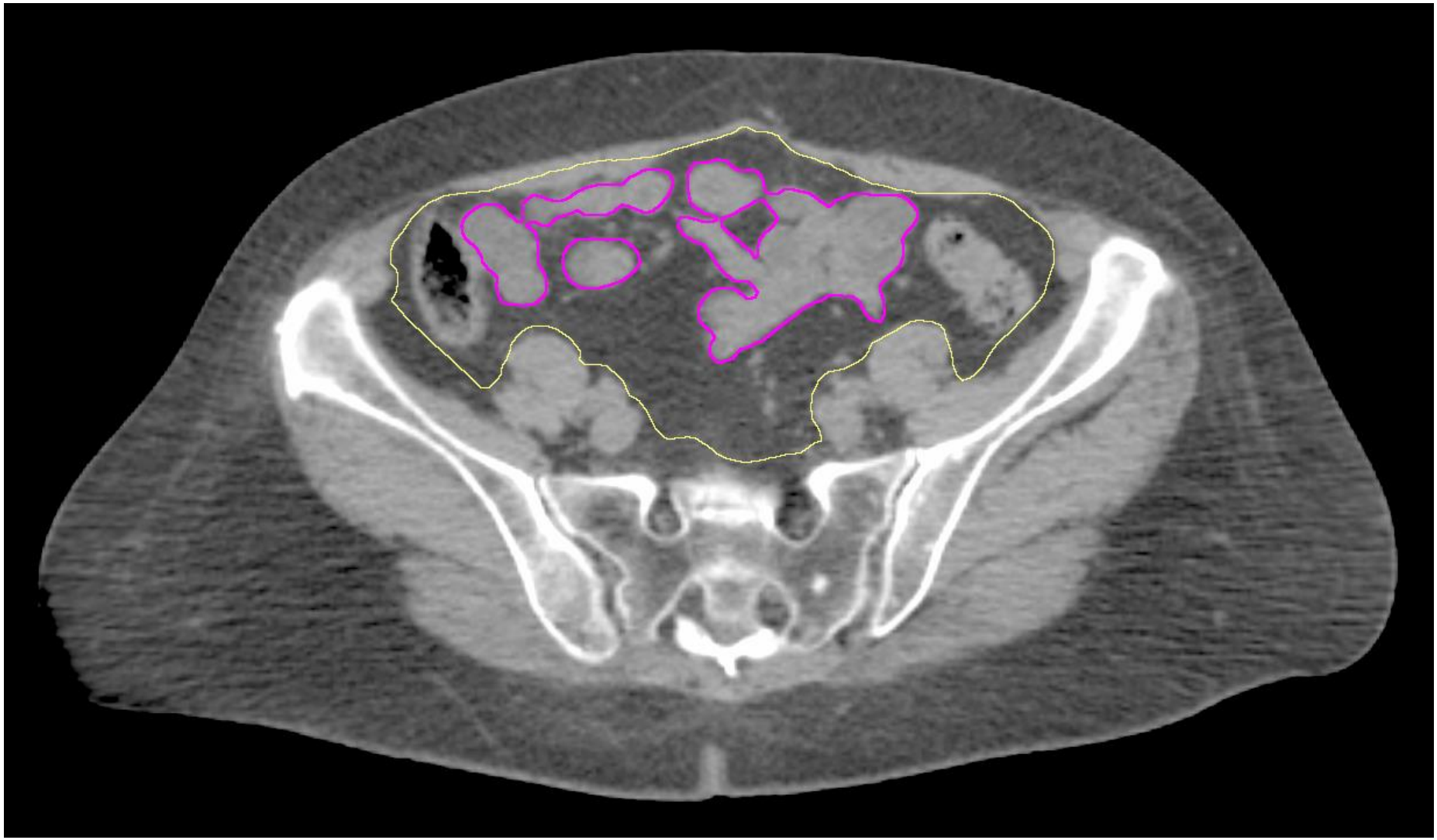
Parameters for clinical outcome: Small bowel

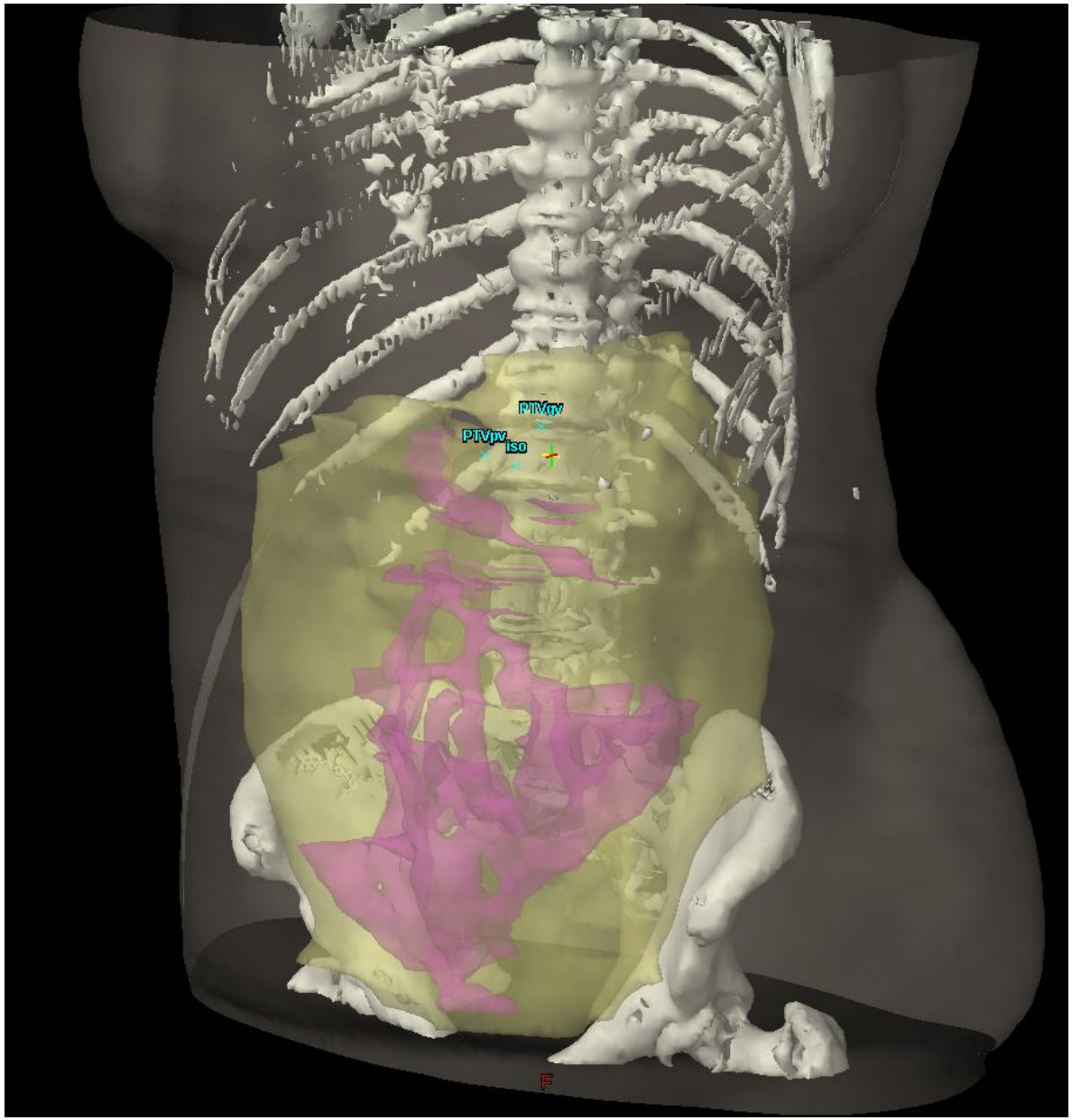
Problems in evaluating small bowel toxicity:

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



Parameters for clinical outcome: Small bowel



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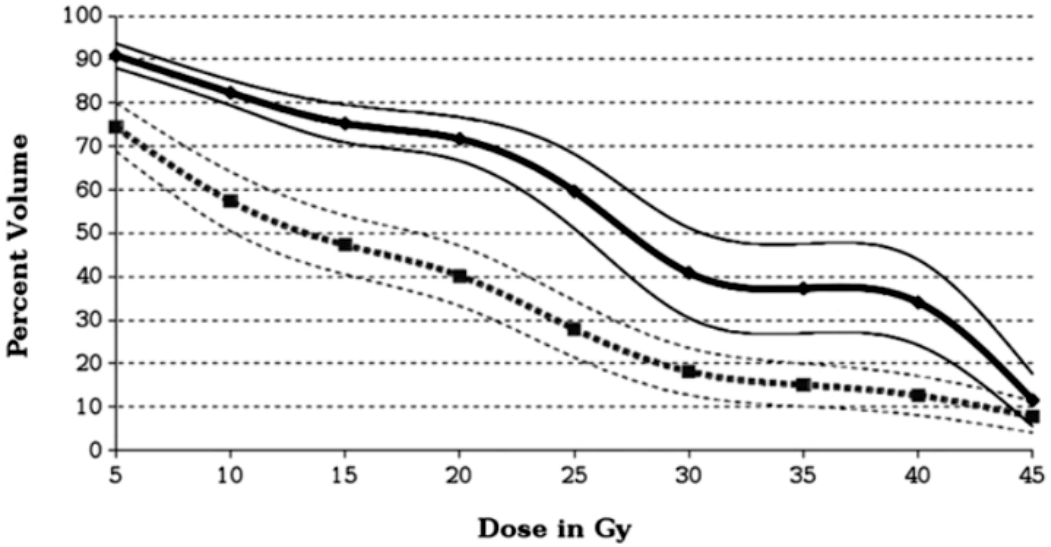
Parameters for clinical outcome: Small bowel

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



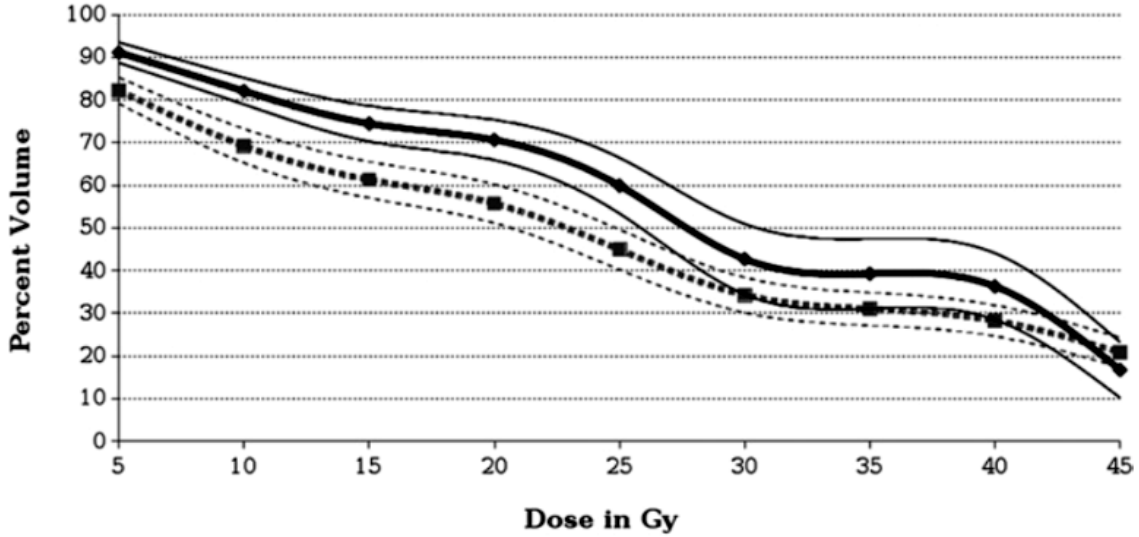


Table 3 ROC analysis for small bowel and peritoneal space volumes and association with grade ≥3 acute small bowel toxicity

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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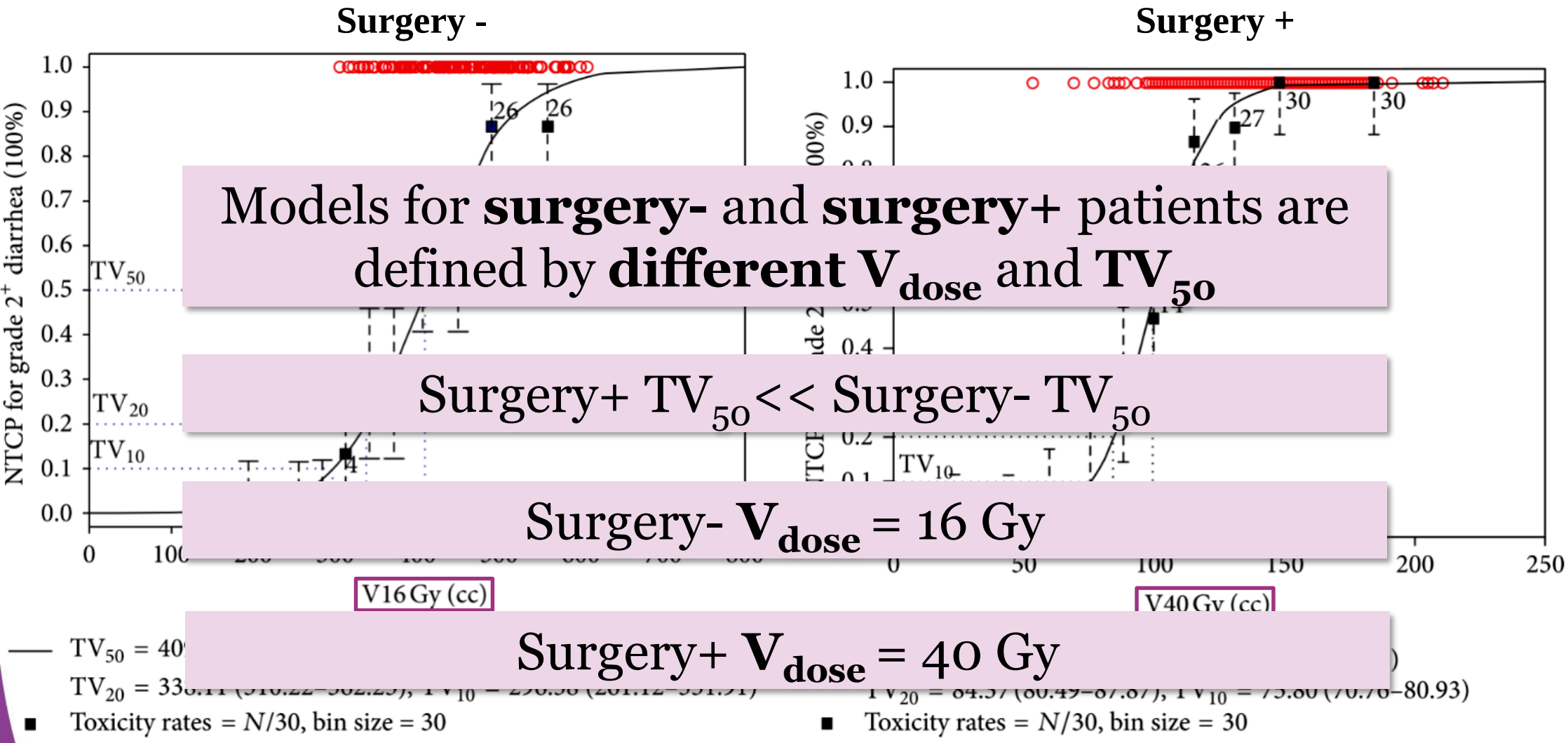
Parameters for clinical outcome: Small bowel



Models for **surgery-** and **surgery+** patients are defined by **different V_{dose}** and **TV_{50}**

Surgery+ TV_{50} << Surgery- TV_{50}

Surgery- V_{dose} = 16 Gy

Surgery+ V_{dose} = 40 Gy

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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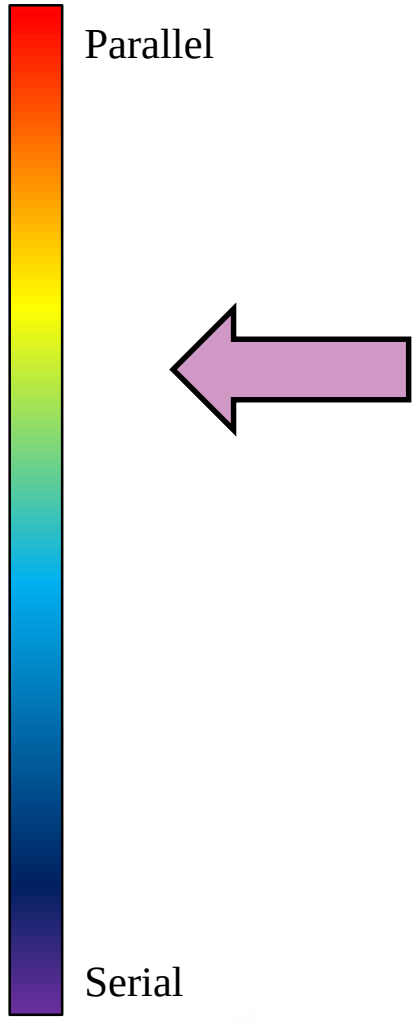
ATP: small bowel summary

Small bowel single loops[1]
Small bowel as peritoneal space[2]

Dose (Gy), or dose/volume parameters	**Outcome**
[1]V_{15} < 120 cc	<10%
[2]V_{45} < 195 cc	<10%

Grade 3 or worse acute toxicity

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



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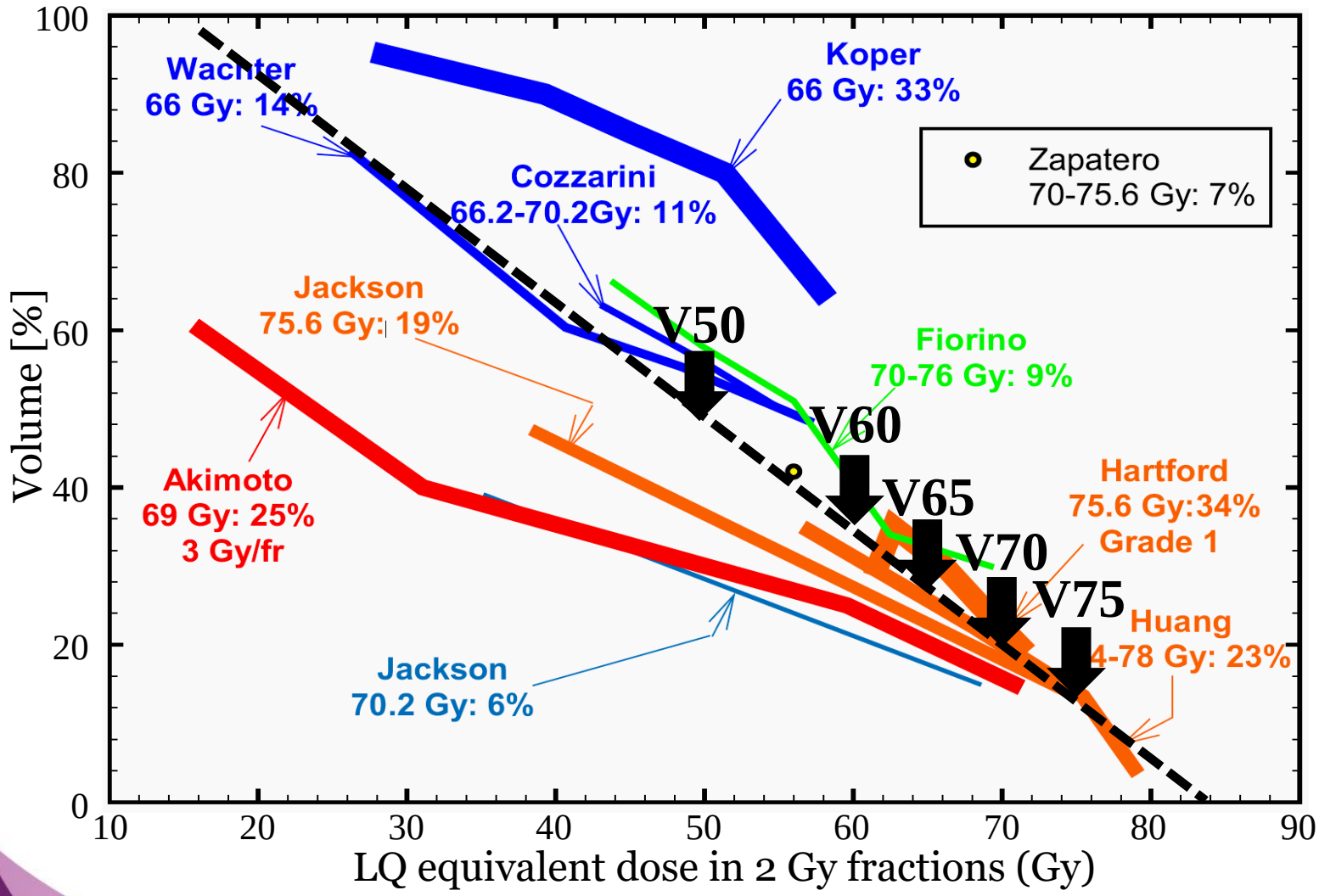
Parameters for clinical outcome: Rectum

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
Whole organ	3D-CRT	Grade ≥ 3 late rectal toxicity	V60 <35%	<10	
		Grade ≥ 2 late rectal toxicity,		<15	
Whole organ	3D-CRT	Grade ≥ 3 late rectal toxicity	V65 <25%	<10	
		Grade ≥ 2 late rectal toxicity,		<15	
Whole organ	3D-CRT	Grade ≥ 3 late rectal toxicity	V70 <20%	<10	
		Grade ≥ 2 late rectal toxicity,		<15	
Whole organ	3D-CRT	Grade ≥ 3 late rectal toxicity	V75 <15%	<10	
		Grade ≥ 2 late rectal toxicity,		<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 an *a* higher lower than other endpoints (11)
- 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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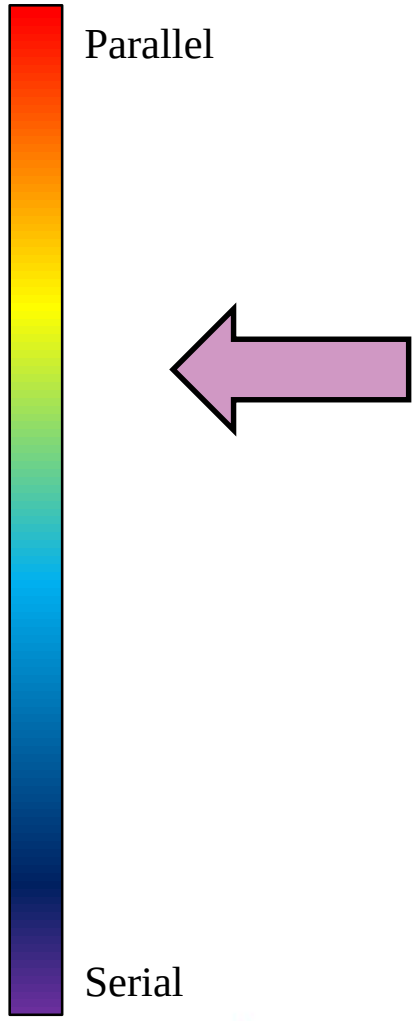
ATP: rectum summary

Rectum from anal verge to the turn into sigmoid colon

Dose (Gy), or dose/volume parameters	**Outcome**
$V_{50} < 50\%$ $V_{60} < 35\%$ $V_{65} < 25\%$ $V_{70} < 20\%$ $V_{75} < 20\%$	**<15%**

Grade 2 or worse late toxicity

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



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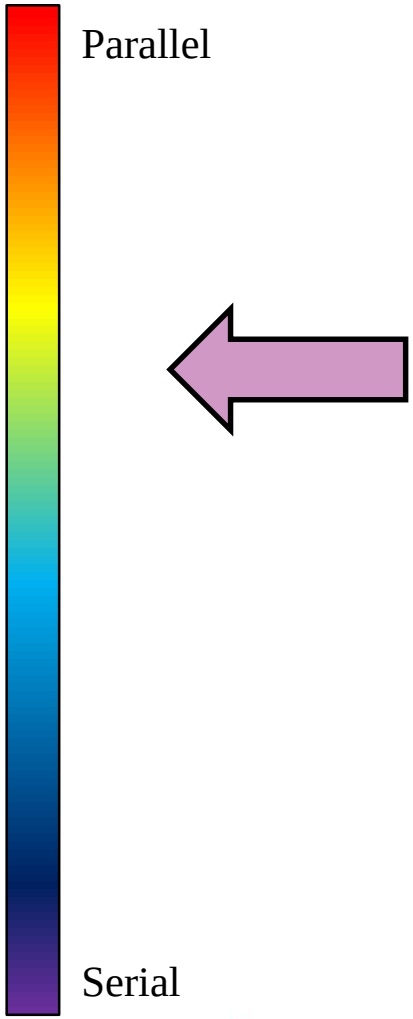
ATP: rectum summary

Rectum from anal verge to the turn into sigmoid colon

Dose (Gy), or dose/volume parameters	**Outcome**
$V_{50} < 50\%$ $V_{60} < 35\%$ $V_{65} < 25\%$ $V_{70} < 20\%$ $V_{75} < 20\%$	**<10%**

Grade 3 or worse late toxicity

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



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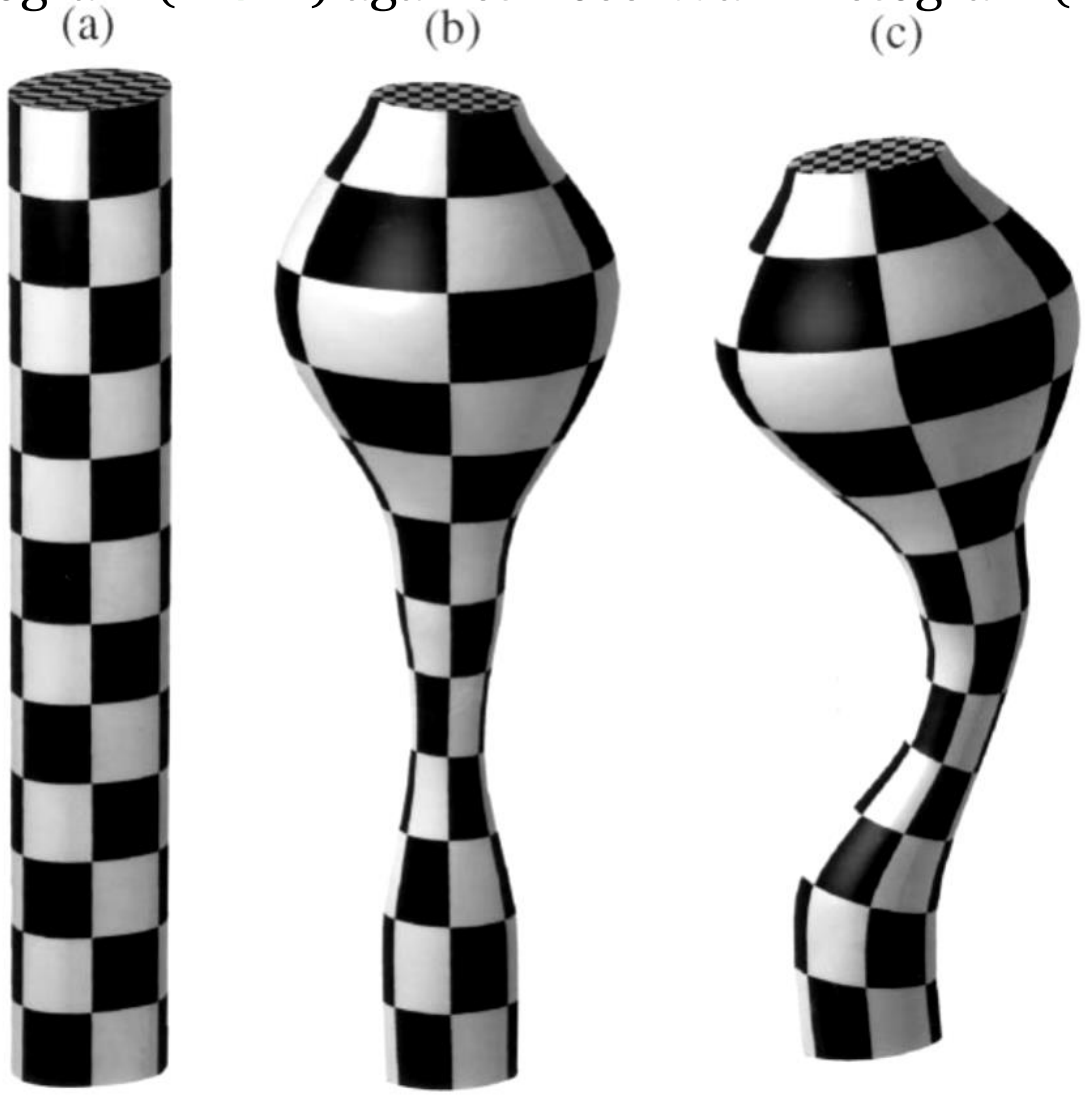
Parameters for clinical outcome: Rectum

- 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)
Mean dose	MD_{50} (Gy)		
	s (Gy^{-1})	0.112 (0.056, 0.174)	0.154 (0.083, 0.230)
	LL		
Cutoff dose			
Parallel model			
	v_{50}		
	LL	−60.46	−57.83

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

Model	AIC		AUC	
			DVH	DWH
Lyman model	126.9	121.4	0.731	0.763
Mean-dose model	124.9	121.0	0.733	0.765
			0.727	0.761
			0.731	0.759

Criterion; AUC = togram; DWH = g characteristic.

DWH better predicts Rectal Toxicity than DVH

The difference in model accuracy is not so high

$AvAUC_{DVH}$ = **0,73**

$AvAUC_{DWH}$ = **0,76**

- 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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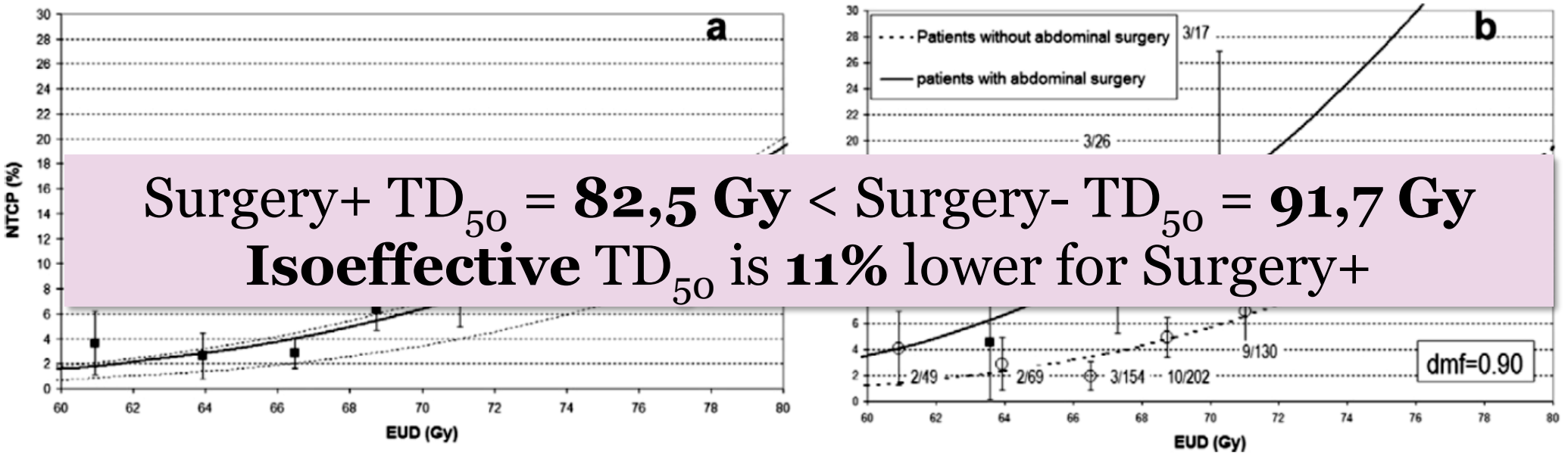
Parameters for clinical outcome: Rectum

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



Surgery+ TD_{50} = **82,5 Gy** < Surgery- TD_{50} = **91,7 Gy**
Isoeffective TD_{50} is **11%** lower for Surgery+

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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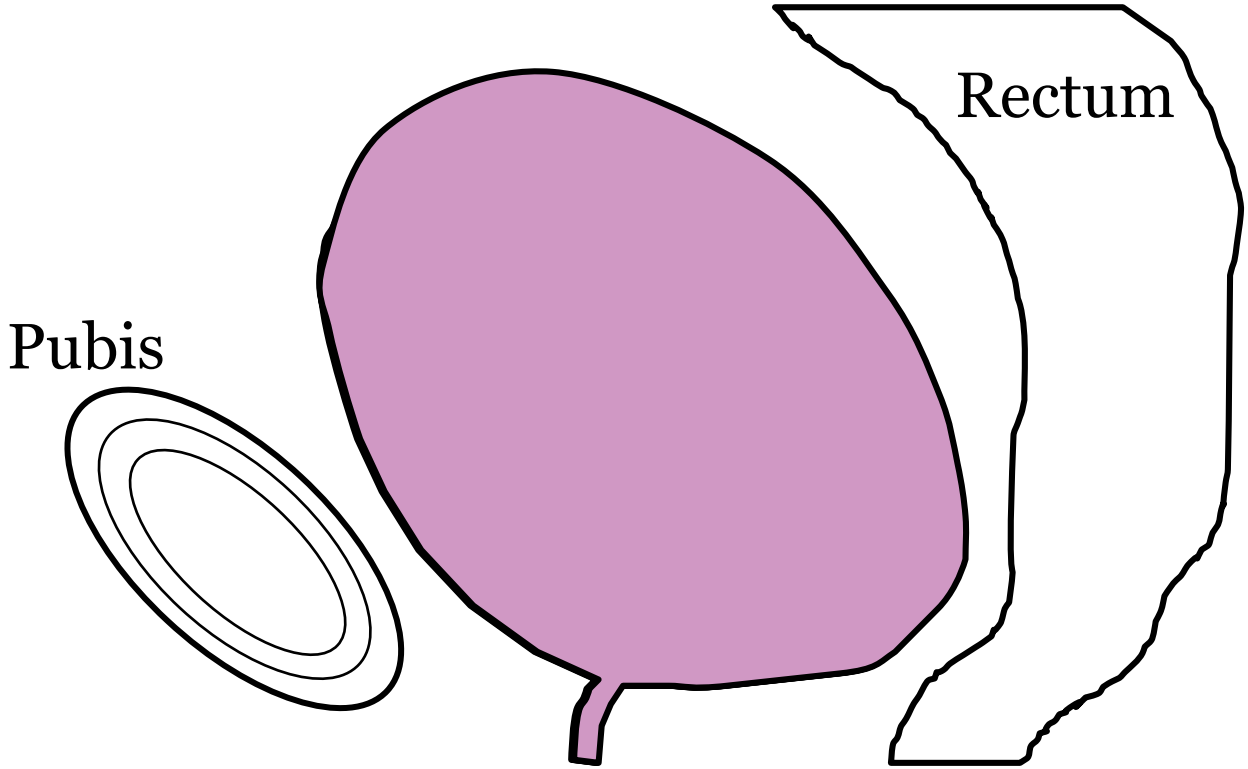
Parameters for clinical outcome: Urinary bladder

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
4) Asymmetric emptying filling process



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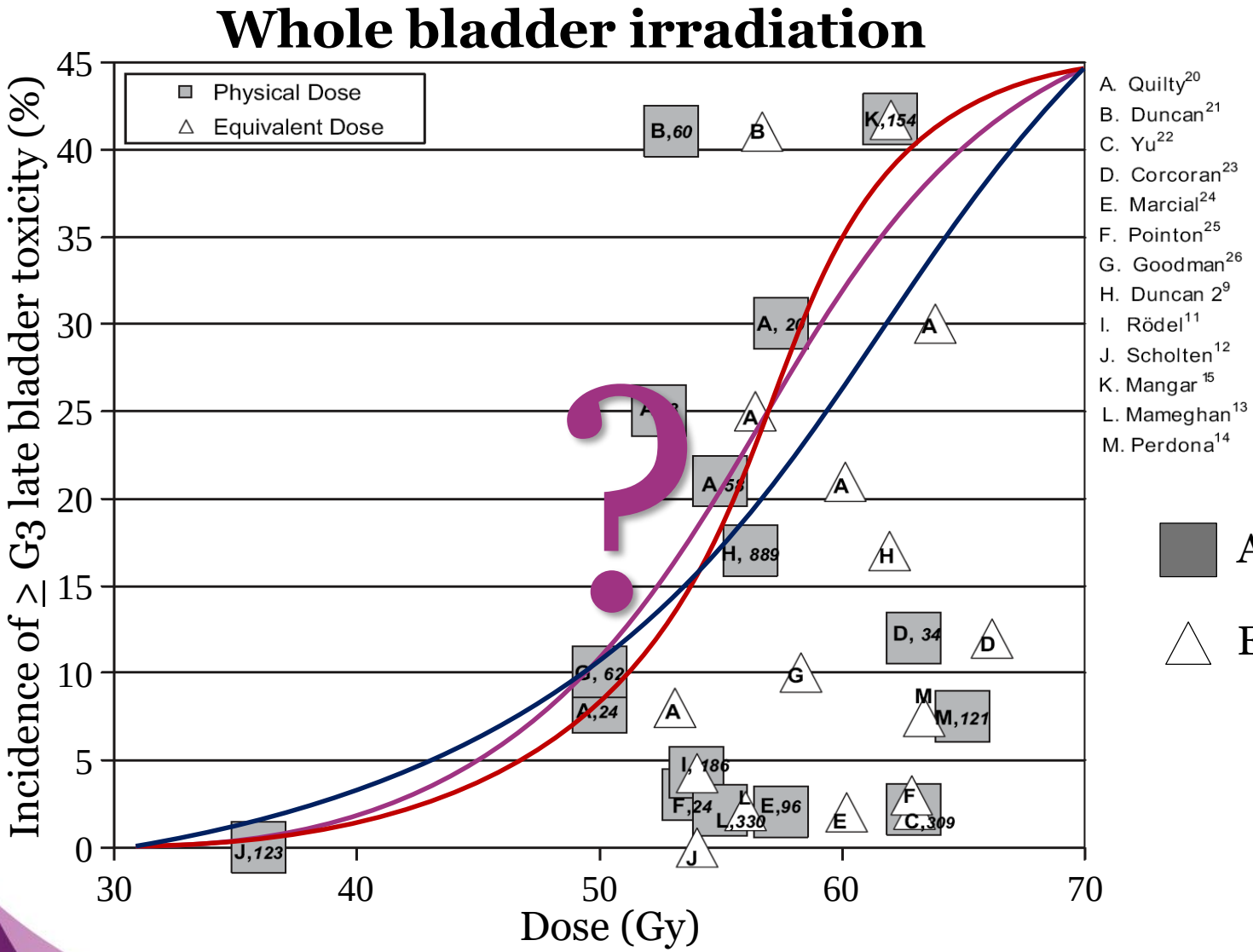
Parameters for clinical outcome: Urinary bladder



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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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.

Parameters for clinical outcome: Urinary bladder

Problems in urinary bladder toxicity evaluation:

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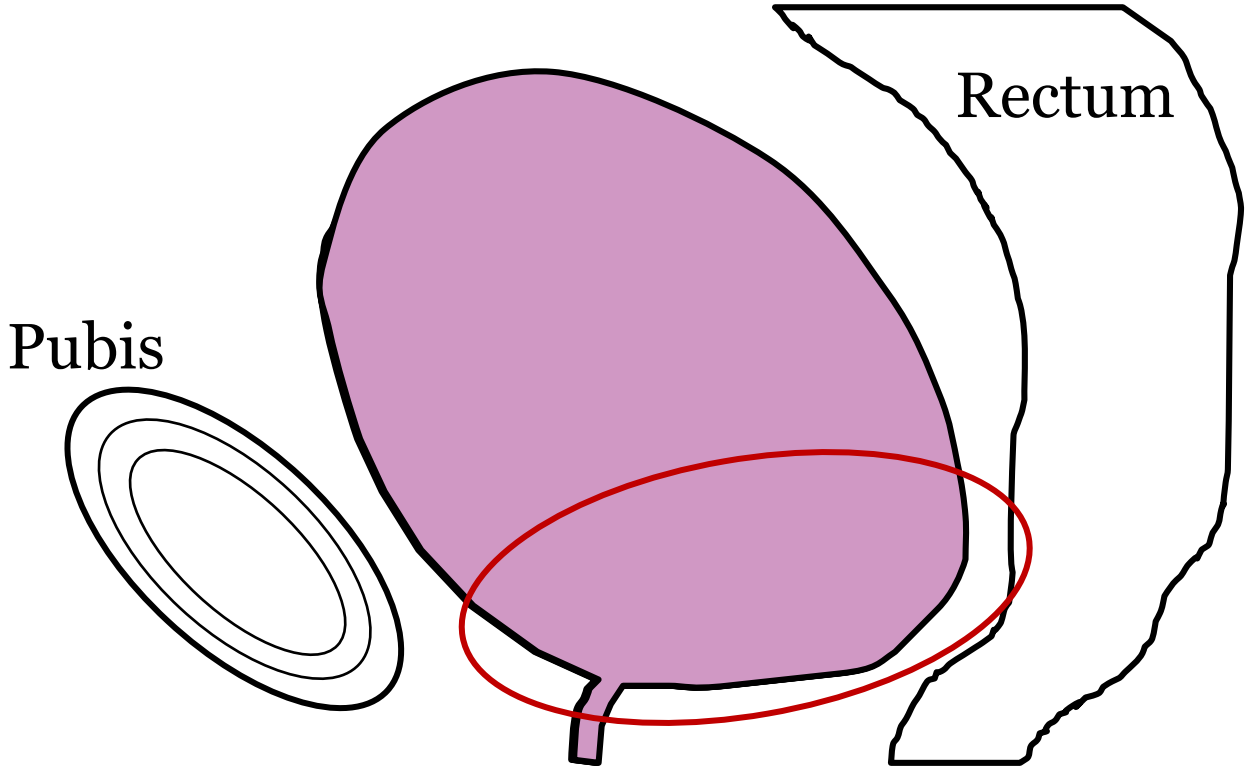

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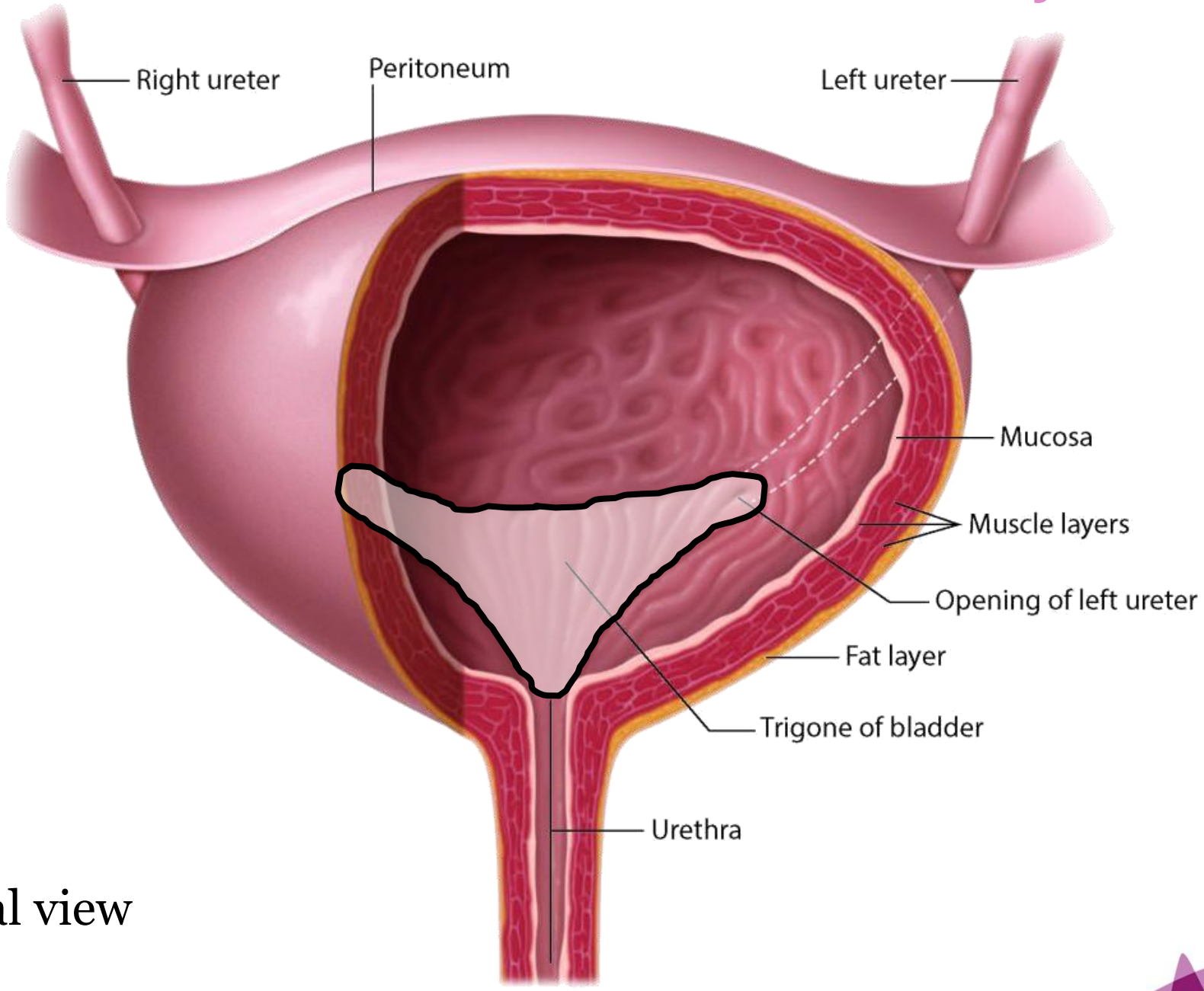
Parameters for clinical outcome: Urinary bladder



Frontal view

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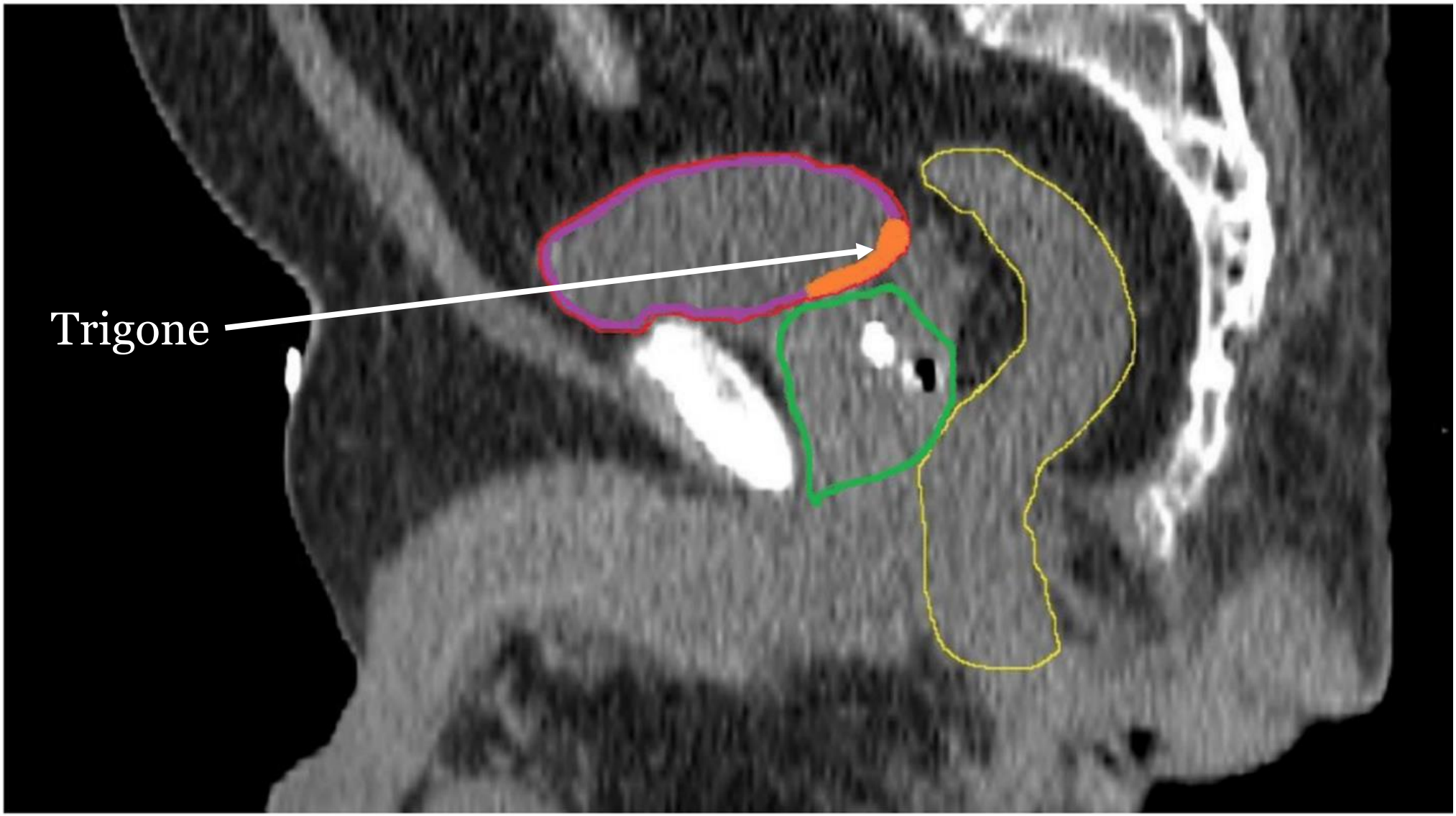
Parameters for clinical outcome: Urinary bladder



Schaake W, Van Der Schaaf A, Van Dijk L V., van den Bergh ACM, Langendijk JA. Development of a prediction model for late urinary incontinence, hematuria, pain and voiding frequency among irradiated prostate cancer patients. PLoS One. 2018;13:1–12.

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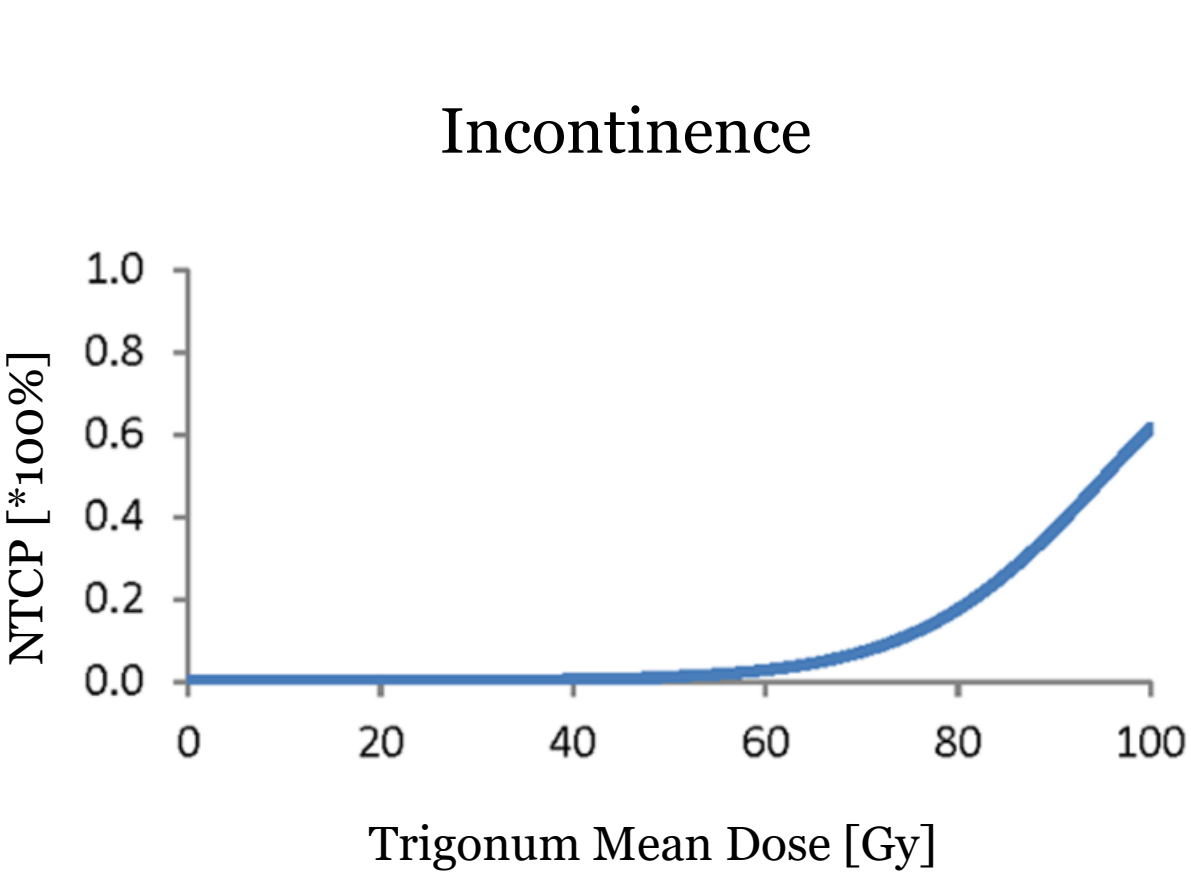
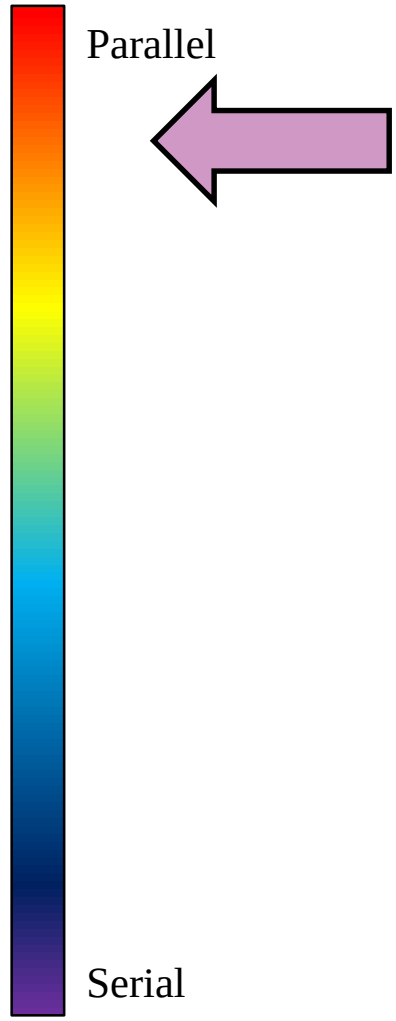
Parameters for clinical outcome: Urinary bladder



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



Schaake W, Van Der Schaaf A, Van Dijk L V., van den Bergh ACM, Langendijk JA. Development of a prediction model for late urinary incontinence, hematuria, pain and voiding frequency among irradiated prostate cancer patients. PLoS One. 2018;13:1–12.

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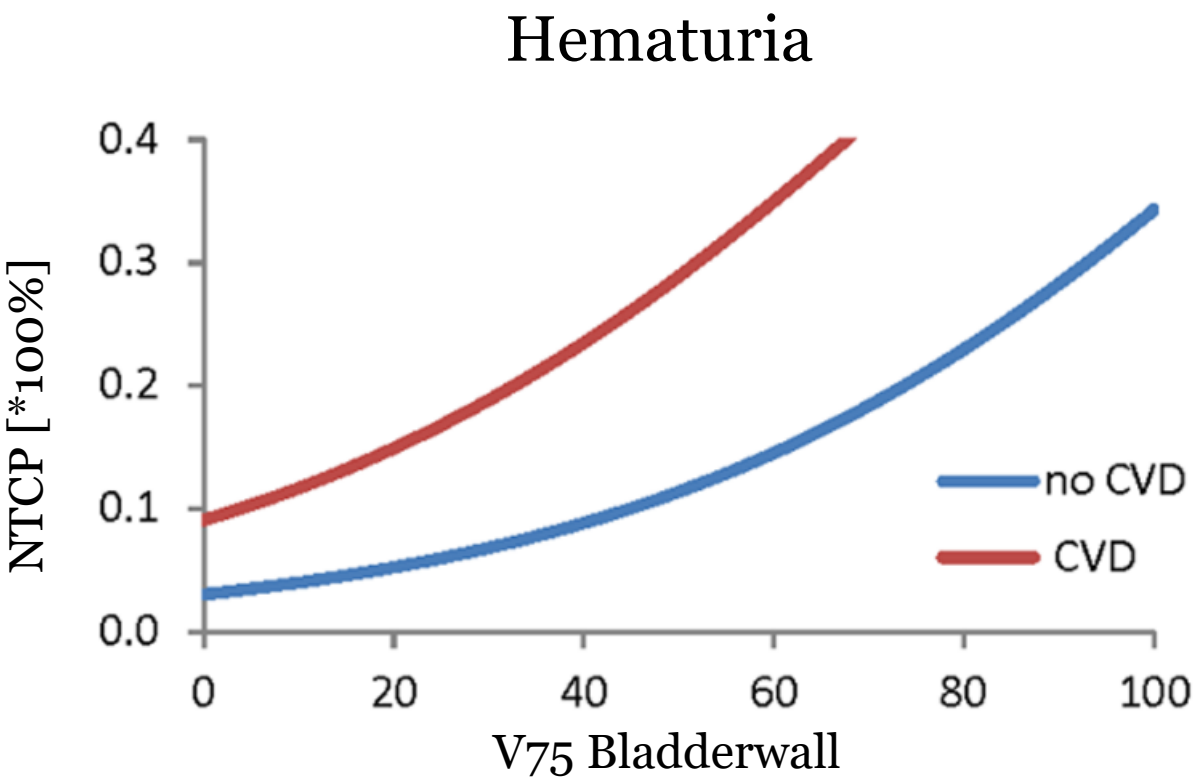
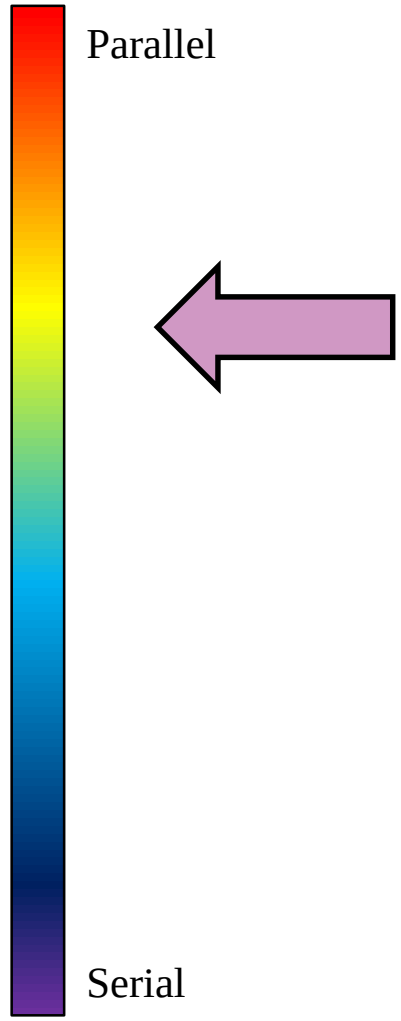
Parameters for clinical outcome: Urinary bladder



* CVD: cardiovascular disease

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



Schaake W, Van Der Schaaf A, Van Dijk L V., van den Bergh ACM, Langendijk JA. Development of a prediction model for late urinary incontinence, hematuria, pain and voiding frequency among irradiated prostate cancer patients. PLoS One. 2018;13:1–12.

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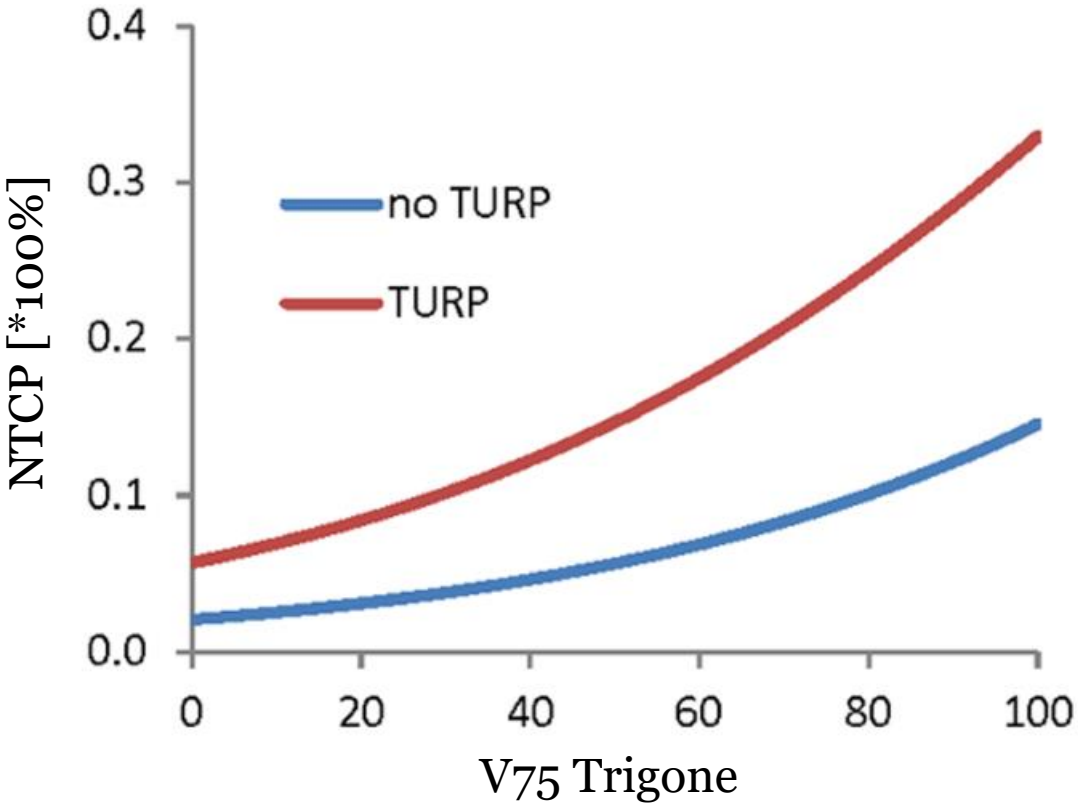
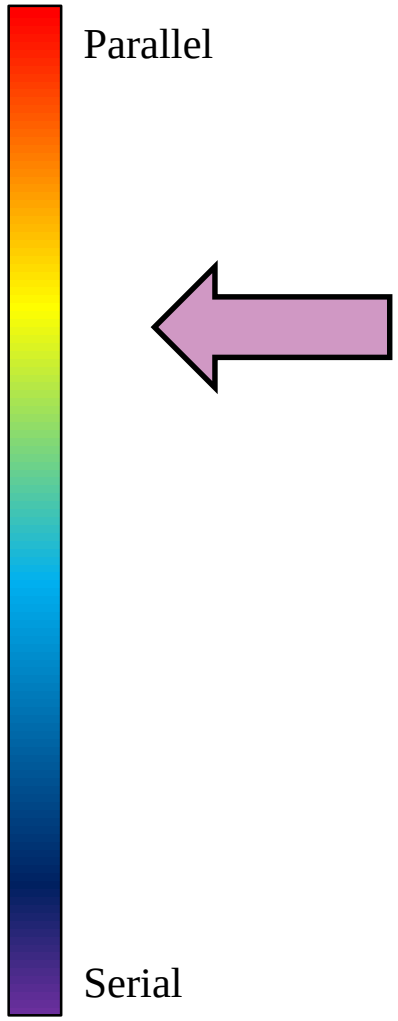
Parameters for clinical outcome: Urinary bladder

Pain/discomfort during voiding



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



Schaake W, Van Der Schaaf A, Van Dijk L V., van den Bergh ACM, Langendijk JA. Development of a prediction model for late urinary incontinence, hematuria, pain and voiding frequency among irradiated prostate cancer patients. PLoS One. 2018;13:1–12.

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thank you!

grazie!

ευχαριστίες!

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Planning aspects in breast irradiation

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

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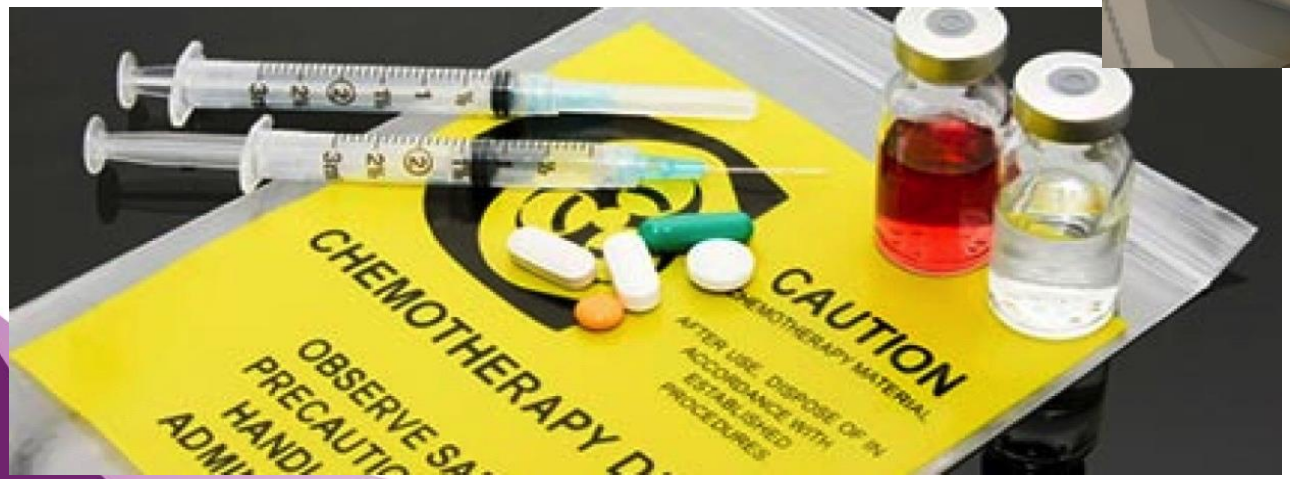
Breast cancer - Multidisciplinary treatment



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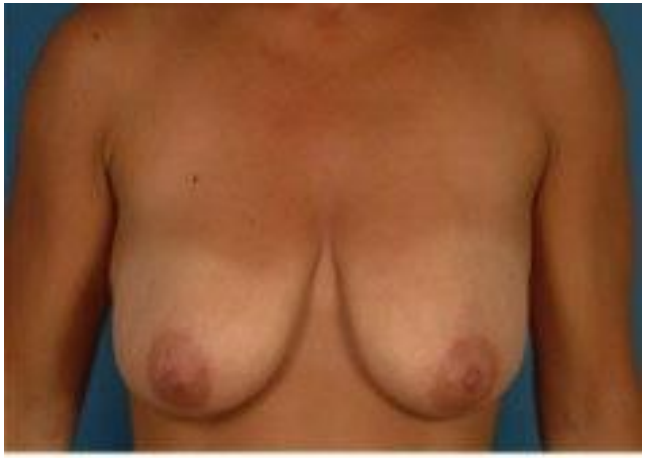
Introduction - Breast cancer radiotherapy

Local treatment:

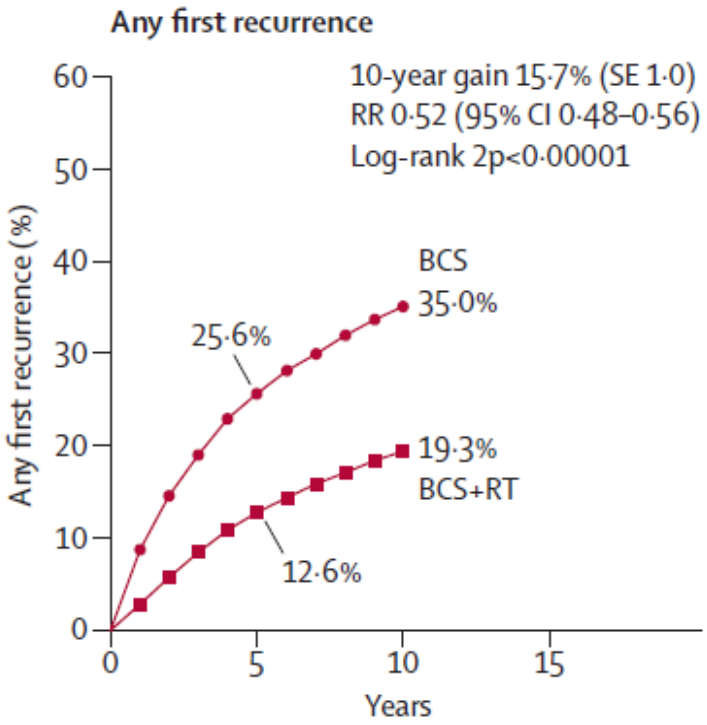
- Breast-conserving therapy:

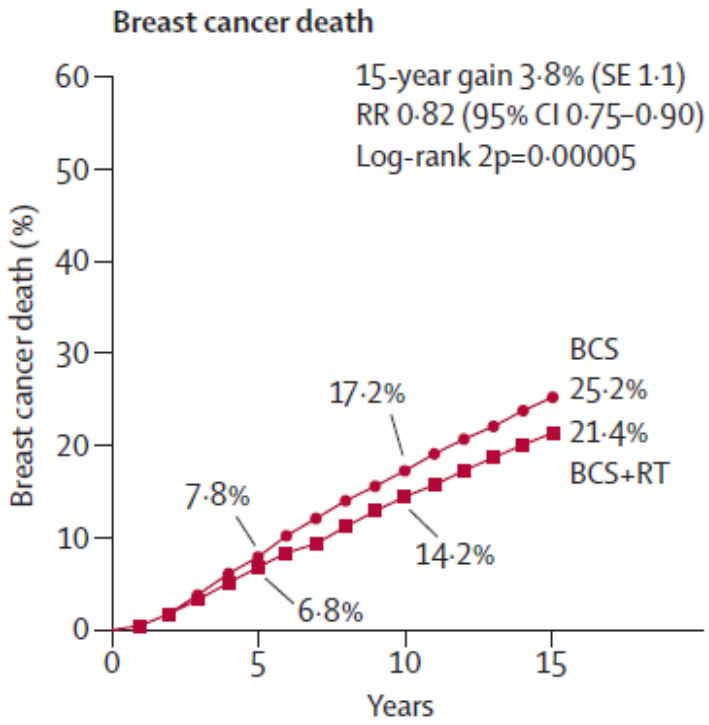
  Breast-conserving surgery →

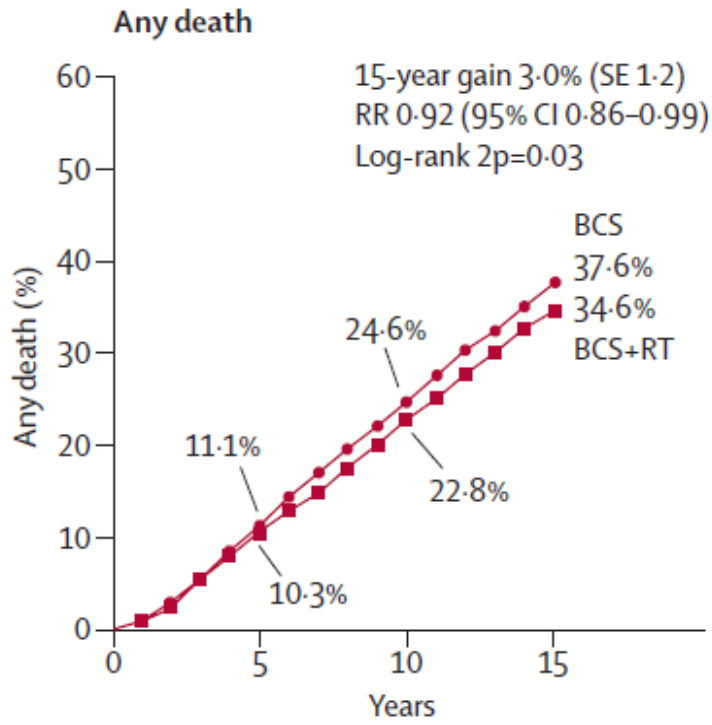
  Whole breast irradiation +/- boost tumor bed



Breast-conserving surgery +/- whole breast RT







EBCTCG Lancet 2011

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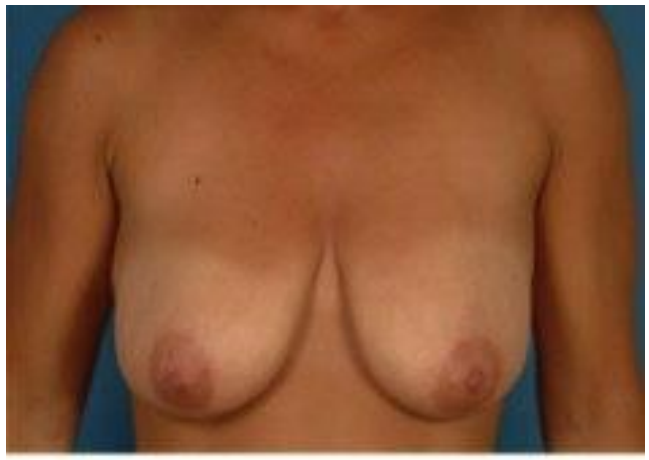
Breast cancer treatment

Local treatment:

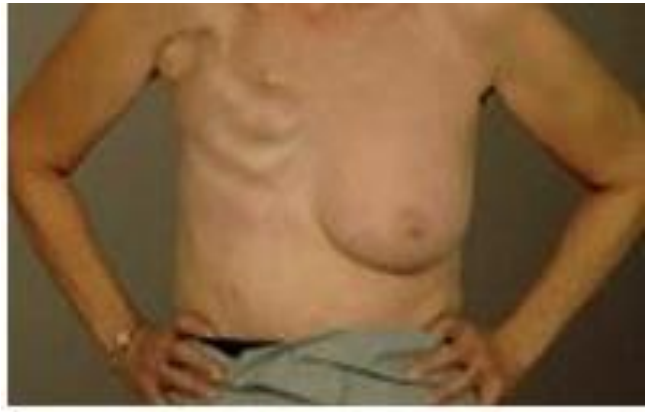
- Breast-conserving therapy:

  Breast-conserving surgery →

  Whole breast irradiation +/- boost tumor bed



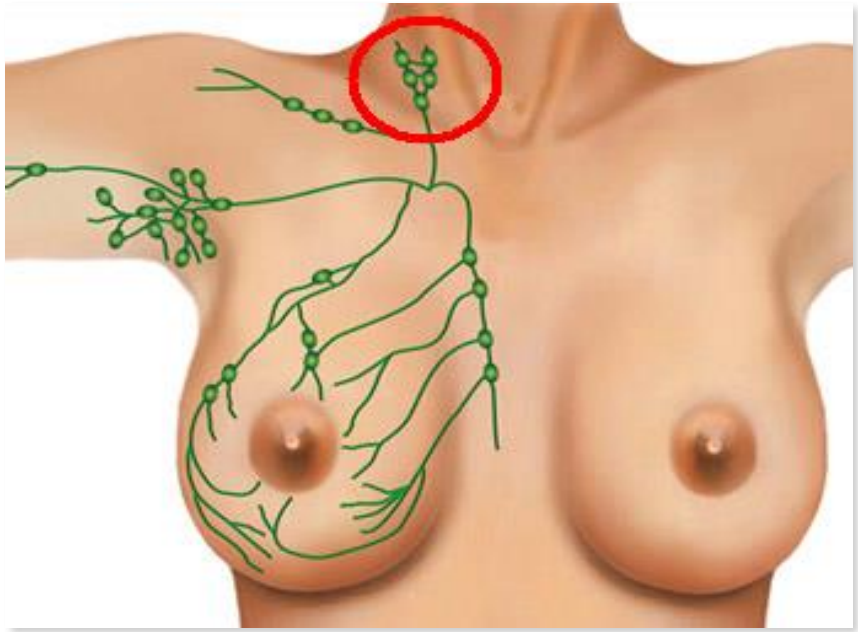
- Mastectomy +/- Radiotherapy Chest wall



Breast cancer treatment

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

- **Regional lymph node treatment:**
  - Axillary lymph node dissection
  - Lymph node irradiation:
    - axilla
    - supraclavicular fossa
    - internal mammary nodes



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Introduction – Survival and Toxicity

During the last decades: **Improved survival**

- Breast cancer screening
- Improved imaging, e.g. digital mammography, tomography, MRI
- Improved surgical and radiotherapeutic techniques
- Increased use of and more effective systemic treatment

Introduction – Survival and Toxicity

During the last decades: **Improved survival**

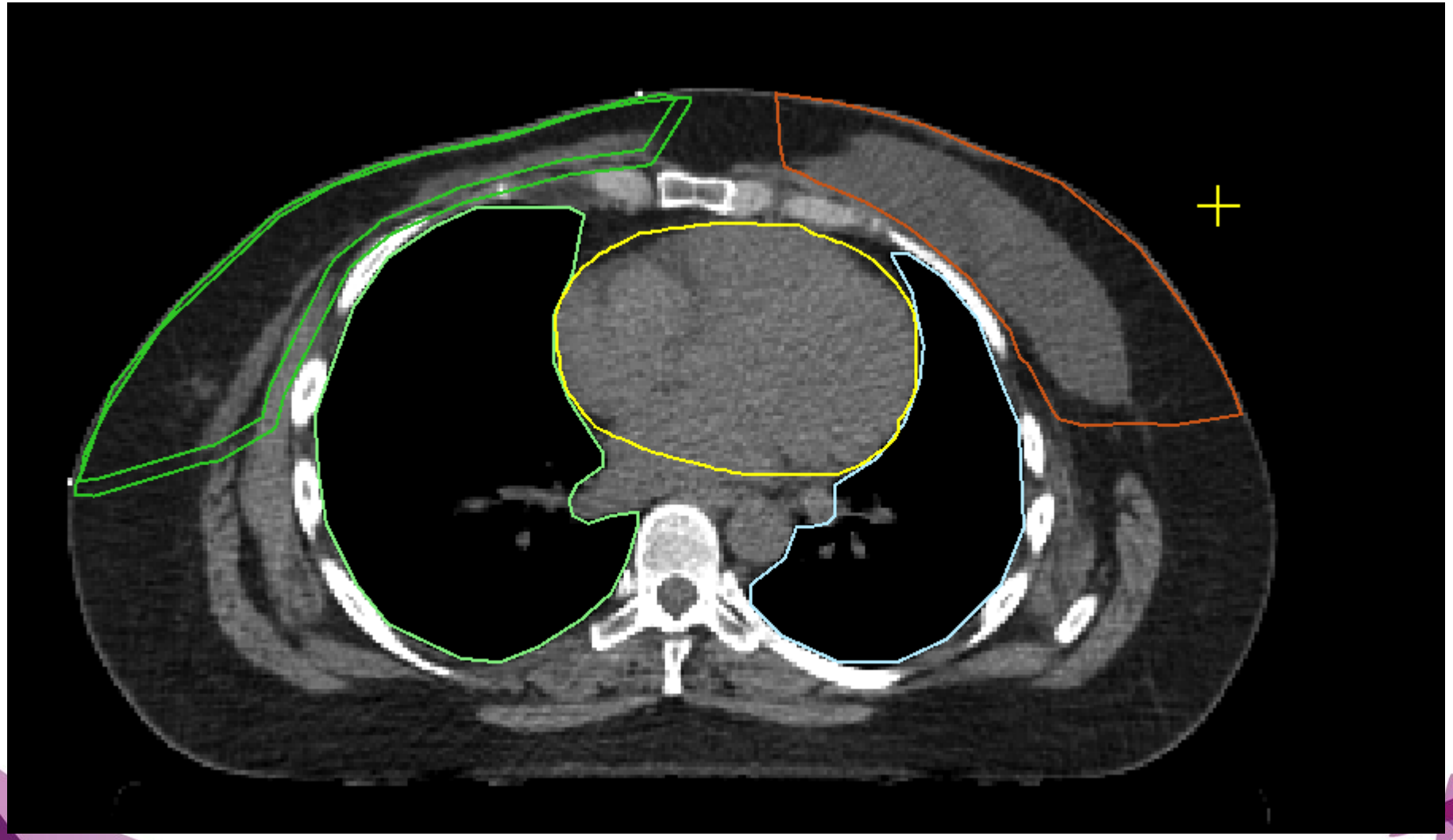
- Breast cancer screening
- Improved imaging, e.g. digital mammography
- Improved surgical and radiotherapeutic techniques
- Increased use of and more effective systemic treatment

Treatment-induced **toxicity** in breast cancer survivors:

- Cardiac morbidity → decreased quality of life
- Non-breast cancer mortality

Radiotherapy-induced toxicity
Local radiotherapy (Breast / Chest wall)

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



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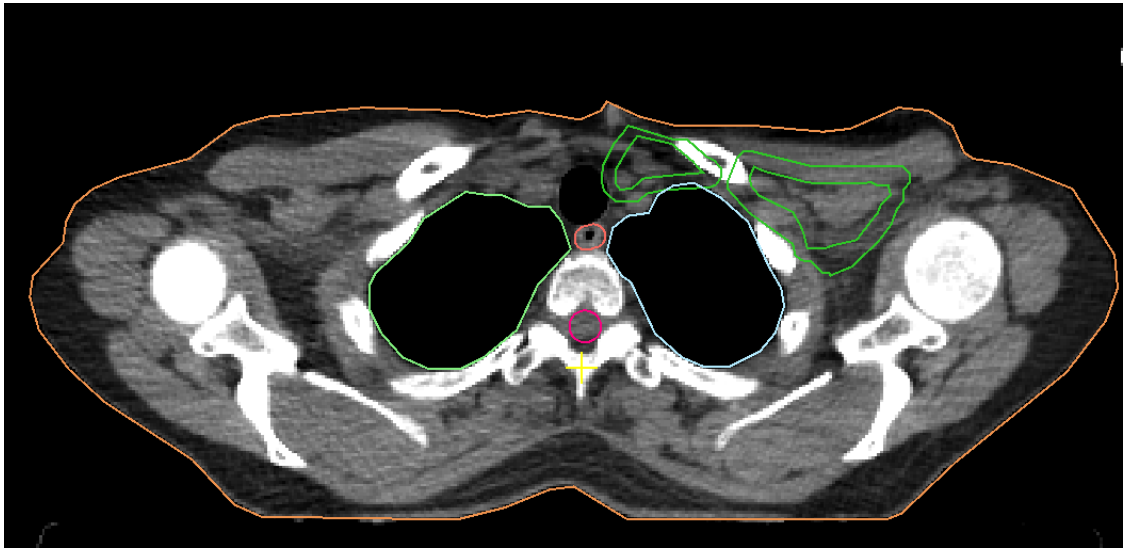
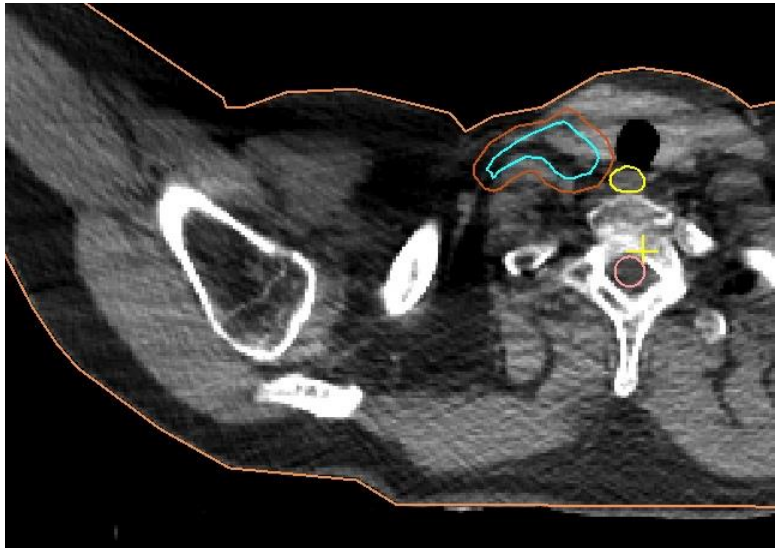
Radiotherapy-induced toxicity
Regional (lymph node) radiotherapy

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





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Which is the most important normal tissue in RT breast cancer?

1. Brachial plexus
2. Skin
3. Contralateral breast
4. Heart
5. Ipsilateral breast
6. Lung
7. Esophagus

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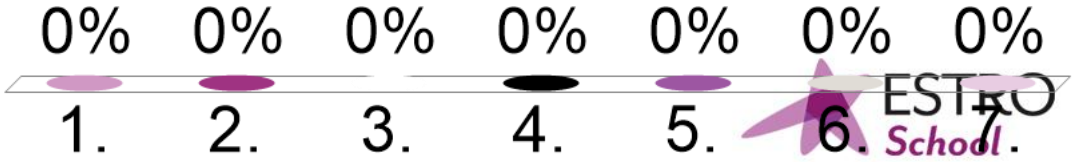
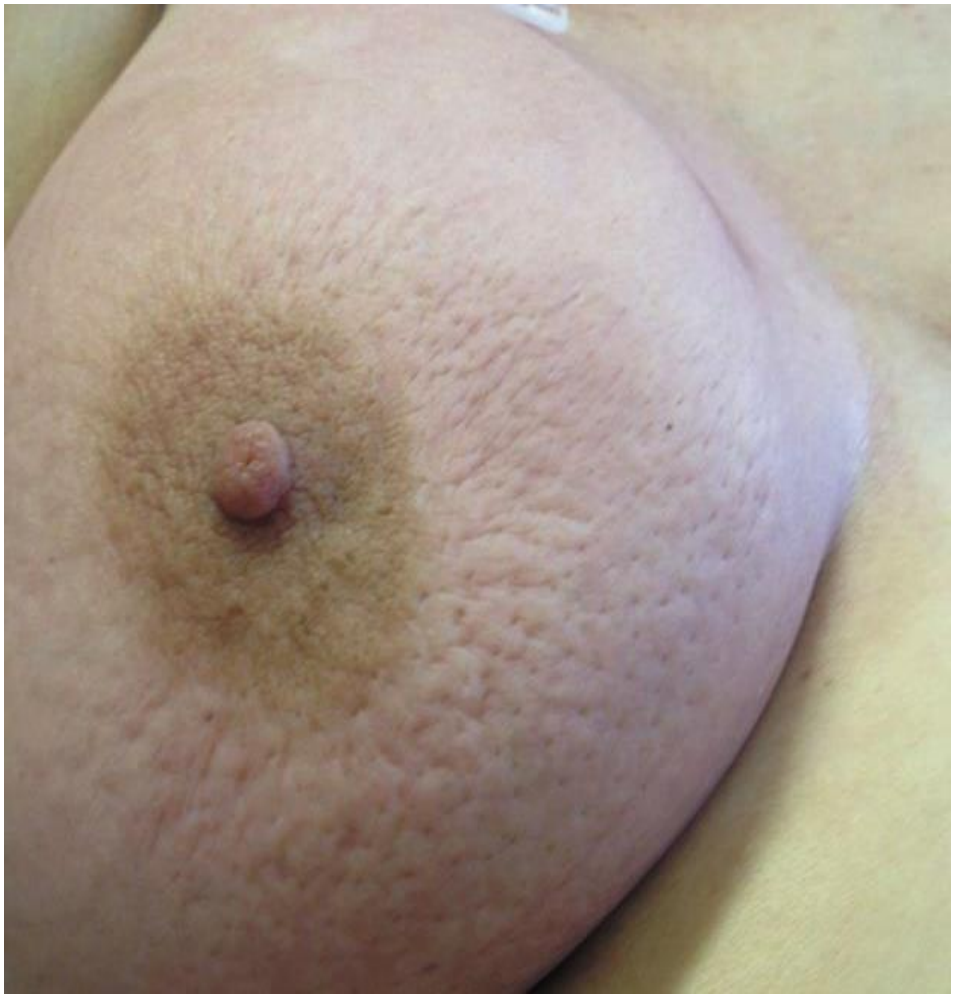
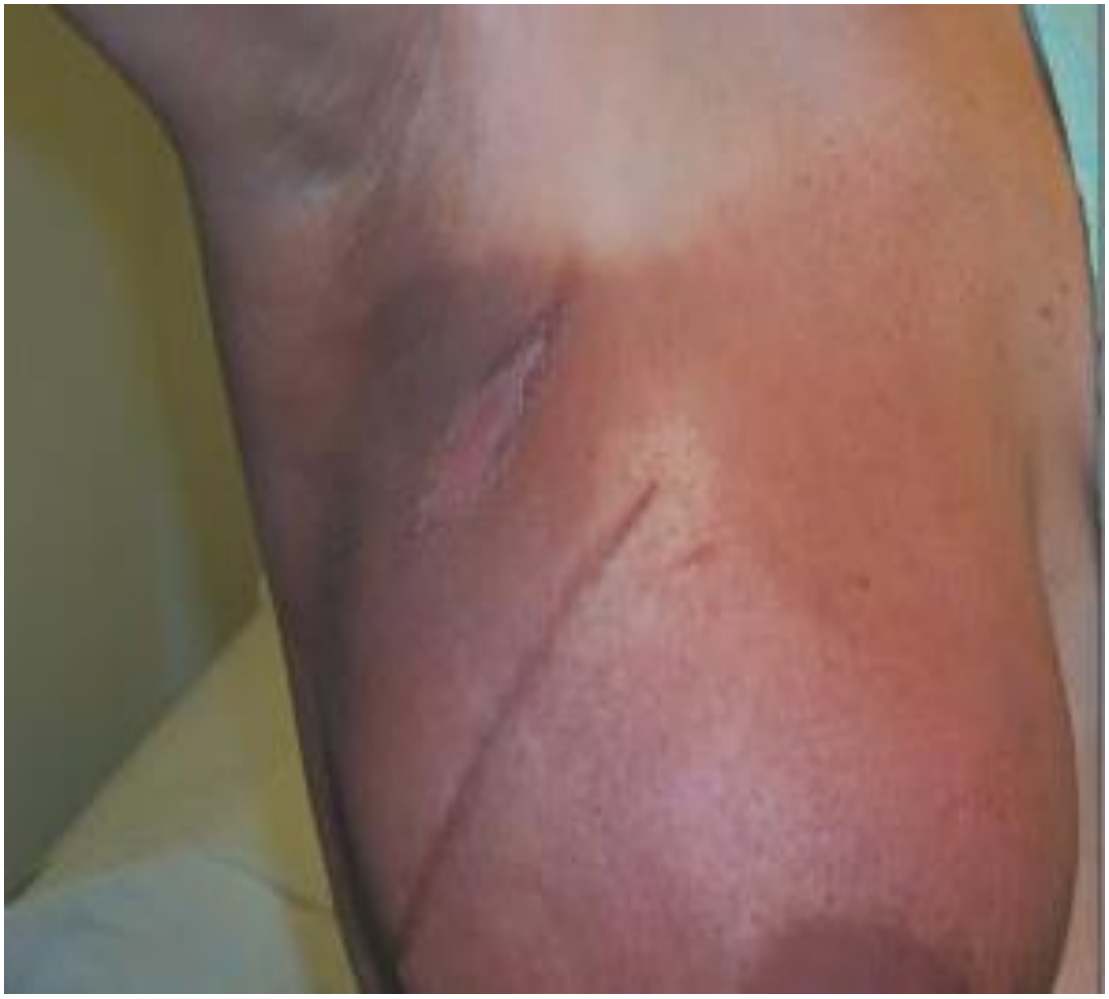
ID: ATP18



Acute toxicity skin - Radiation dermatitis





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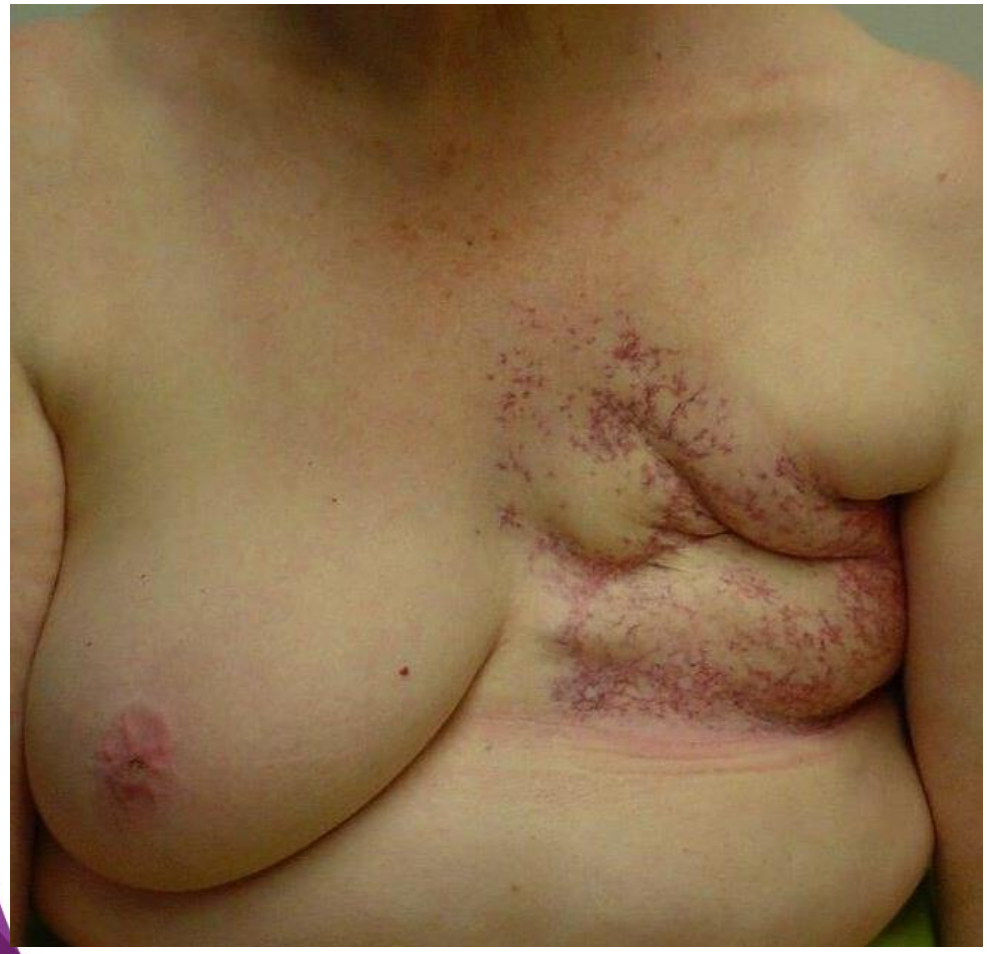
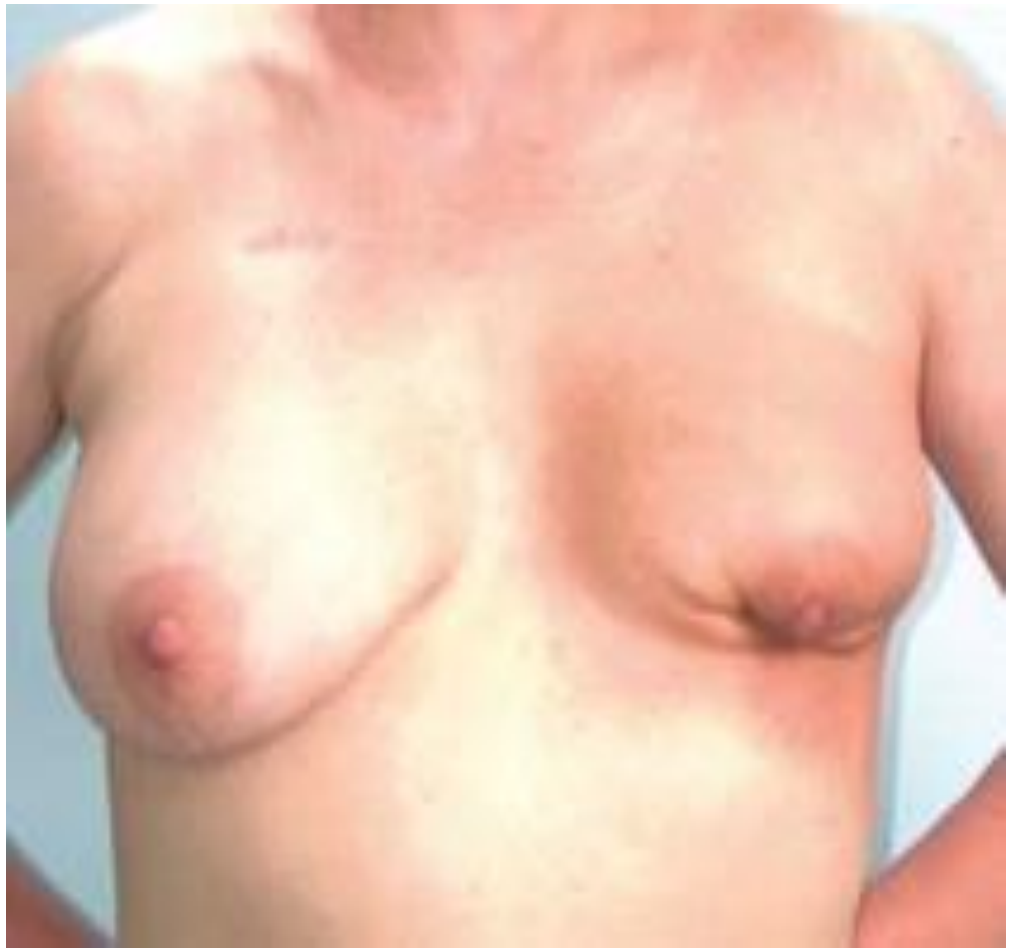
Late skin / breast toxicity

Telangiectasia



Breast fibrosis:



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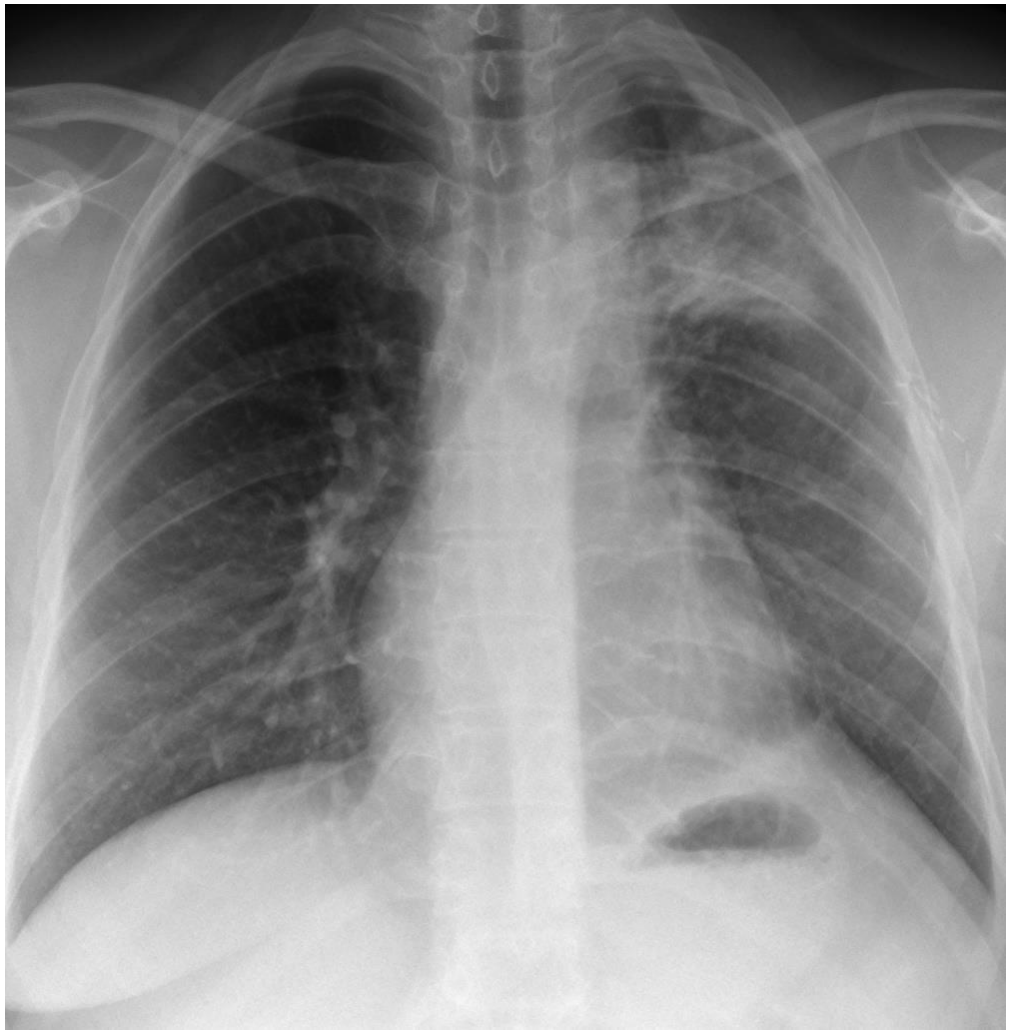
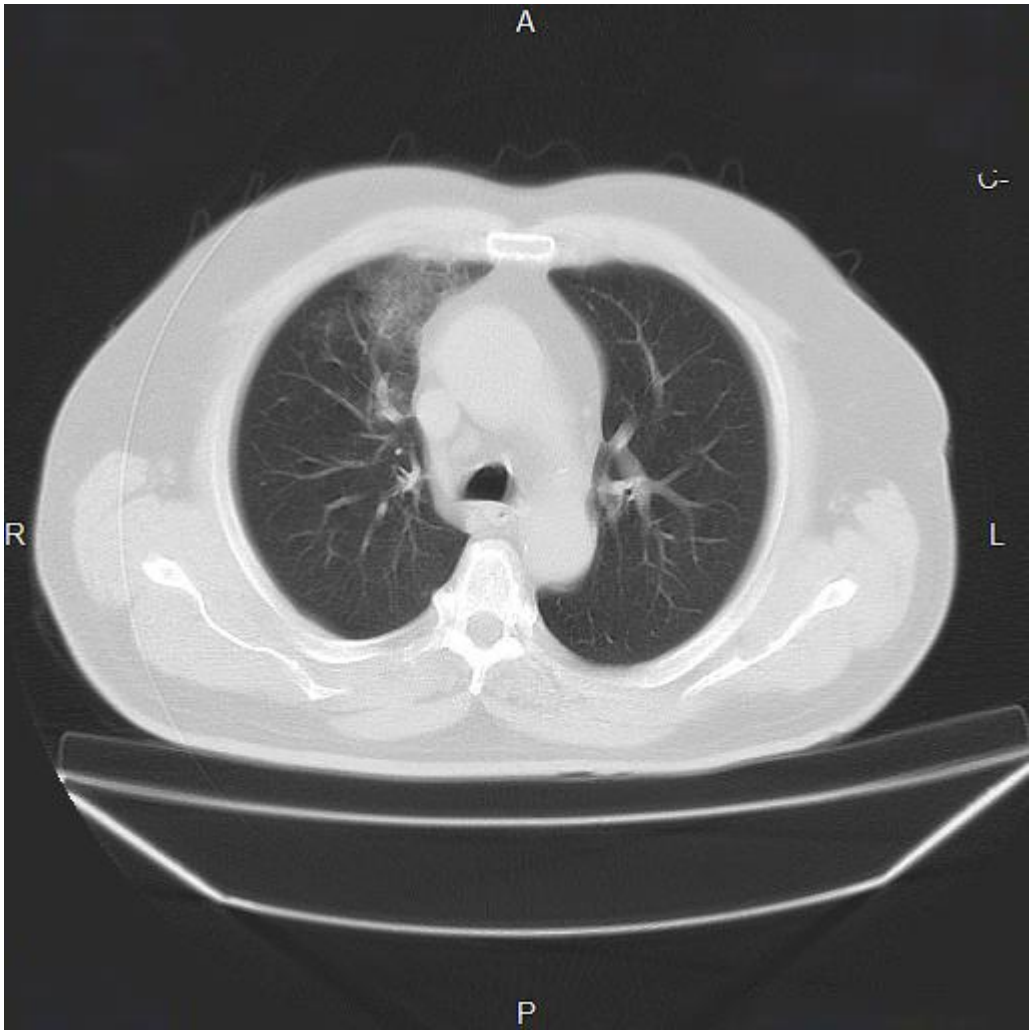
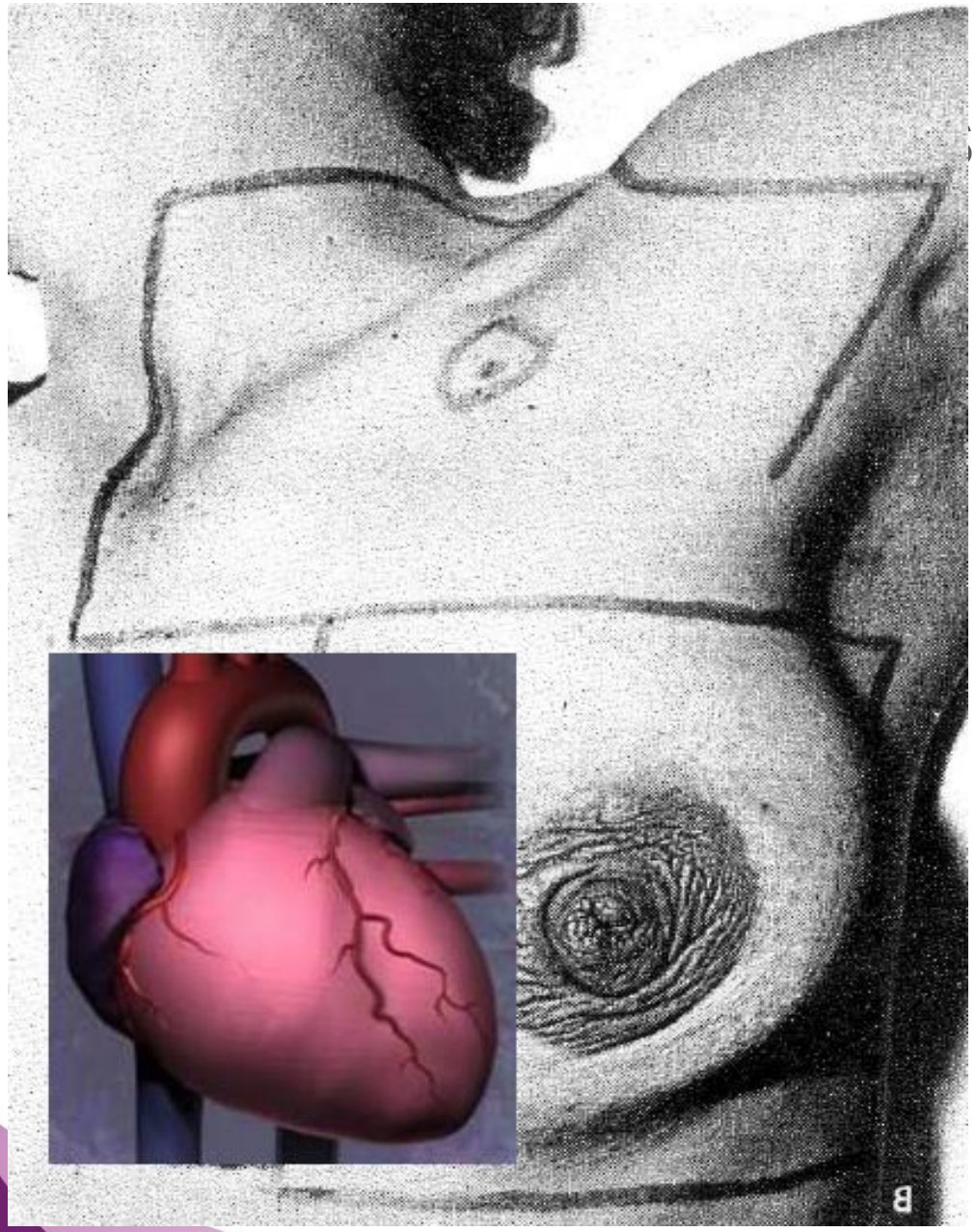
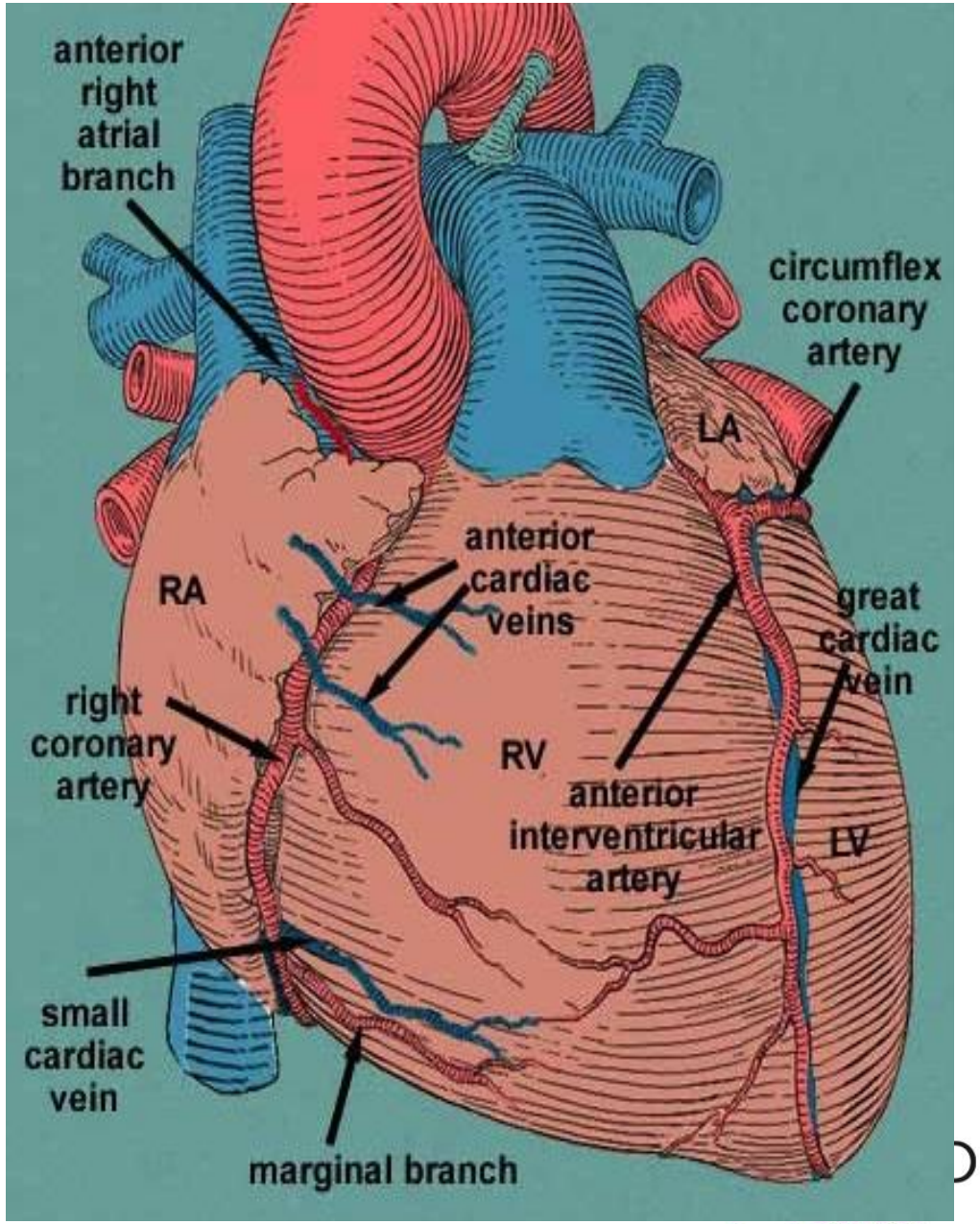
Lung - Radiation pneumonitis (subacute toxicity)





Heart - Left-sided breast radiotherapy

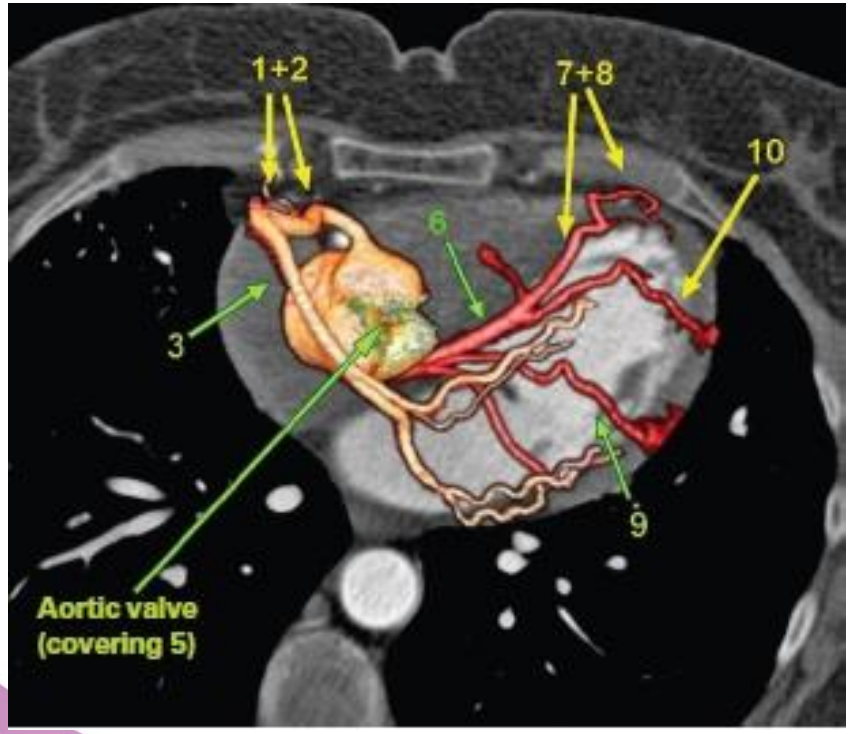


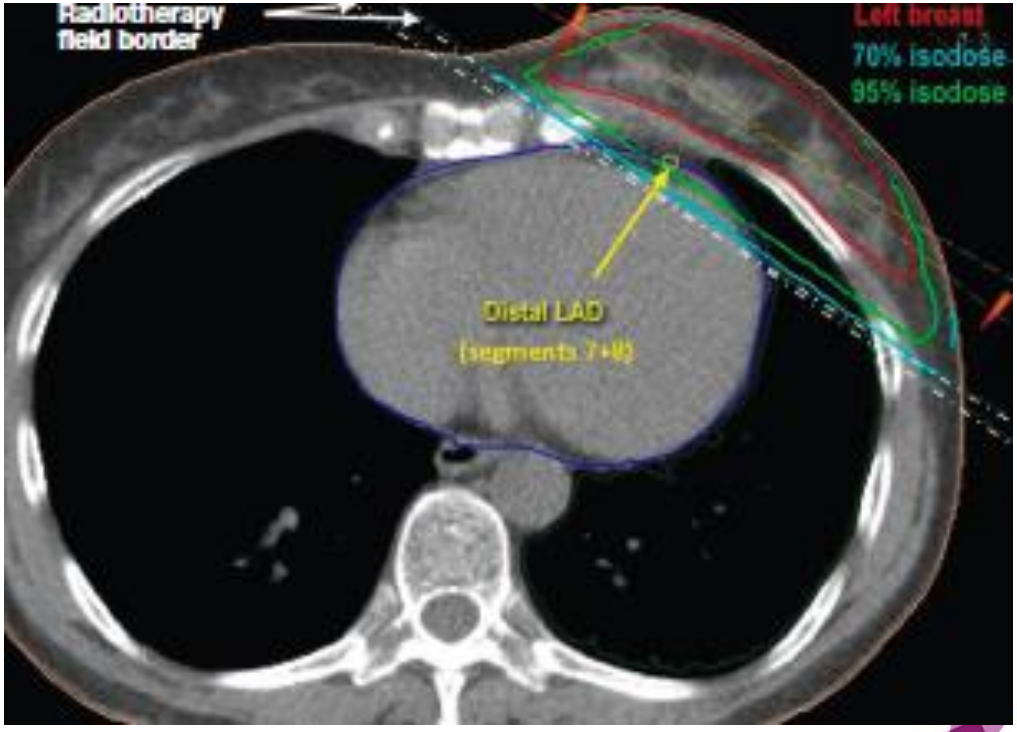


Radiation-induced heart disease

5-20 years after RT

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





Nilsson JCO 2012, Senkus-Konefka Cancer Treatment Rev 2007, Adams Crit Rev Oncol/Hematol 2003, Darby NEJM 2013

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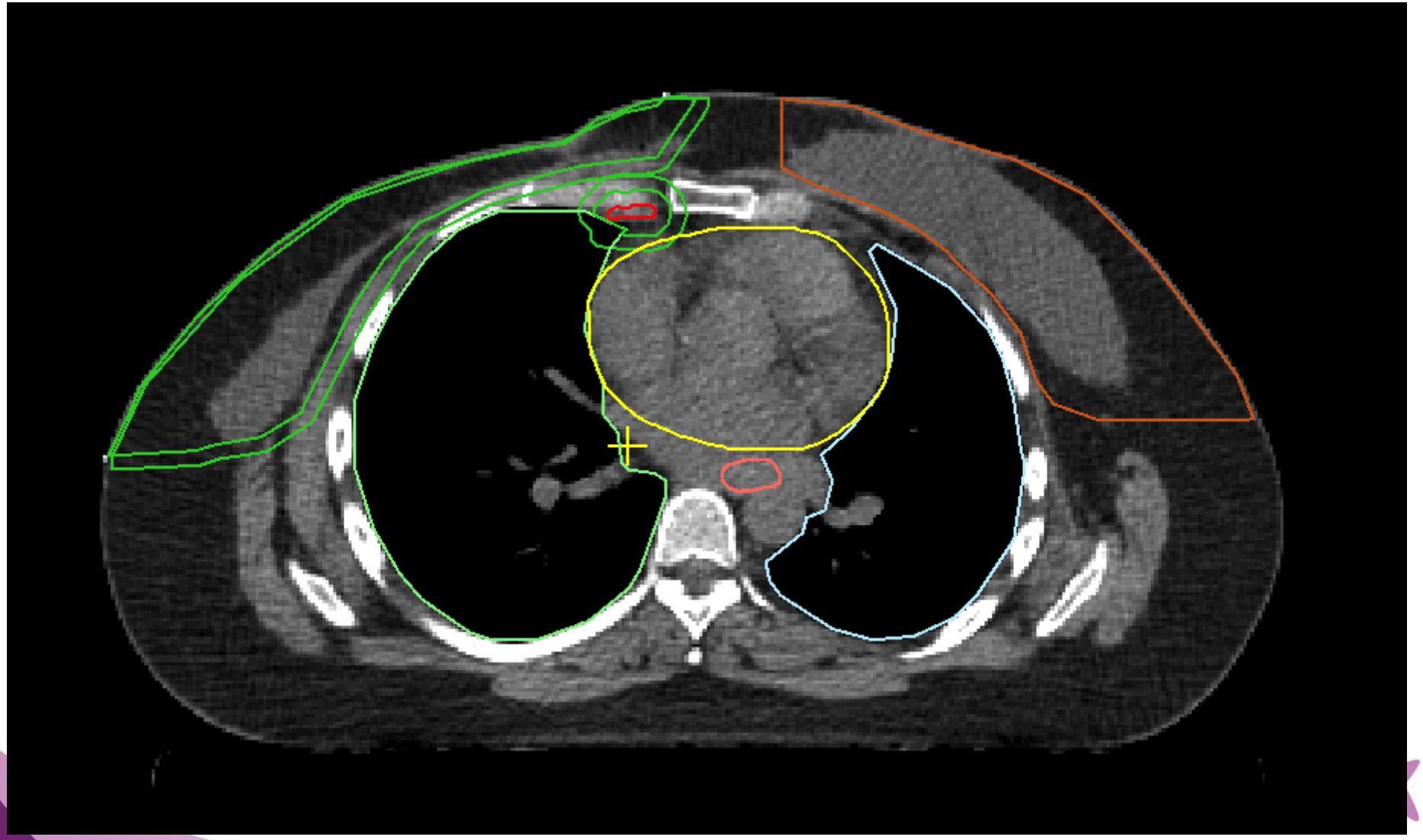
Radiation-induced heart disease
Regional radiotherapy

Internal mammary nodes: including heart



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Cardiac toxicity and mortality due to RT

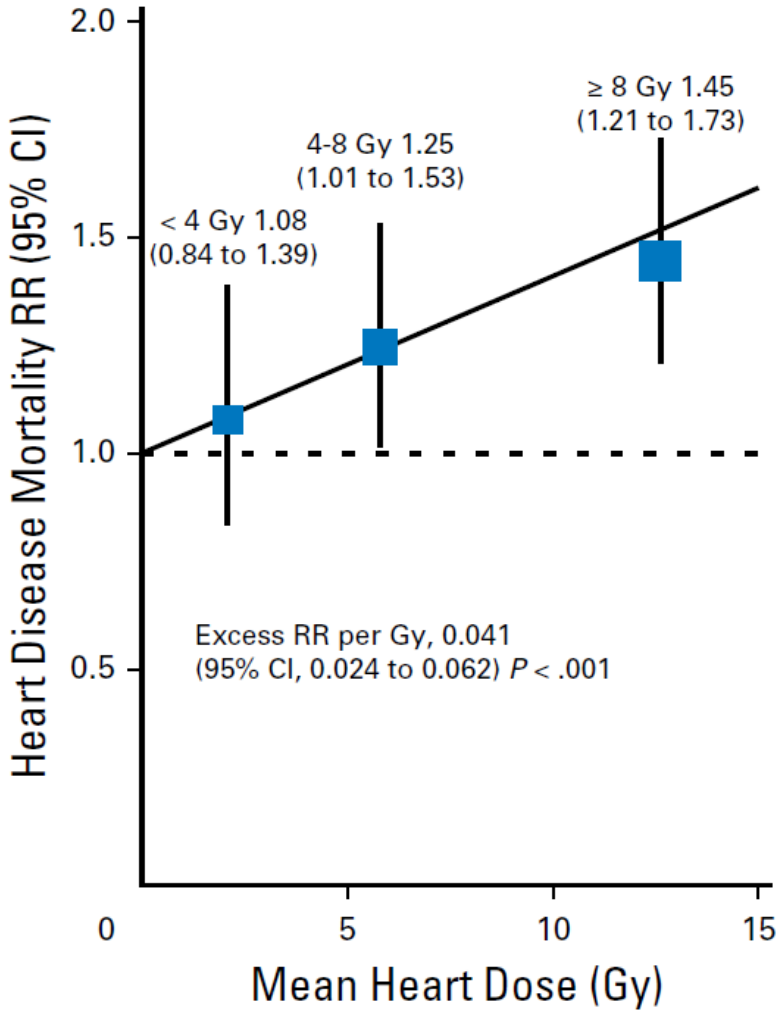
- 1 Gy increase in mean heart dose → 7% increased risk on cardiac events

- Increased mean heart dose: risk of cardiac disease mortality

Darby NEJM 2013, Taylor JCO 2017

Cardiac toxicity and mortality due to RT

- 7% increased risk on cardiac events per 1 Gy increase in mean heart dose
- Increased mean heart dose: ↑ risk of cardiac disease mortality



Darby NEJM 2013, Taylor JCO 2017

Cardiac toxicity and mortality due to RT

- 7% increased risk on cardiac events per 1 Gy increase in mean heart dose
- Increased mean heart dose: ↑ risk of cardiac disease mortality

- Higher risk in patients treated with systemic therapy, e.g. chemotherapy, trastuzumab

Darby NEJM 2013, Taylor Clinical Oncol 2015, Barlett Clin Oncol 2013, Taylor JCO 2017

Cardiac toxicity and mortality due to RT

- 7% increased risk on cardiac events per 1 Gy increase in mean heart dose
- Increased mean heart dose: ↑ risk of cardiac disease mortality

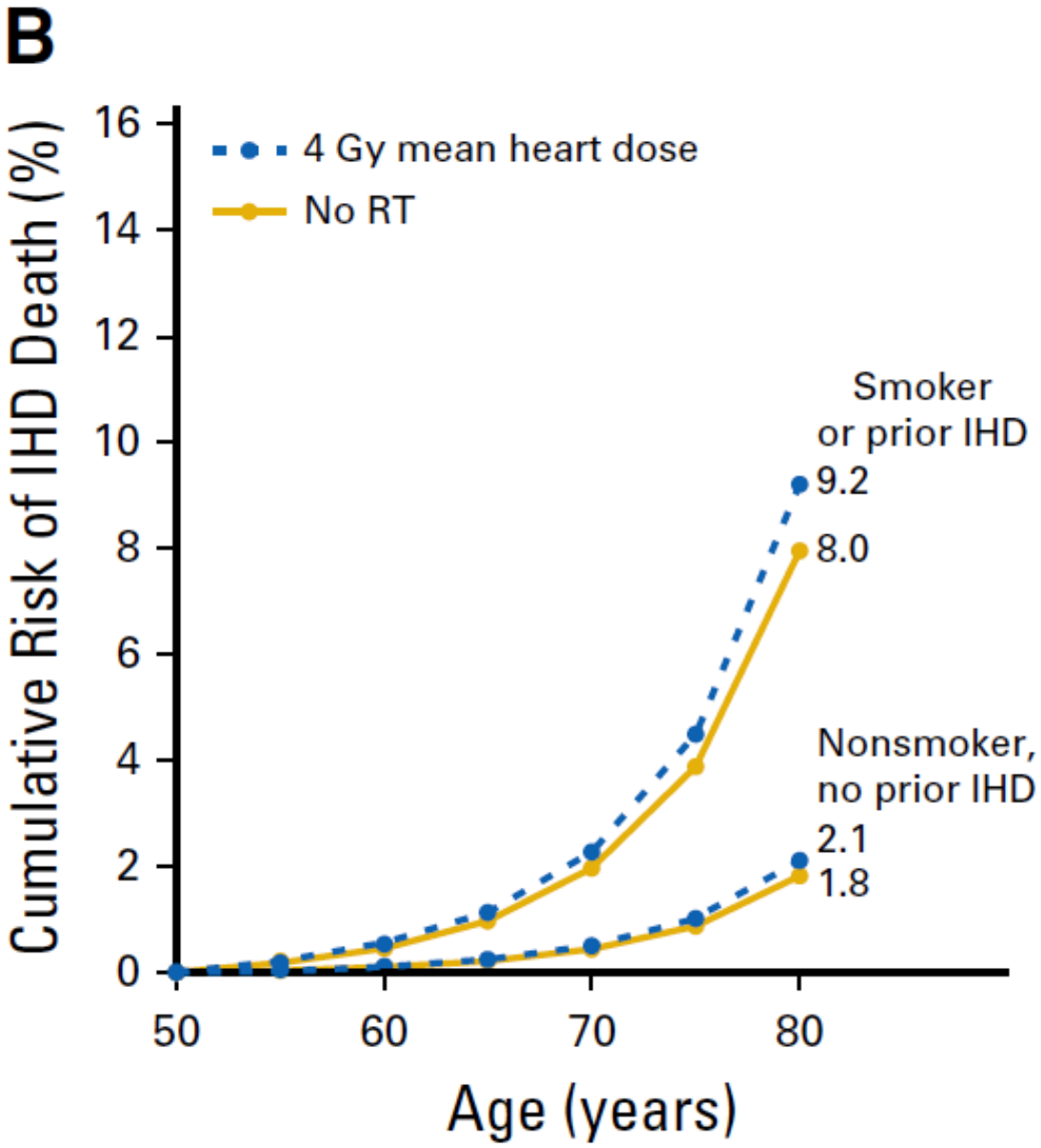
- Higher risk in patients treated with systemic therapy, e.g. chemotherapy, trastuzumab

- Other cardiac risk factors:
  - pre-existing cardiac disease
  - comorbidity (diabetes, hypertension, hypercholesterolaemia)
  - older age
  - family history of cardiac disease
  - lifestyle (smoking, obesity)

Darby NEJM 2013, Taylor Clinical Oncol 2015, Barlett Clin Oncol 2013, Taylor JCO 2017

Cardiac mortality due to RT +/- smoking

- 7% incr mean heart dose
  →A !
- Higher g. chemotherapy, trastuzu
- Cardiac
  - sterolaemia)



Darby NEJM 2013, Taylor Clinical Oncol 2015, Barlett Clin Oncol 2013, Taylor JCO 2017

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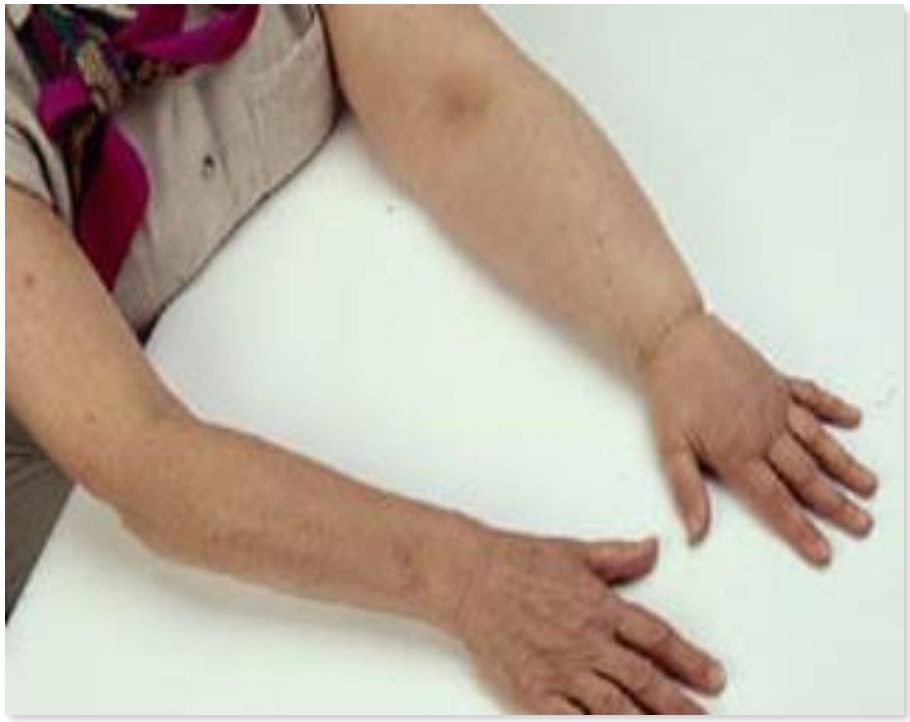
Arm oedema -
After axillary surgery +/- regional radiotherapy

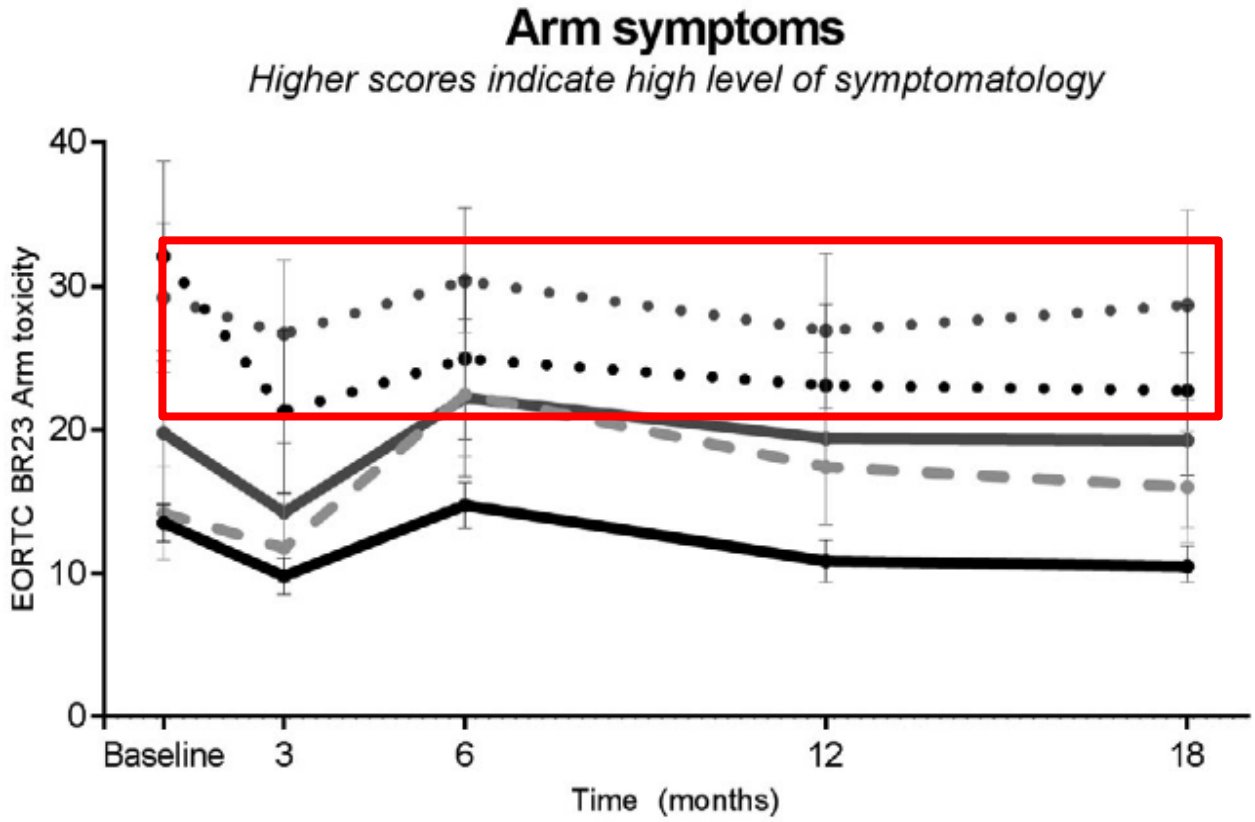


Increased use of regional radiotherapy instead of axillary surgery

Increased use of regional radiotherapy instead of axillary surgery

Patient-reported outcomes
N=964

Last decade – Regional radiotherapy instead of axillary surgery



No axillary lymph node dissection (ALND)
- Sentinel lymph node biopsy only
- Axillary radiotherapy levels I-II
- Axillary radiotherapy levels I-IV

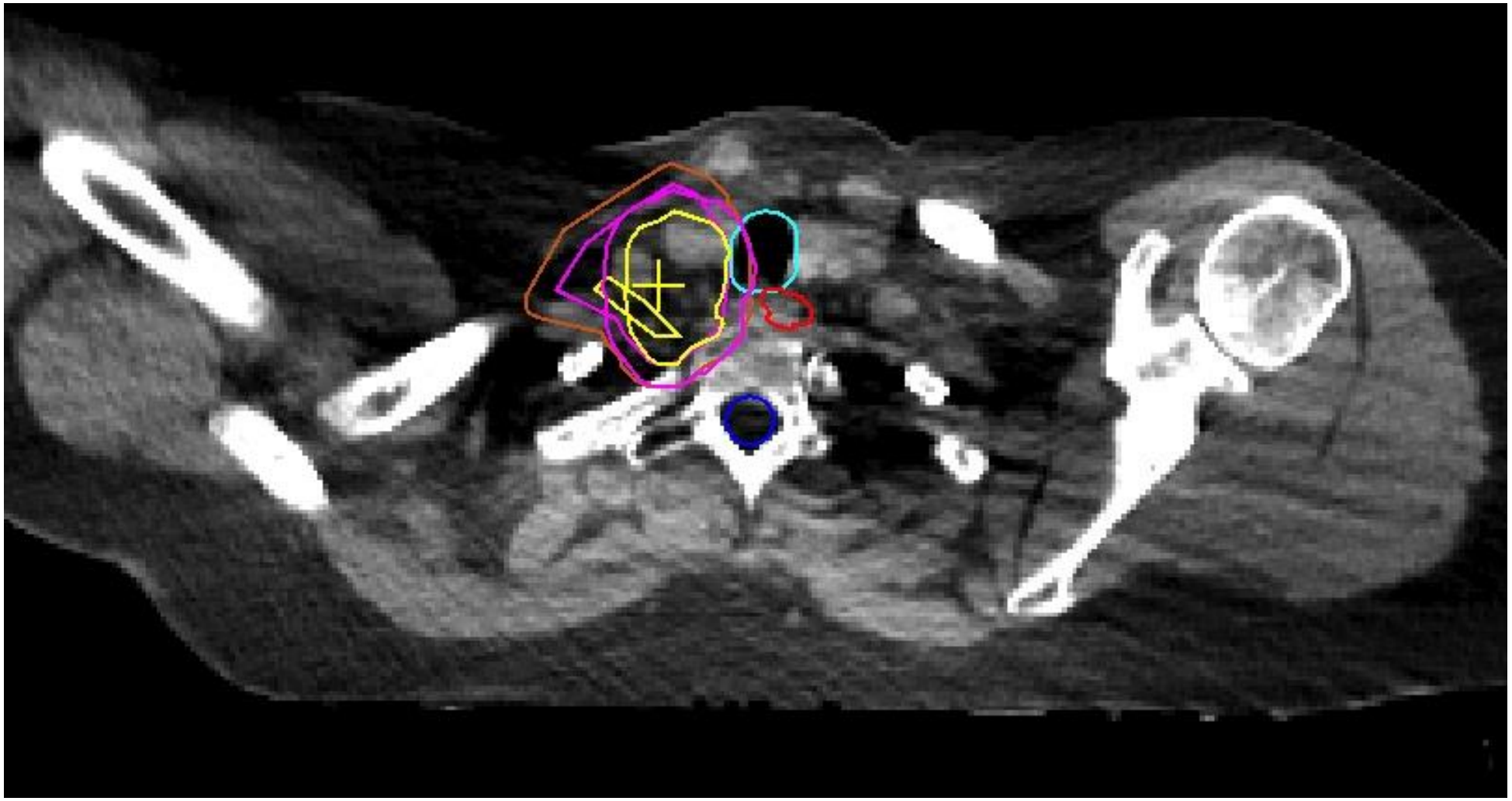
Axillary lymph node dissection (ALND)
- Axillary lymph node dissection only
- Axillary radiotherapy

ction					
y (n)	563	546	517	466	430
n)	81	76	76	74	69
(n)	59	57	57	53	45
on					
only (n)	45	52	45	50	43
	73	72	65	58	44

No axillary lymph node dissection
Sentinel lymph node biopsy only (n)
Axillary radiotherapy levels I-II (n)
Axillary radiotherapy levels I-IV (n)

Axillary lymph node dissection
Axillary lymph node dissection only (n
Axillary radiotherapy (n)

Brachial plexus
Regional radiotherapy boost



- Plexopathy: paresthesias, decreased muscular strength, paralysis

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Radiation-induced secondary cancer after breast cancer radiotherapy

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

  Berrington de Gonzales Lancet Oncol 2011

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- Contralateral breast cancer:

  In patients < 40 years: if mean dose > 1 Gy

  Stovall IJROBP 2008

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Radiation-induced secondary cancer after breast cancer radiotherapy

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

  Berrington de Gonzales Lancet Oncol 2011

- Contralateral breast cancer:

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

  Stovall IJROBP 2008

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

  Low risk compared to benefit of radiotherapy

  Grantzau RO 2015, Taylor JCO 2017

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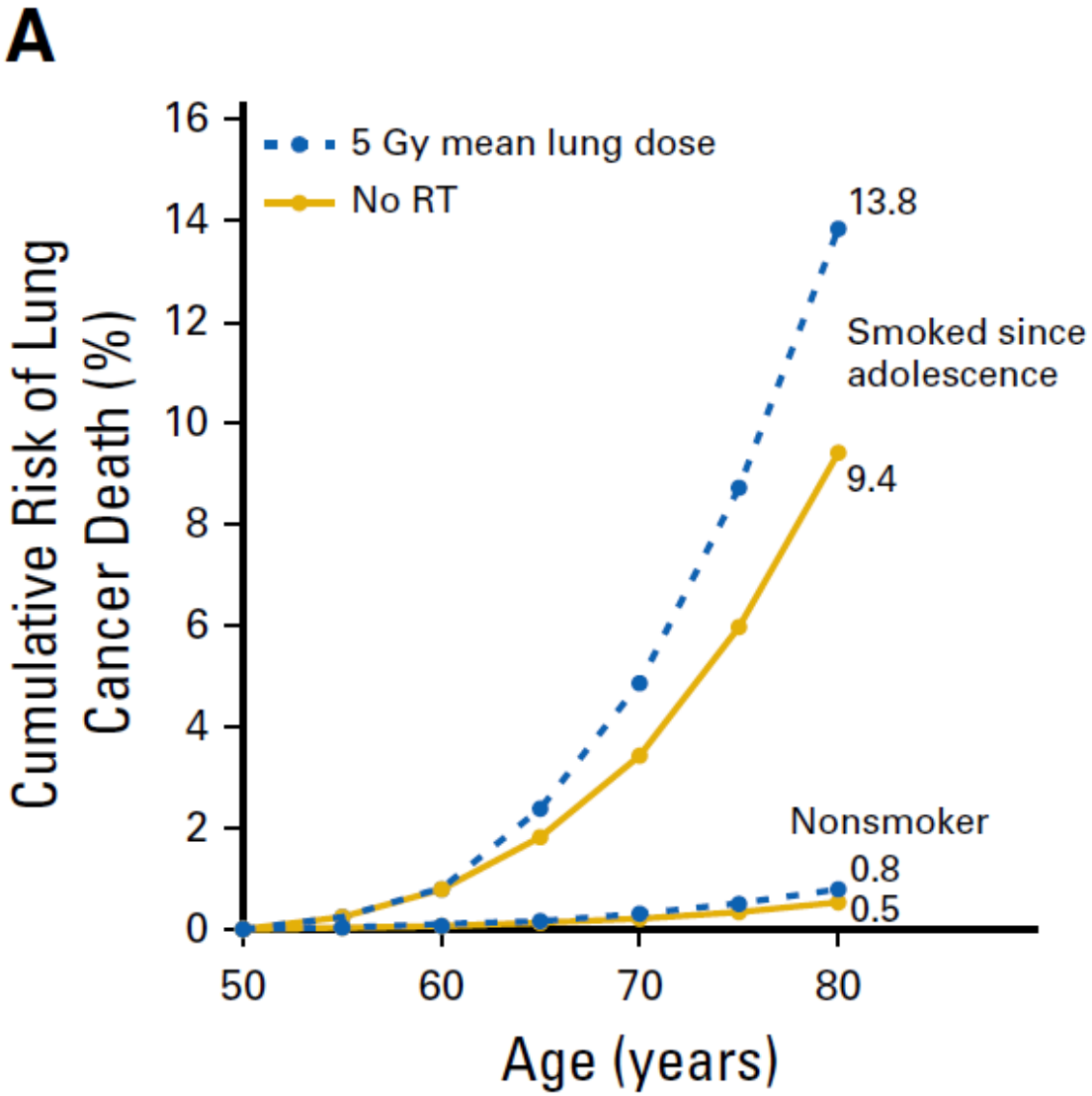
Radiation-induced lung cancer after breast cancer radiotherapy +/- smoking



Taylor JCO 2017

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Innovation in breast RT planning to reduce RT-induced toxicity

Innovation in breast RT planning to reduce RT-induced toxicity

- **Hypofractionation**

  instead of conventional scheme 25x2 Gy

Do you use hypofractionated schedules in breast RT?

1. Yes, in local RT (breast / chest wall)
2. Yes, in local and/or regional RT
3. No
4. I don’t know

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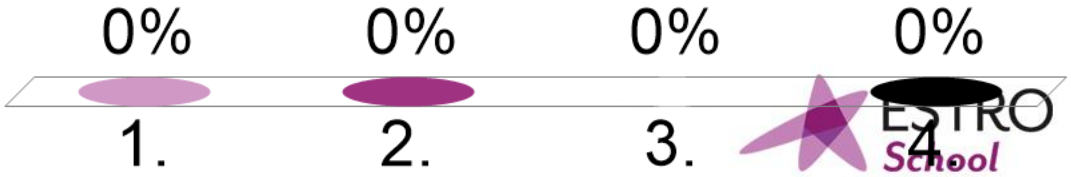
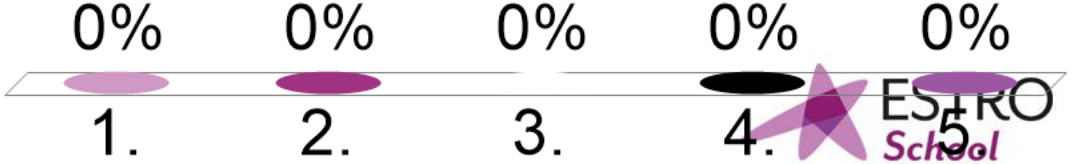
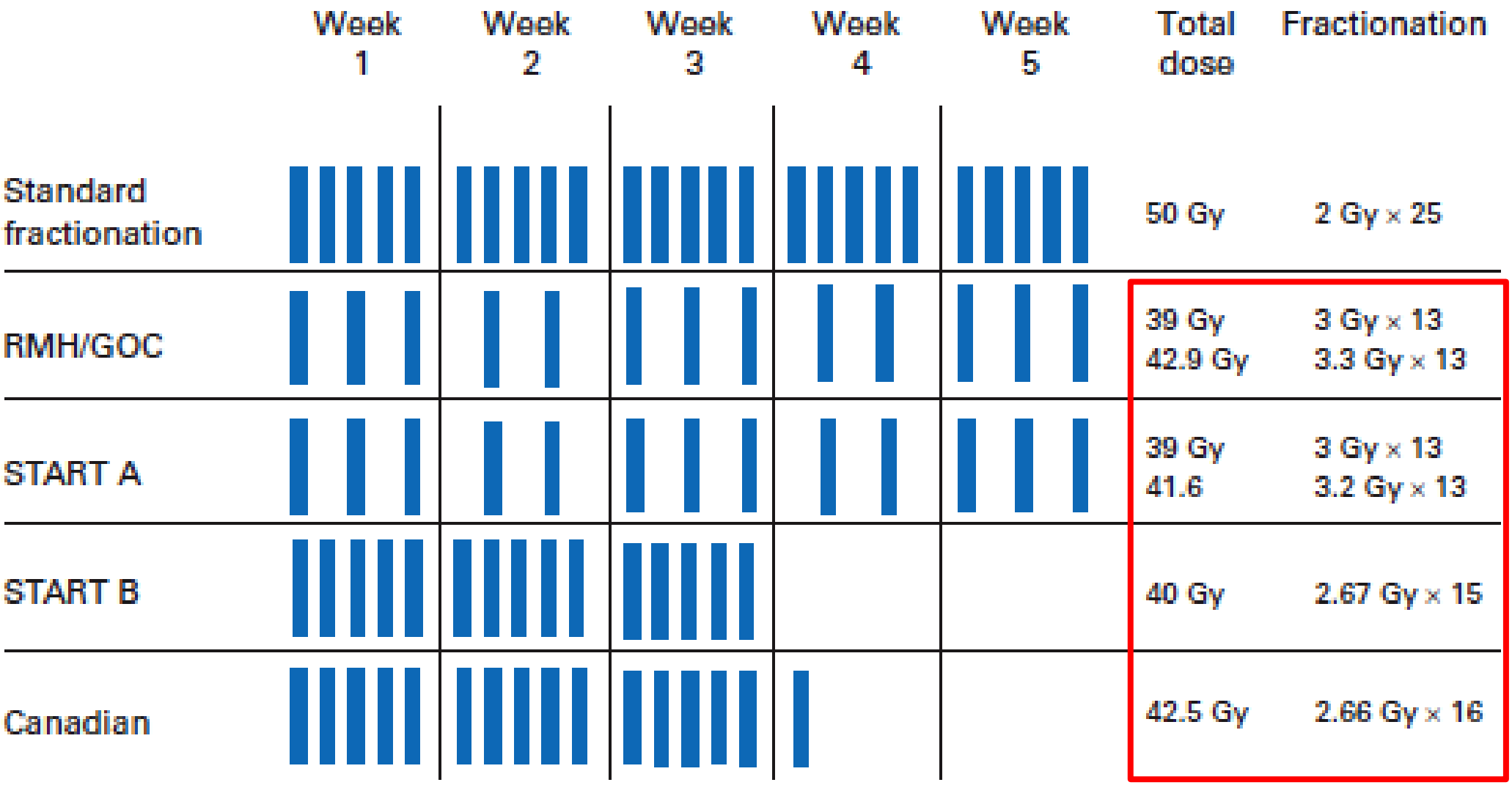


How many fractions do you use in local / (loco)regional RT?

1. 10-16 fractions or less (if no boost)
2. Less than 10 fractions (if no boost)
3. 25 (if no boost)
4. More than 25 fractions
5. I don’t know



Hypofractionation – whole breast irradiation



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

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Hypofractionation – Breast cancer Radiotherapy

- 4 phase III studies whole breast irradiation:

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

  Canada: 16 x 2.66 Gy

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

- Adjusted α/β 3.5

  Breast cancer is more sensitive to fraction size:

  No advantage in using $\leq$ 2 Gy fractions

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

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

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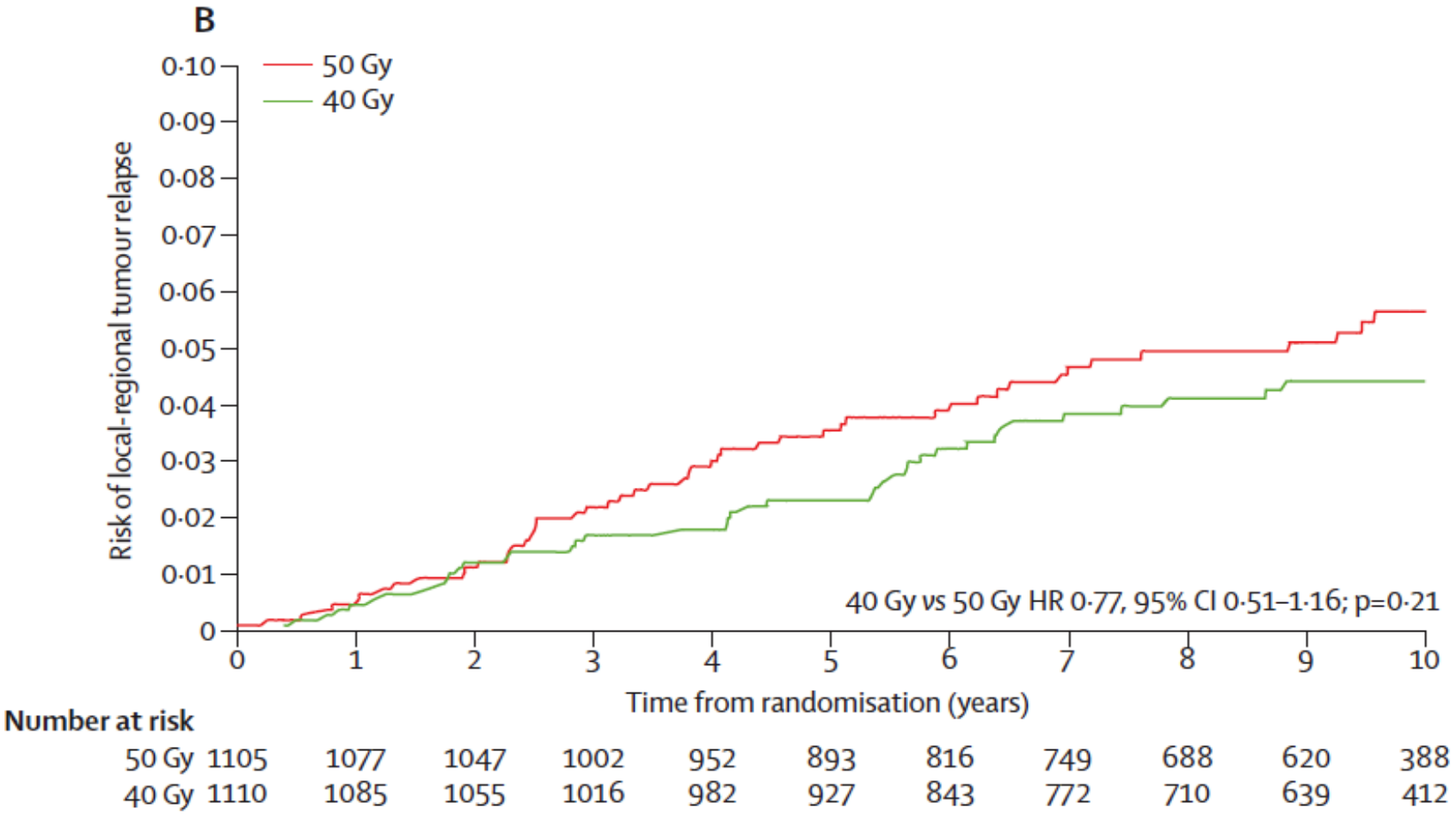
UK START B- Locoregional recurrence

START B: 50 Gy/25# vs. 40 Gy/15#



Trend:↓ Locoregional recurrences in 40 Gy arm

Haviland, Lancet Oncol 2013

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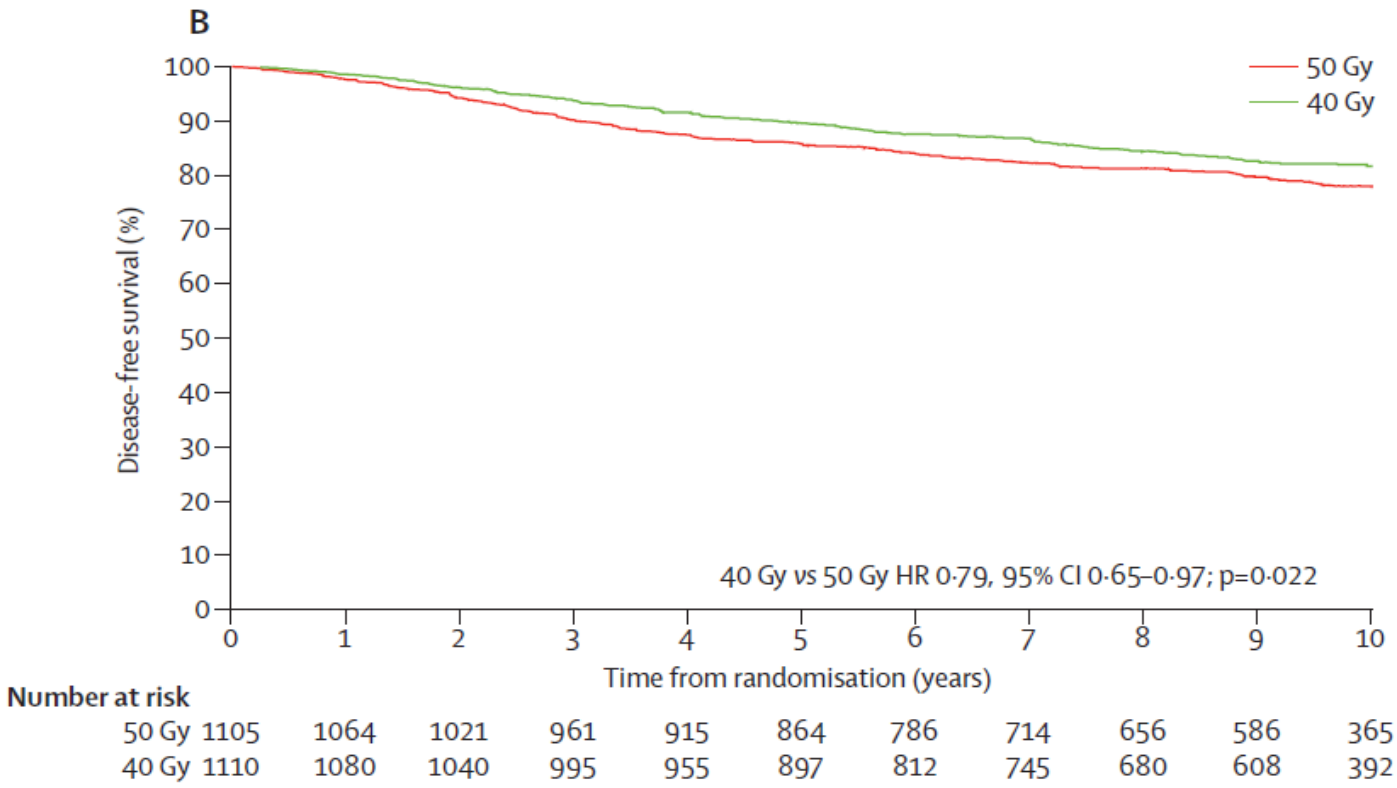
UK START B – Disease-free survival

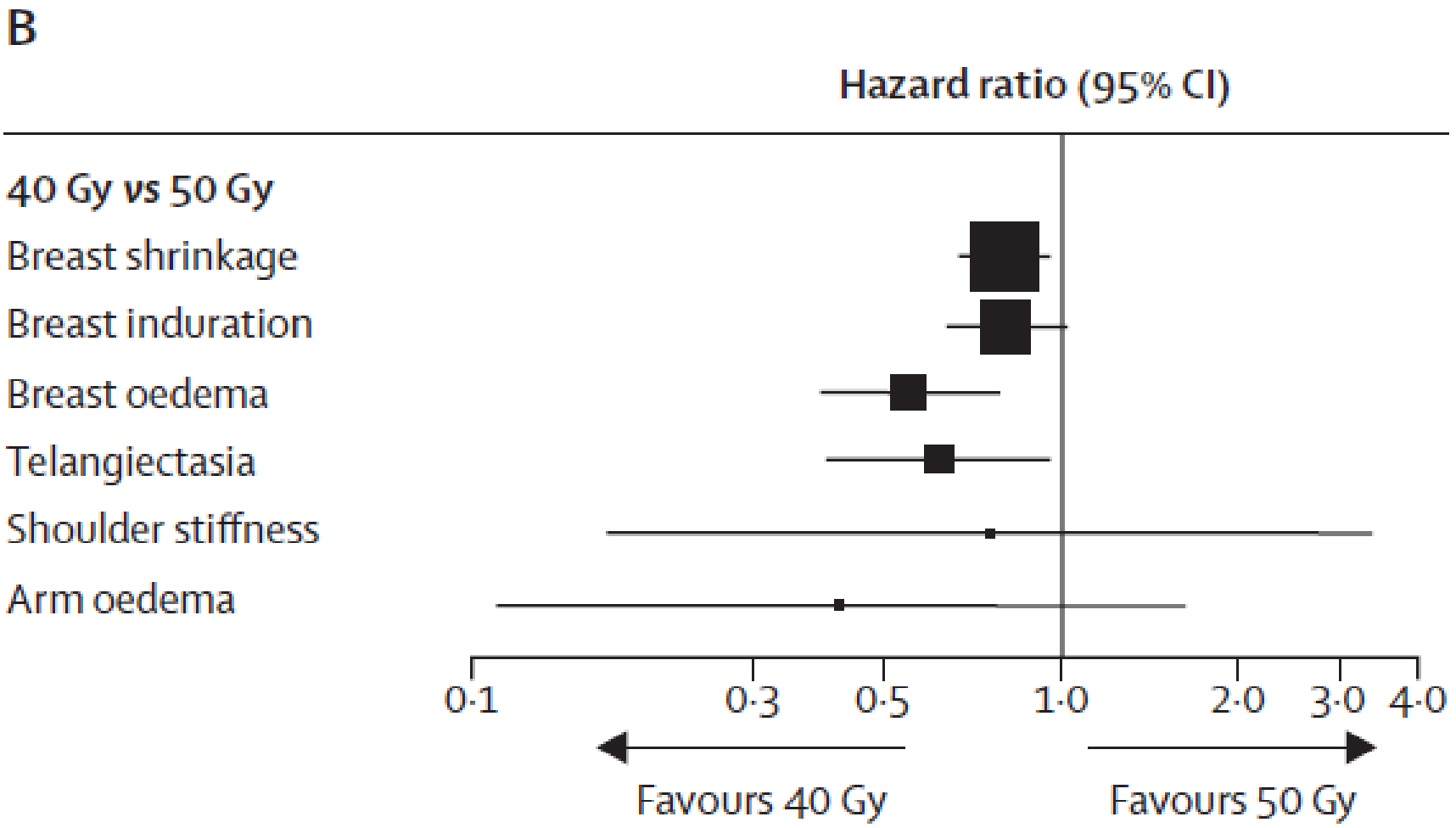
START B: 50 Gy/25# vs. 40 Gy/15#



Significant better disease-free survival in 40 Gy arm

Haviland, Lancet Oncol 2013

UK START B - Toxicity



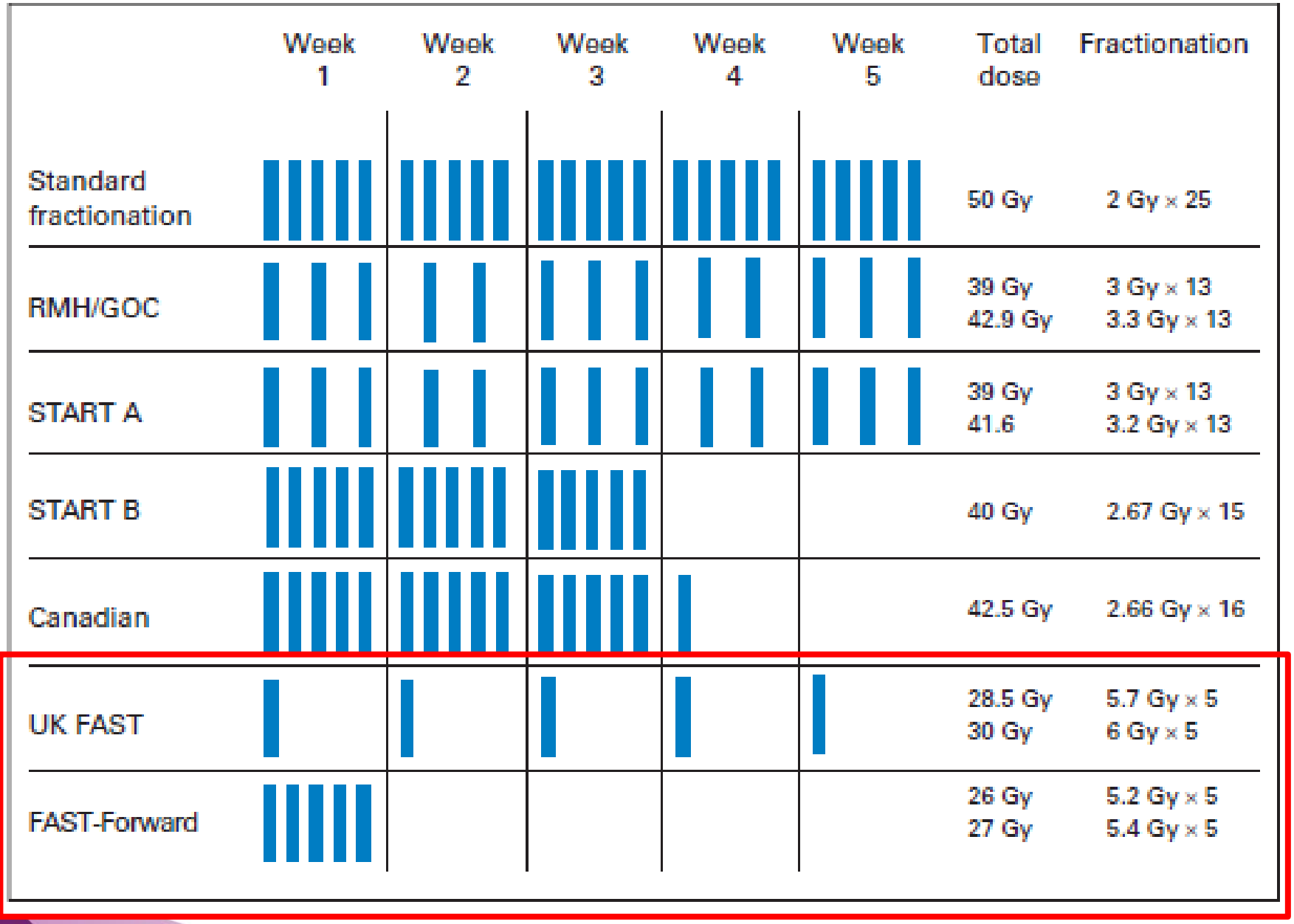
40 Gy: less breast oedema and shrinkage and telangiectasia

Haviland, Lancet Oncol 2013

Hypofractionation – Clinical practice

In the Netherlands: 15 x 2.67 Gy (5x/week)

Hypofractionation – FAST (FORWARD)



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

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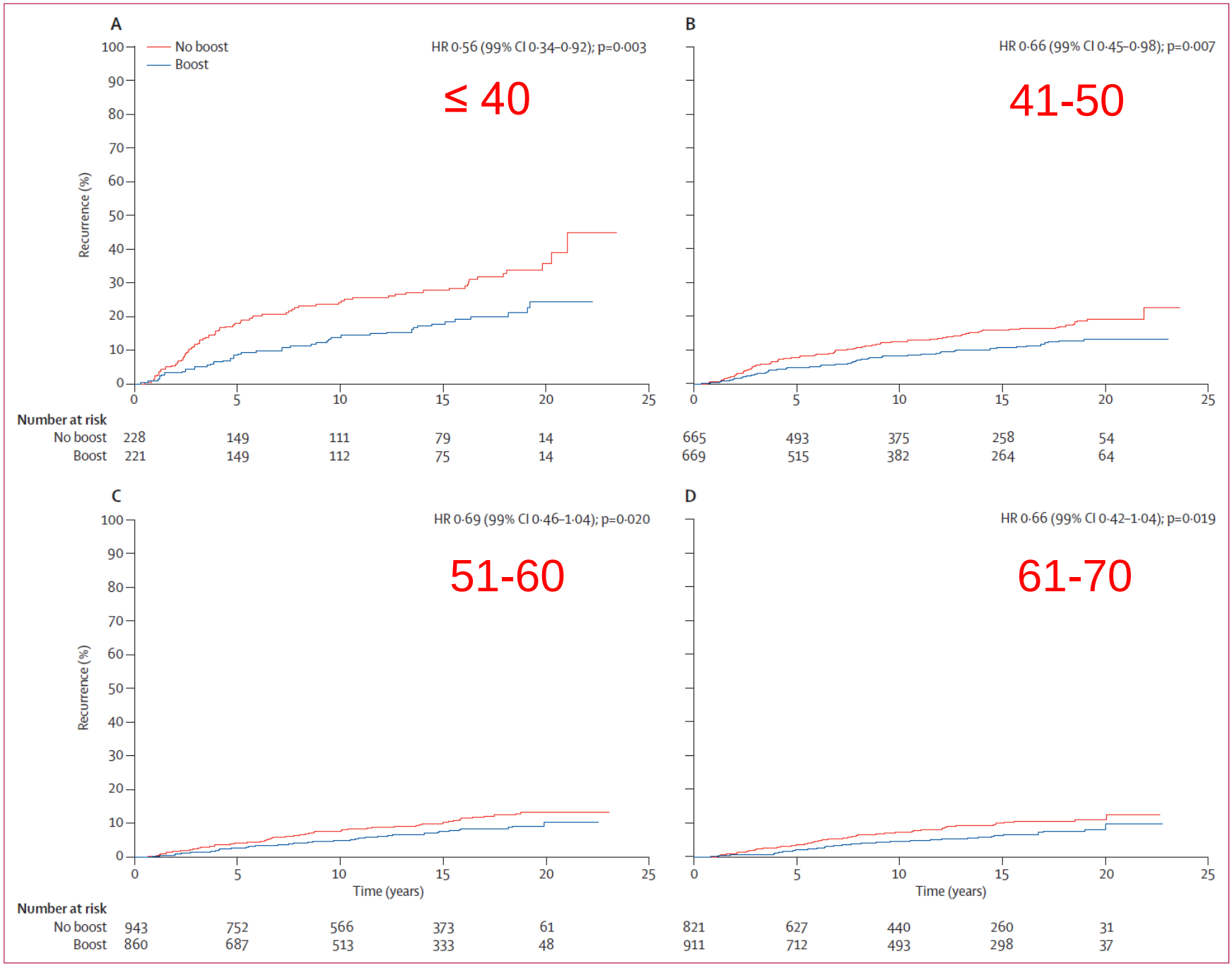
Innovation in breast RT planning to reduce RT-induced toxicity

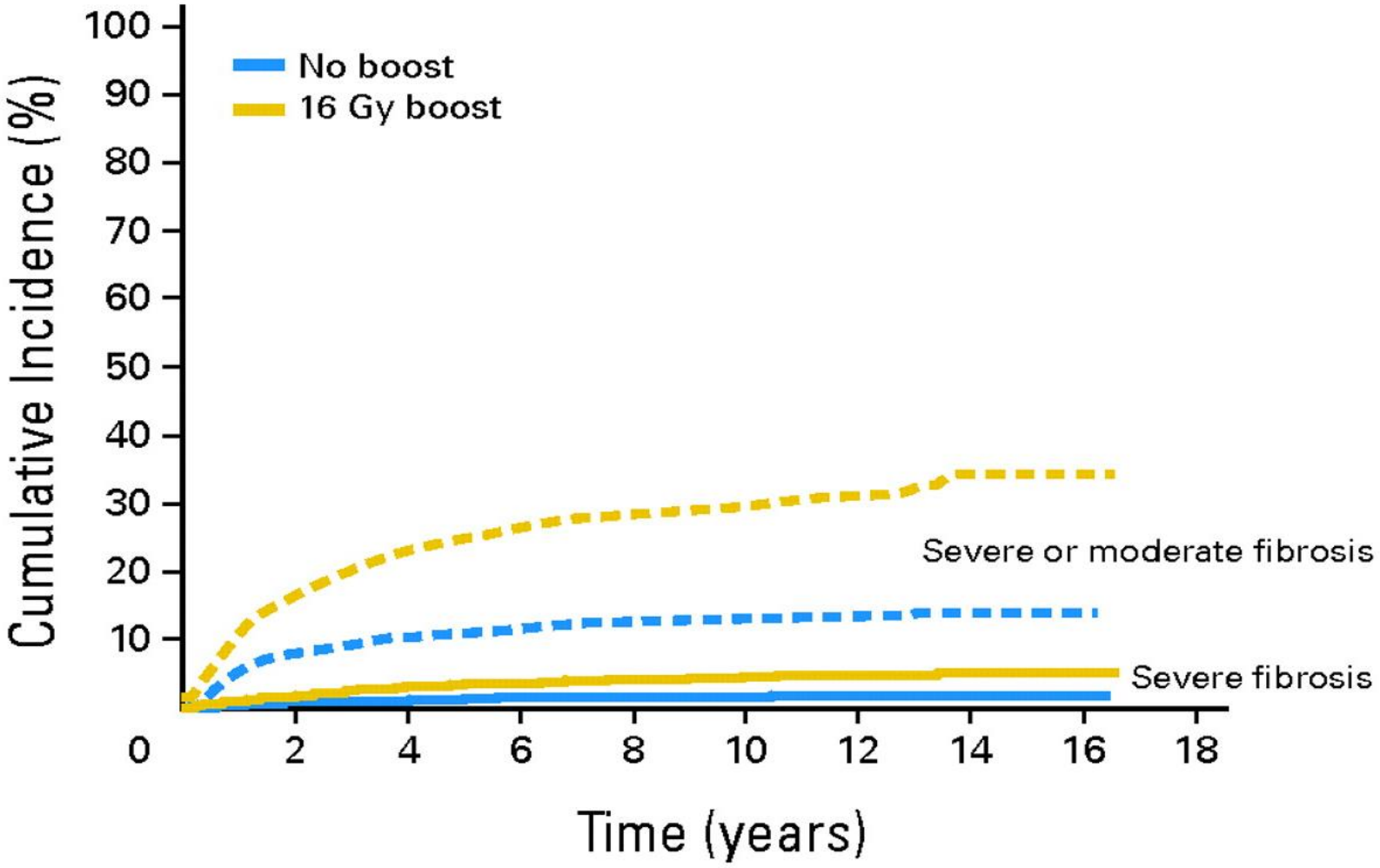
- Hypofractionation
- **Simultaneously integrated boost (SIB)**

Boost on tumor bed: decreased local recurrence



Bartelink Lancet Oncol 2015

Boost on tumor bed – breast fibrosis



Boost tumor bed:
increased rates of moderate-severe breast fibrosis by 15% at 10 years

Bartelink JCO 2007

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Breast fibrosis – Risk factors

- RT boost on tumor bed

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

Breast fibrosis – Risk factors

- RT boost on tumor bed

- RT boost **volume**
-
- RT boost **dose** on tumor bed

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

Breast fibrosis – RT boost dose

Risk is in

- H
- R
- R

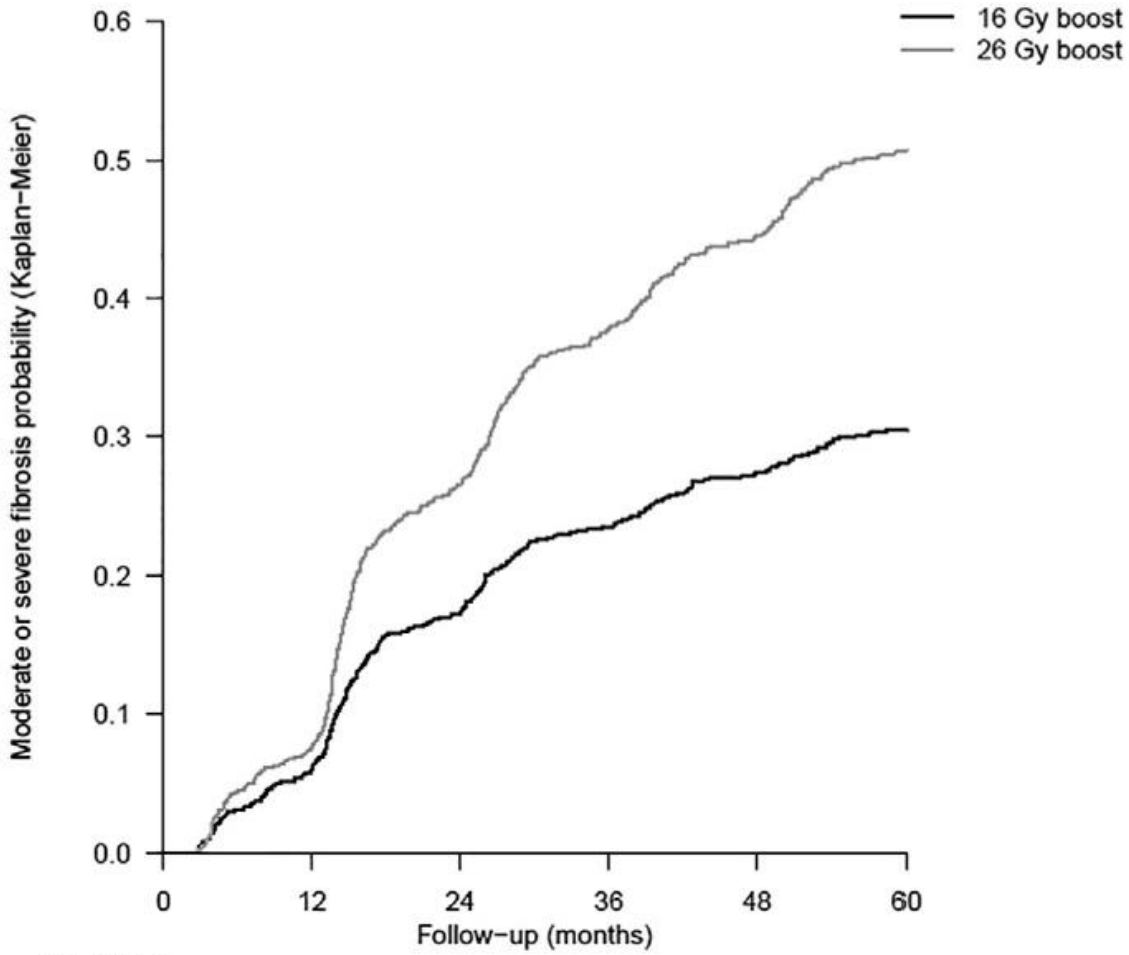

Fig. 2. Cumulative incidence of moderate or severe fibrosis in the boost area.

Brouwers RO 2018

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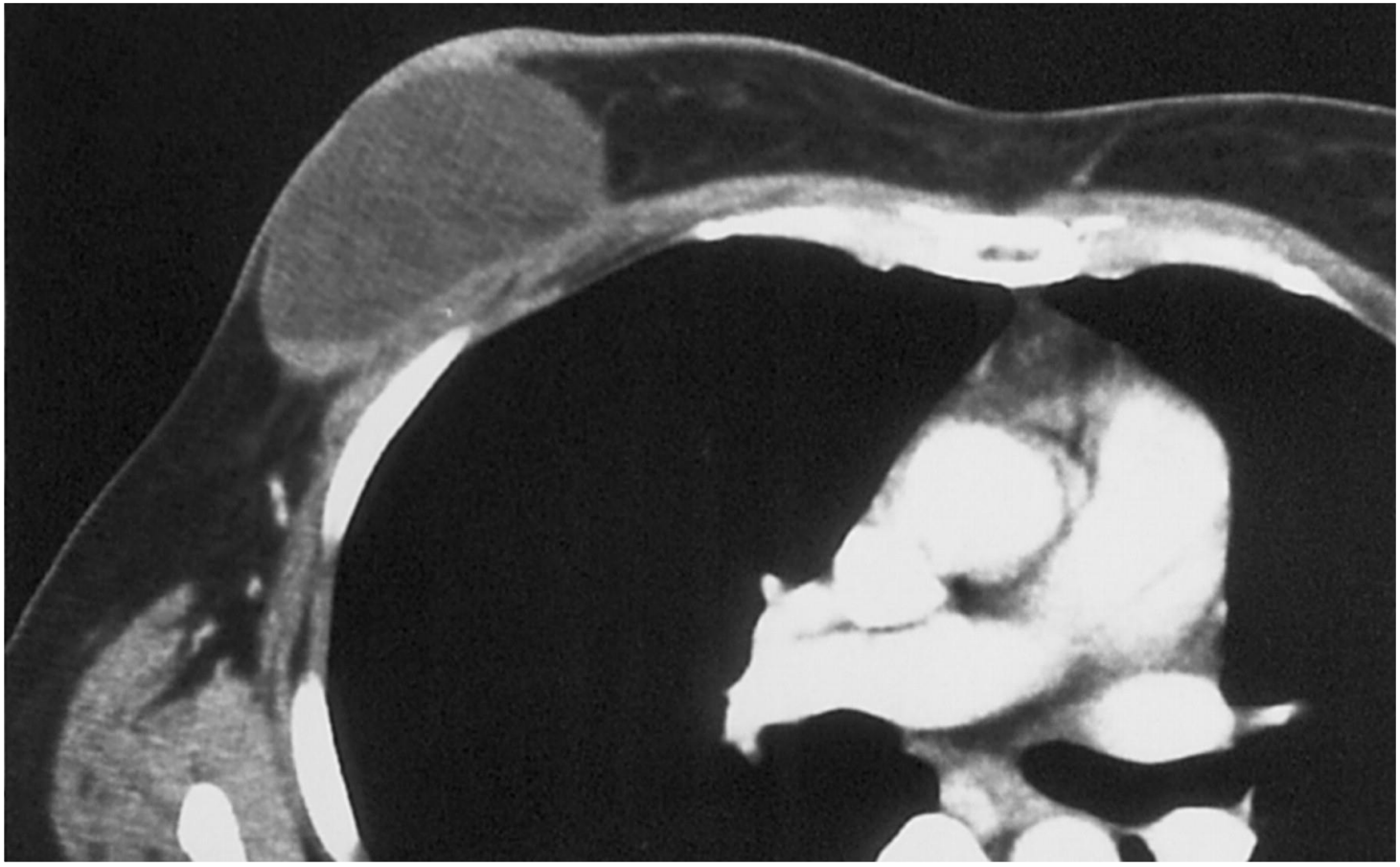
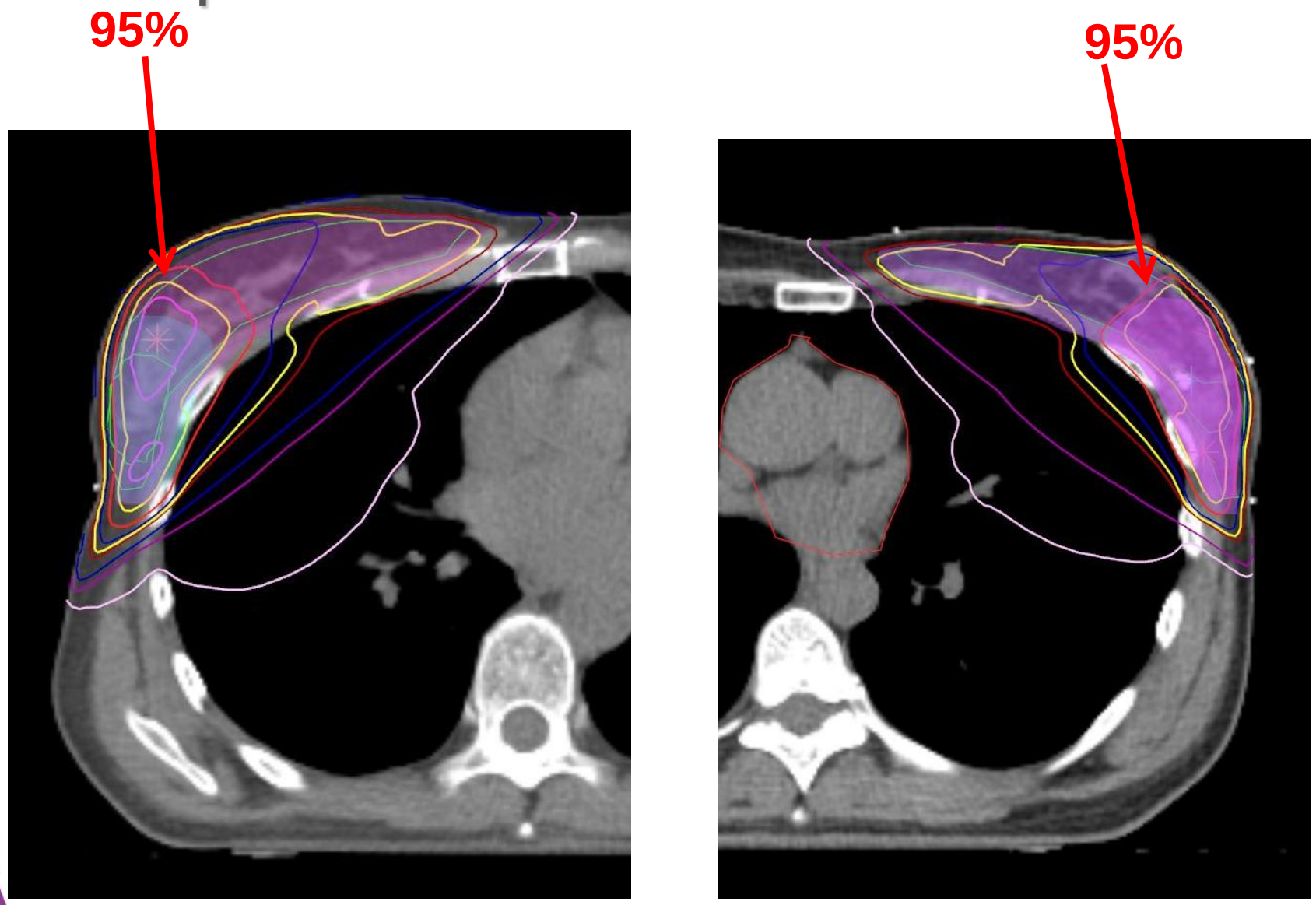
Breast fibrosis – non-RT risk factors

- Adjuvant systemic therapy
- Post-operative breast oedema or hematoma / seroma in tumor bed



Sequential boost *vs.* SIB



Sequential boost

SIB

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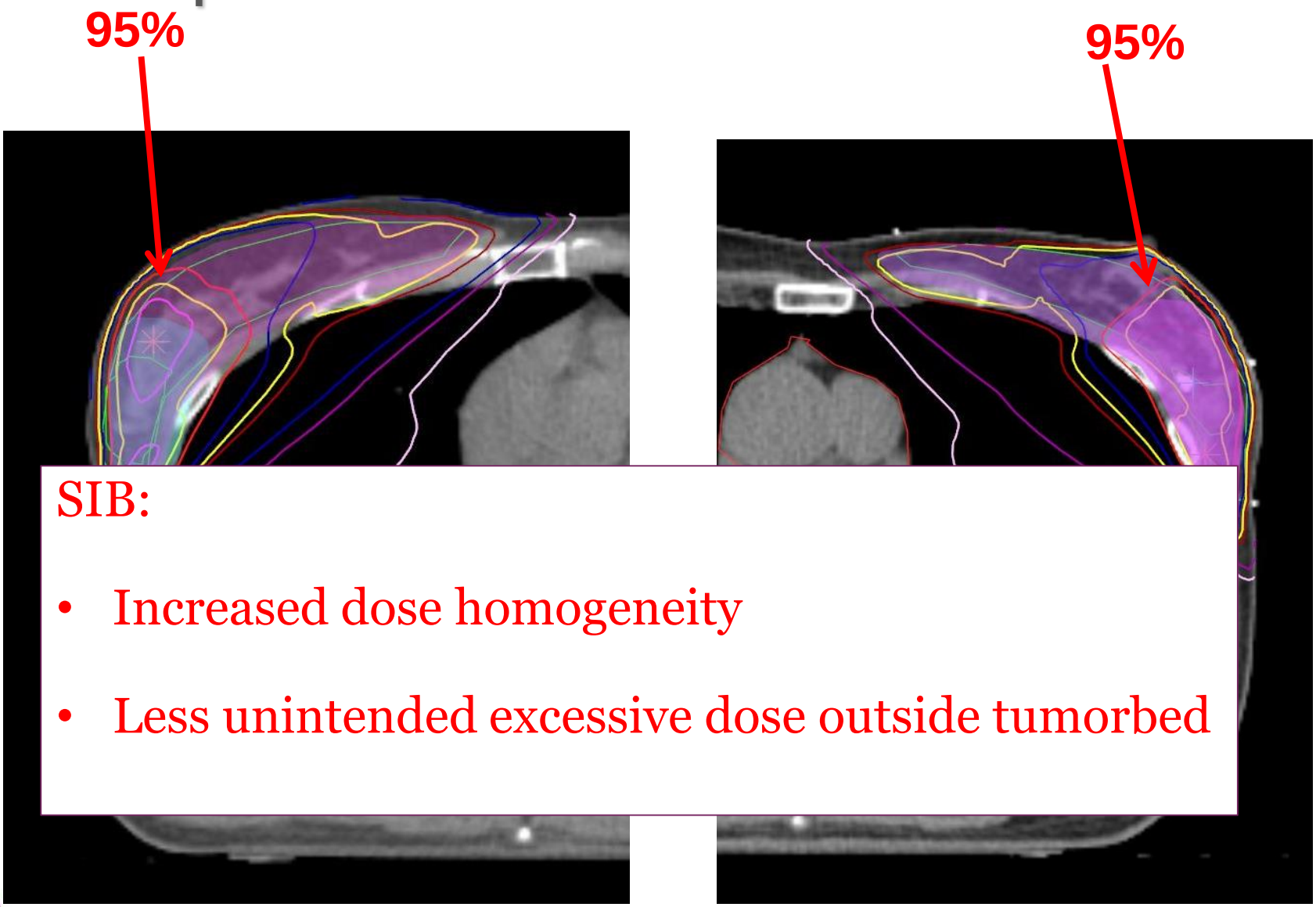
Sequential boost *vs.* SIB



SIB:

- Increased dose homogeneity
- Less unintended excessive dose outside tumorbed

Sequential boost

SIB

Simultaneously integrated boost (SIB)

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

- Excellent 5-year control (99%)

  Bantema-Joppe RO 2013

- Higher dose per fraction to tumor bed →

  Equal toxicity and cosmetic result

  Bantema-Joppe IJROBP 2012

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Innovation in breast RT planning to reduce RT-induced toxicity

- Hypofractionation
- Simultaneously integrated boost (SIB)
- **(Accelerated) partial breast RT**

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Do you use (accelerated) partial breast RT?

1. Yes, is standard treatment (in low-risk patients)
2. Only in trials
3. No
4. I don’t know

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Partial breast irradiation (PBI) - Rationale

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

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

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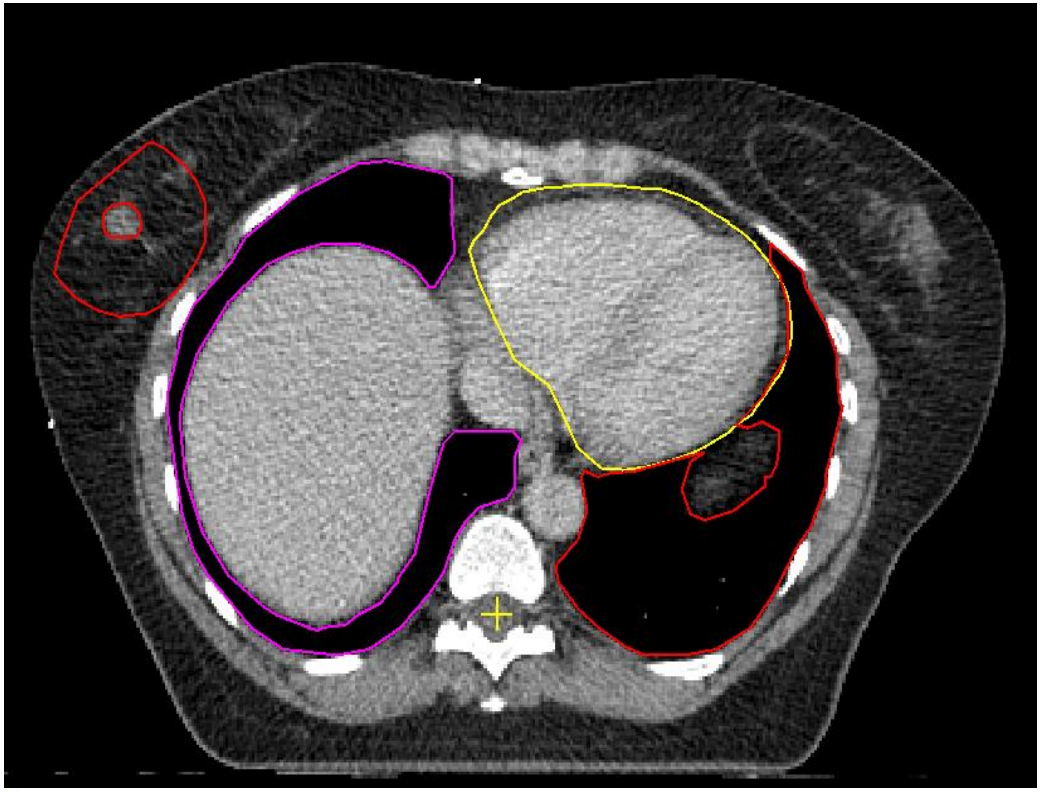
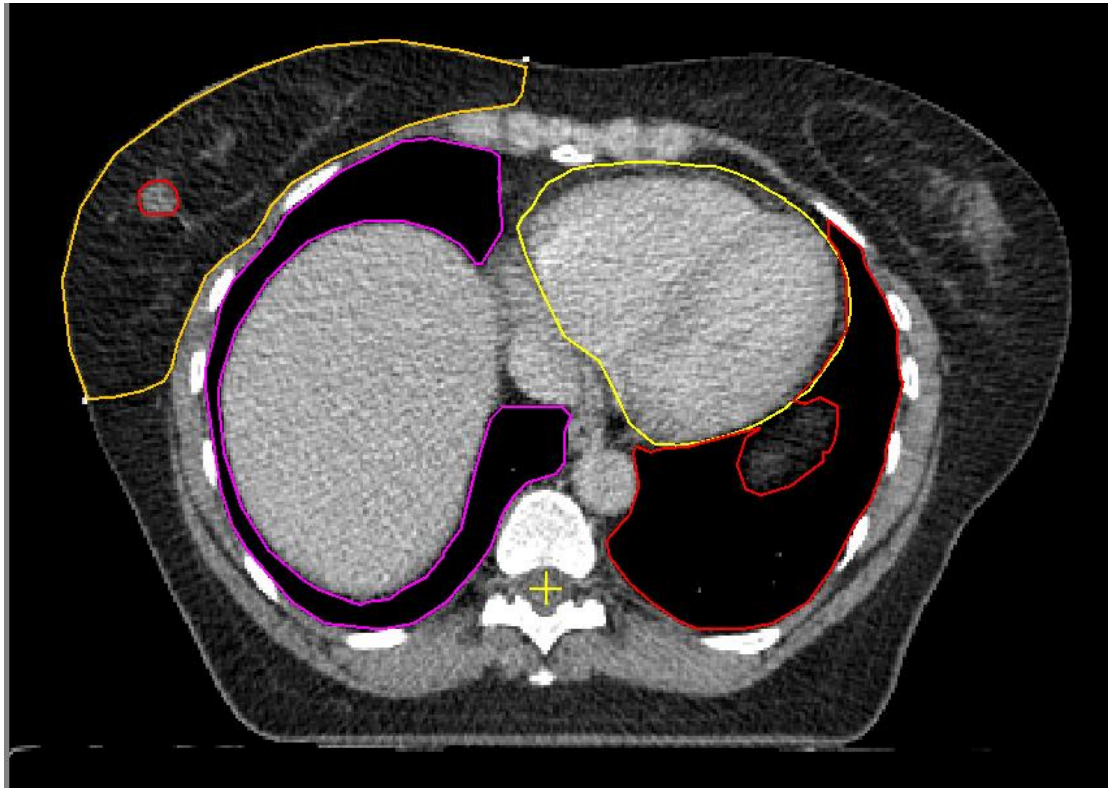
PBI - Smaller target volumes

PBI



WBI



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PBI – smaller target volumes

- Shorter treatment time due to decreased number of RT fractions

- Decreased dose to surrounding organs, e.g heart and lungs

  → less RT-induced toxicity → better Quality of Life

Partial breast irradiation – which patients?

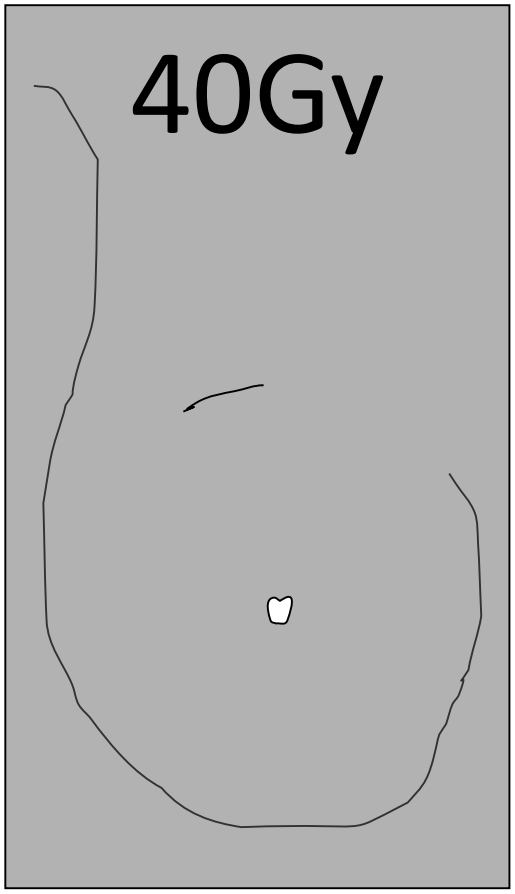
	Age	Tumor size	Histology	Lymph node status	Margin status
ASTRO Correa *et al.* PRO 2017	≥ 50	≤ 2 cm	Non-lobular DCIS Grade 1-2 Unifocal ER+ No LVI	Negative	Negative (> 2 mm)
GEC-ESTRO Polgar *et al.* RO 2010	≥ 50	≤ 3 cm	Non-lobular Unifocal Any ER status No LVI	Negative	Negative (≥ 2 mm)

Partial breast irradiation – low-risk breast cancer

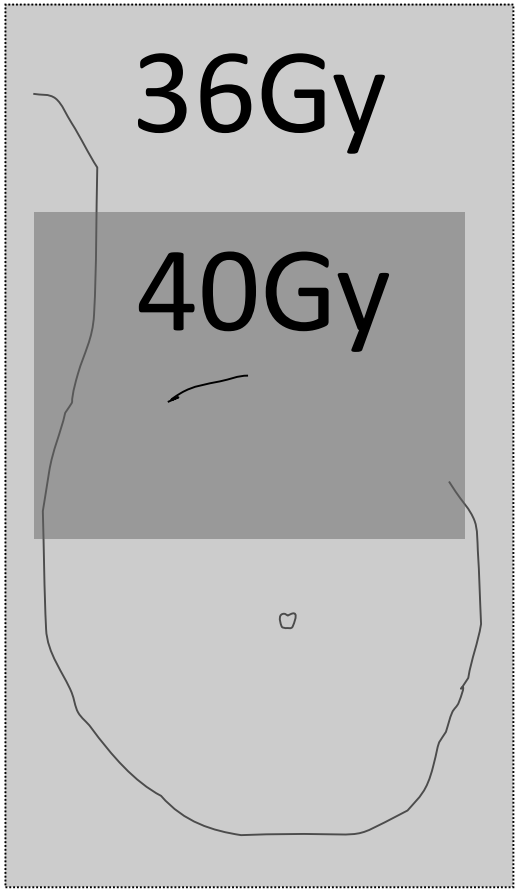
	Age	Tumor size	Histology	Lymph node status	Margin status
ASTRO Correa *et al.* PRO 2017	≥ 50	≤ 2 cm	Non-lobular DCIS Grade 1-2 Unifocal ER+ No LVI	Negative	Negative (≥ 2 mm)
GEC-ESTRO Polgar *et al.* RO 2010	≥ 50	≤ 3 cm	Non-lobular Unifocal Any ER status No LVI	Negative	Negative (≥ 2 mm)

IMPORT LOW study

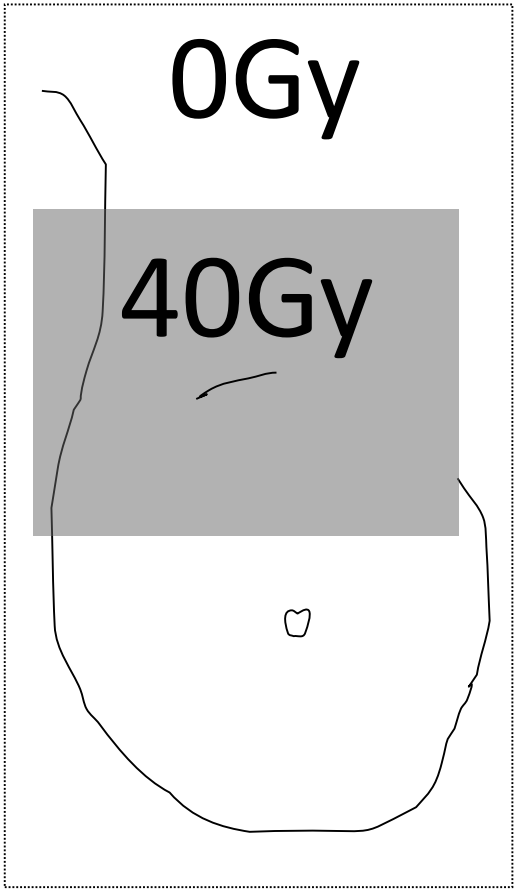
Whole Breast



Reduced Dose



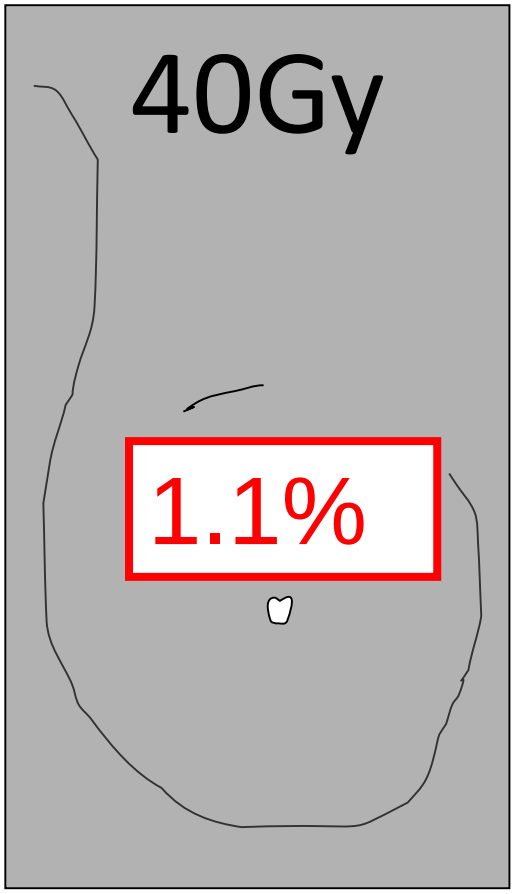
Partial-breast



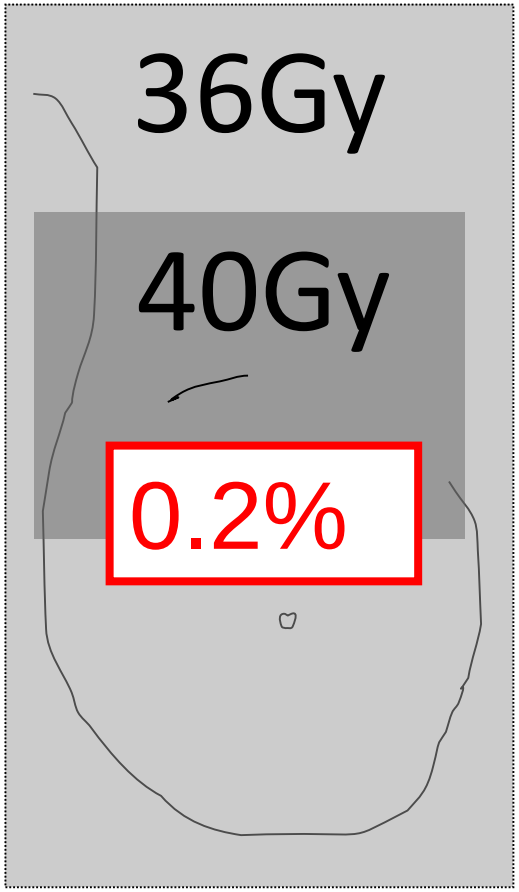
Coles Lancet 2017

IMPORT LOW study – local relapse at 5 years

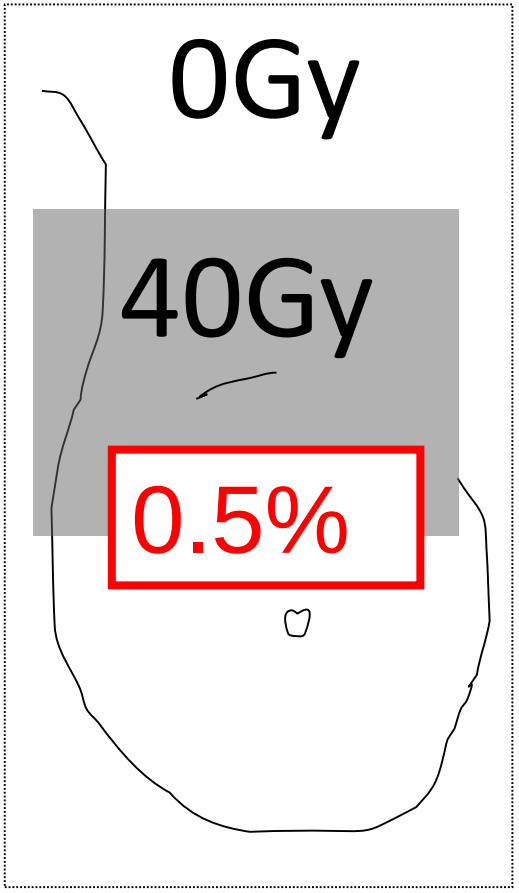
Whole Breast



Reduced Dose



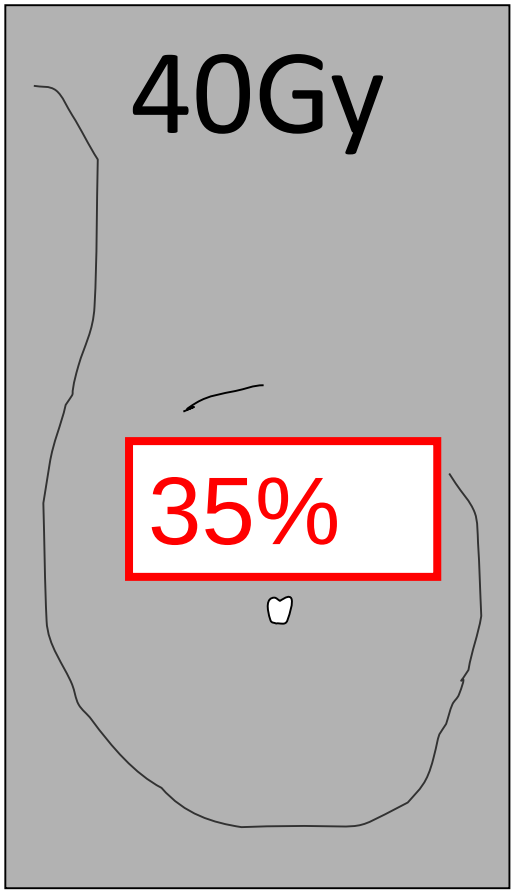
Partial-breast



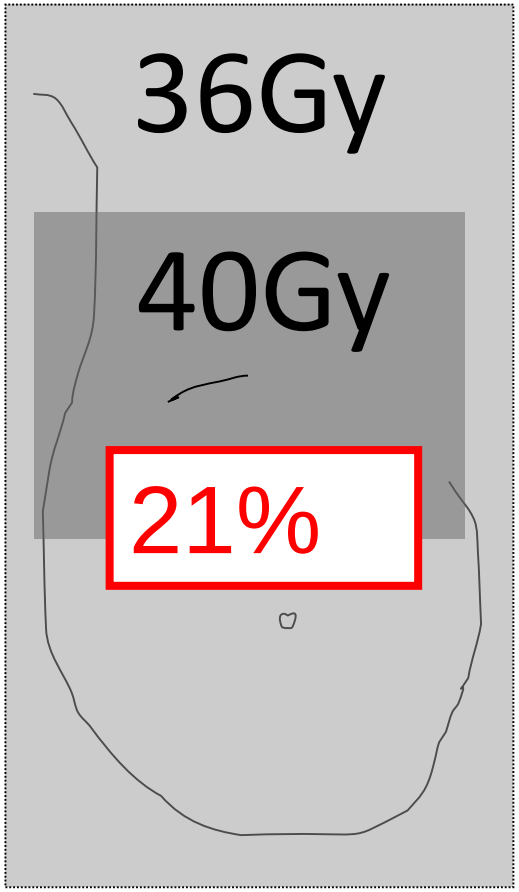
Coles Lancet 2017

IMPORT LOW study – breast firmness

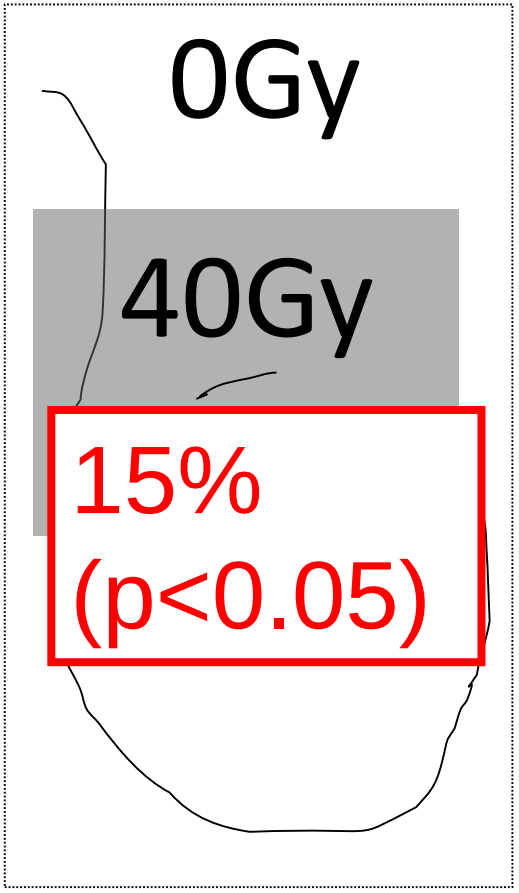
Whole Breast



Reduced Dose



Partial-breast

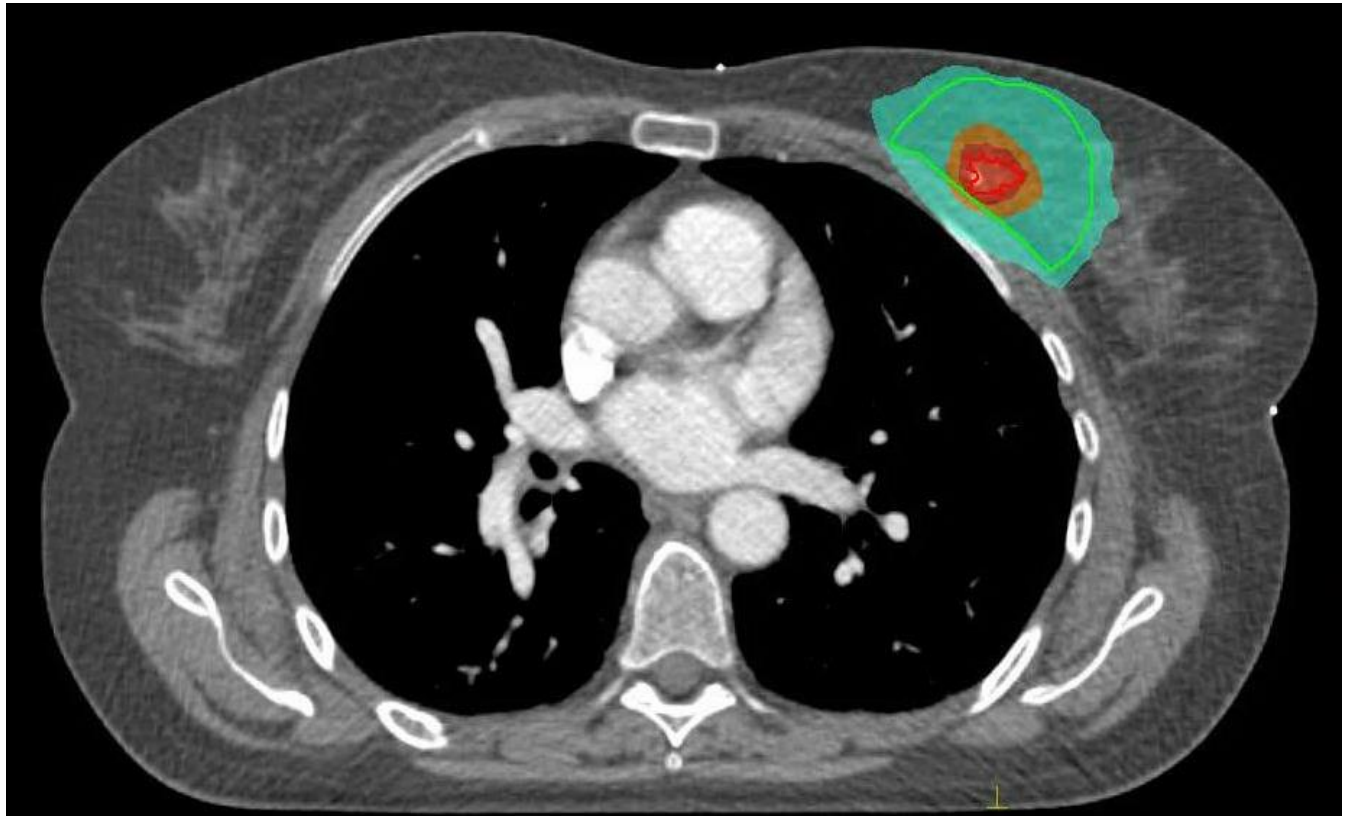


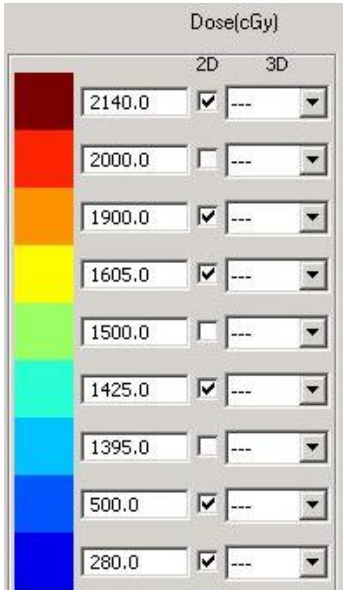
Courtesy of Dr Charlotte Coles

(Accelerated) partial breast irradiation – standard care

- Low local recurrence risk in selected low-risk patients
- Toxicity and cosmetic outcome: In **PBI** similar or less toxicity
- Ongoing phase III trials (i.e. NSABP B-39, RAPID)

Extreme breast hypofractionation – pre-operative single-dose ablative RT





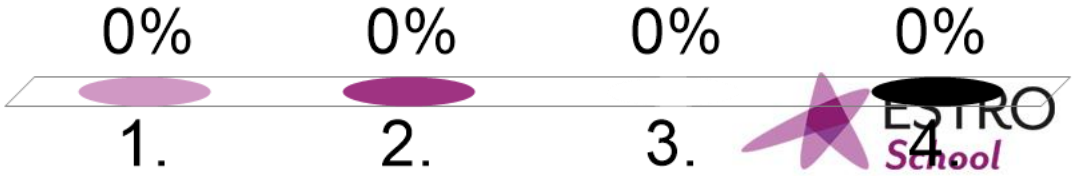
- Feasibility study (n=15)
- 1x20 Gy tumor, 1x15 Gy tumor bed
- At 6 months after RT: lumpectomy

Innovation in breast RT planning to reduce RT-induced toxicity

- Hypofractionation
- Simultaneously integrated boost (SIB)
- (Accelerated) partial breast RT
- **Breath hold technique**

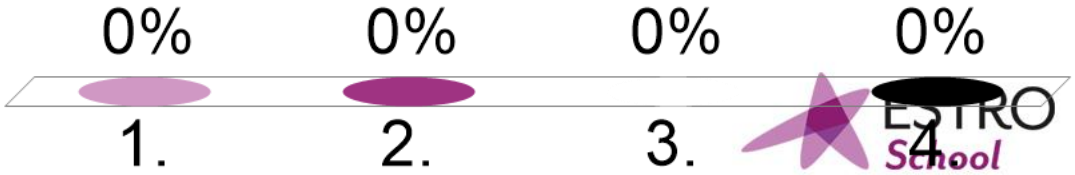
Do you use breath hold technique?

1. Yes, only in local RT (breast / chest wall)
2. Yes, in local and (loco)regional RT
3. No
4. I don’t know

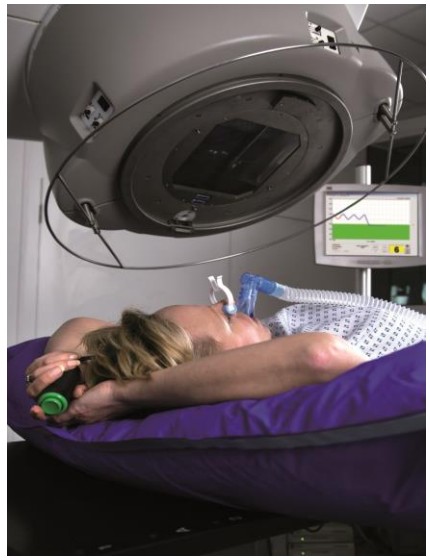


Do you use breath-hold technique in **right**-sided breast cancer patients?

1. Yes
2. No, only in left-sided breast cancer patients
3. No, at our institute we do not use breath-hold technique
4. I don’t know



Breath-hold techniques



- ABC-technique: Active breathing coordinator™

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

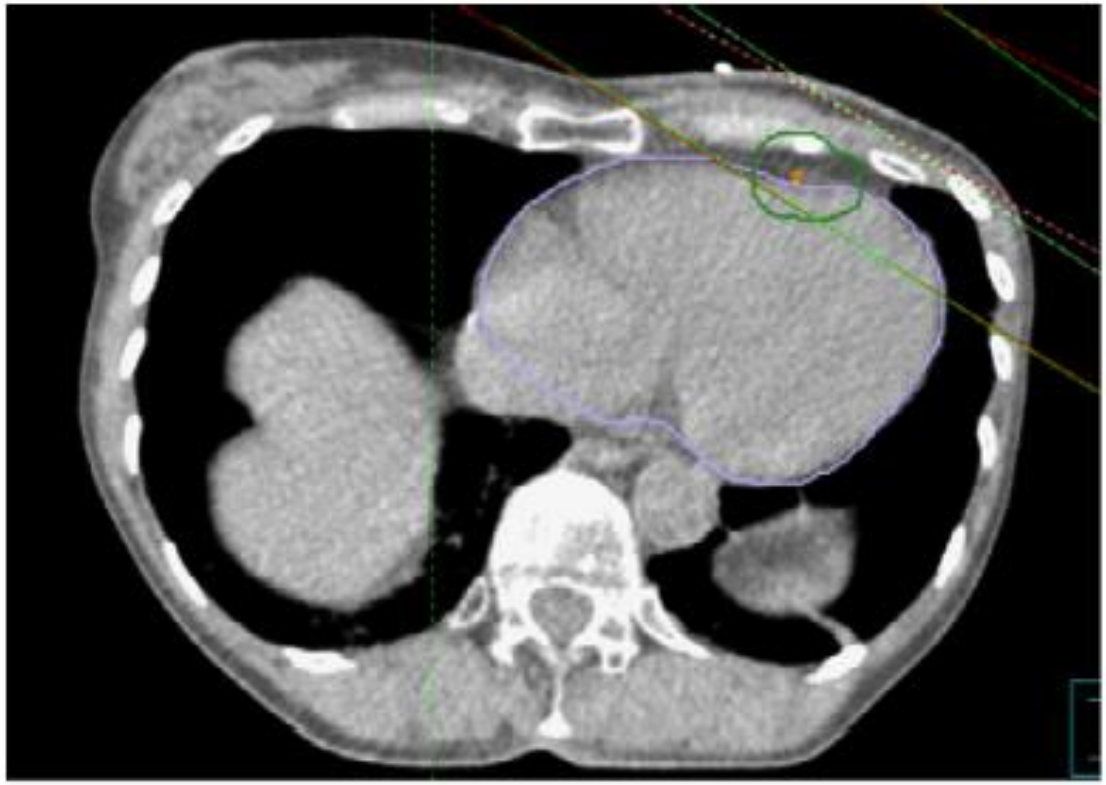
- Gating:

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

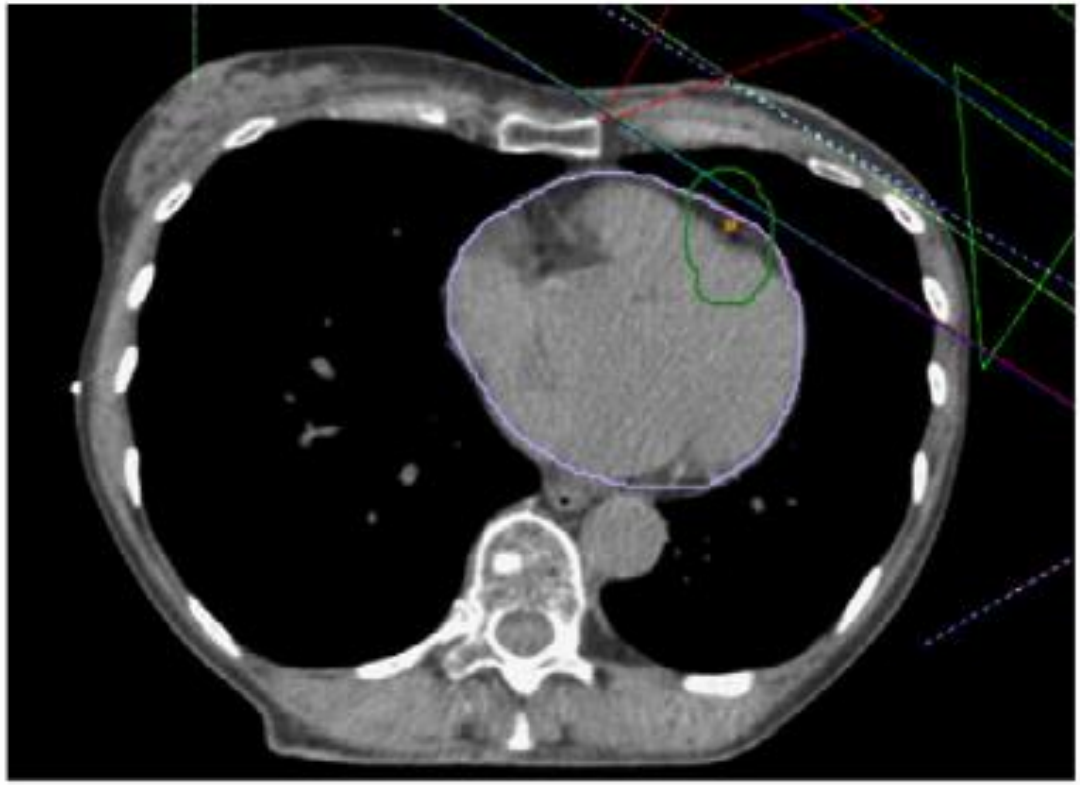
- Voluntary breath-hold technique

Bartlett Radiother Oncol 2013, 2017, Edmunds J Appl Clin Med Phys 2018

Optimal cardiac sparing – Breath-hold technique



Free breathing



v_DIBH

Bartlett Radiother Oncol 2013

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Free-breathing vs. voluntary breath-hold (VBH) techniques

Table 1

Mean normal tissue doses (Gy) for free-breathing and voluntary breath-hold (VBH) techniques with 95% confidence intervals in parentheses

	Free-breathing	VBH	*P*
Heart	1.79 (1.66–1.91)	1.04 (0.97–1.12)	<0.001
LAD	11.9 (10.8–13.1)	5.3 (4.5–6.1)	<0.001
LAD_{max}	35.2 (33.4–37.1)	24.0 (20.8–27.1)	<0.001
Ipsilateral lung	3.9 (3.6–4.2)	4.0 (3.7–4.2)	0.762
Whole lung	1.9 (1.8–2.1)	2.0 (1.9–2.1)	0.374

LAD, left anterior descending coronary artery.

Bartlett Radiother Oncol 2013, 2017, Edmunds J Appl Clin Med Phys 2018

Free-breathing vs. voluntary breath-hold techniques

Table 1
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LAD, left anterior descending coronary artery.

Bartlett Radiother Oncol 2013, 2017, Edmunds J Appl Clin Med Phys 2018

Compliance Breath hold technique

High (99%), except for:

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

Innovation in breast RT planning to reduce RT-induced toxicity

- Hypofractionation
- Simultaneously integrated boost (SIB)
- (Accelerated) partial breast RT
- Breath hold technique
- **Introduction of VMAT/IMRT/Tomotherapy**

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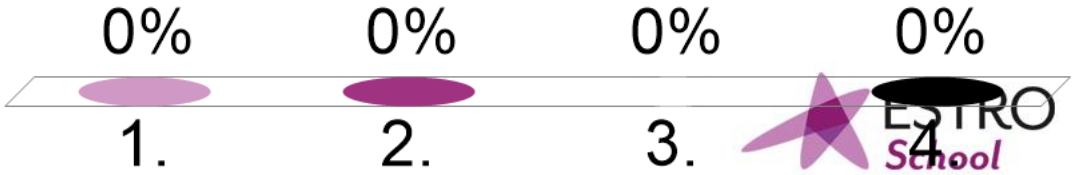
Which planning technique do you use for breast cancer patients?

1. Only 3DCRT / f-IMRT
2. IMRT/VMAT/Tomo
3. 3DCRTor f-IMRT +IMRT/VMAT/Tomo
4. I don’t know

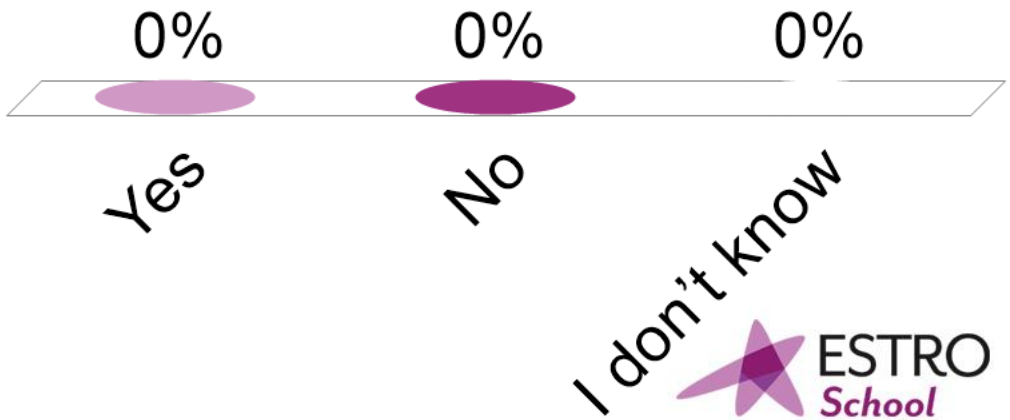
www.responseware.eu

ID: ATP18



Do you use protons for (selected) breast patients?

1. Yes
2. No
3. I don’t know



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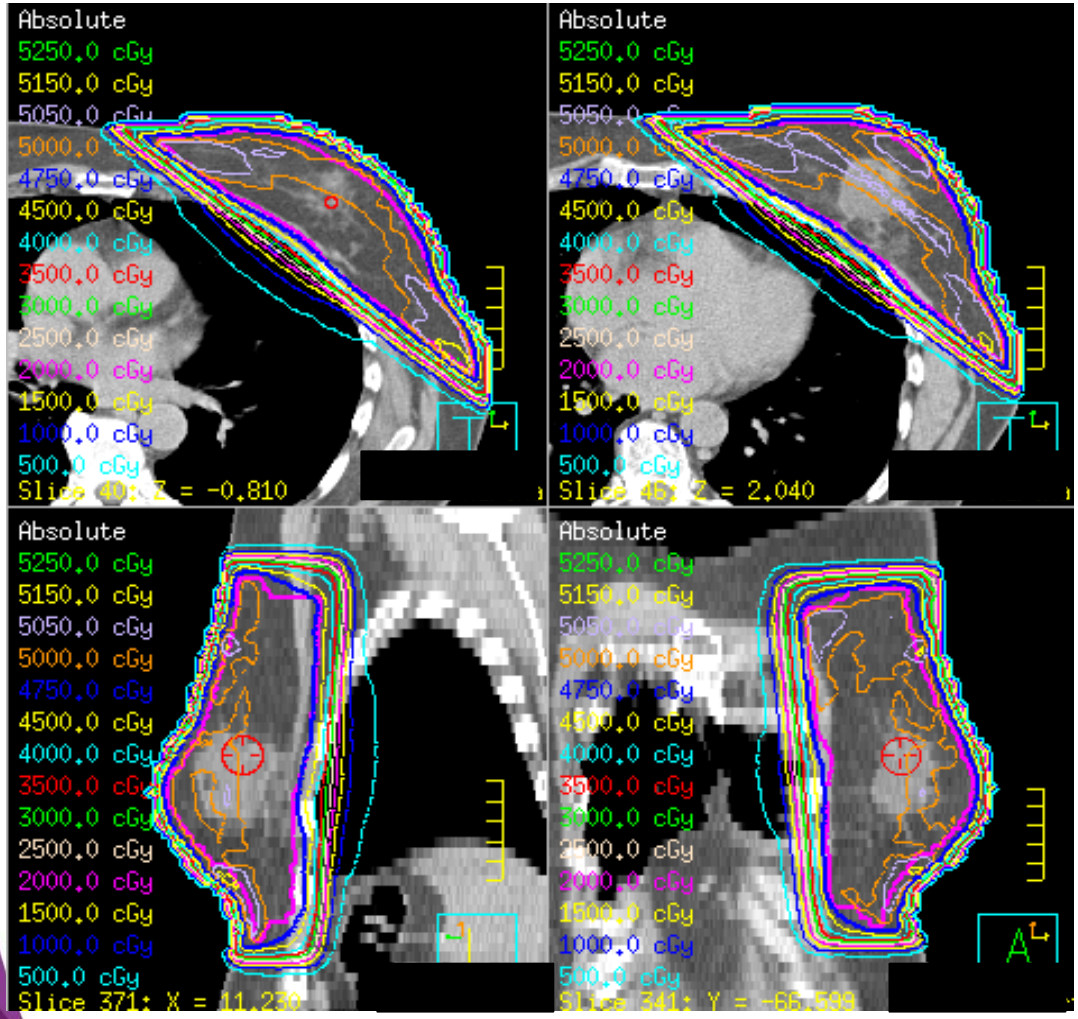
Forward IMRT / 3DCRT



Field-in-field technique / forward IMRT:

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

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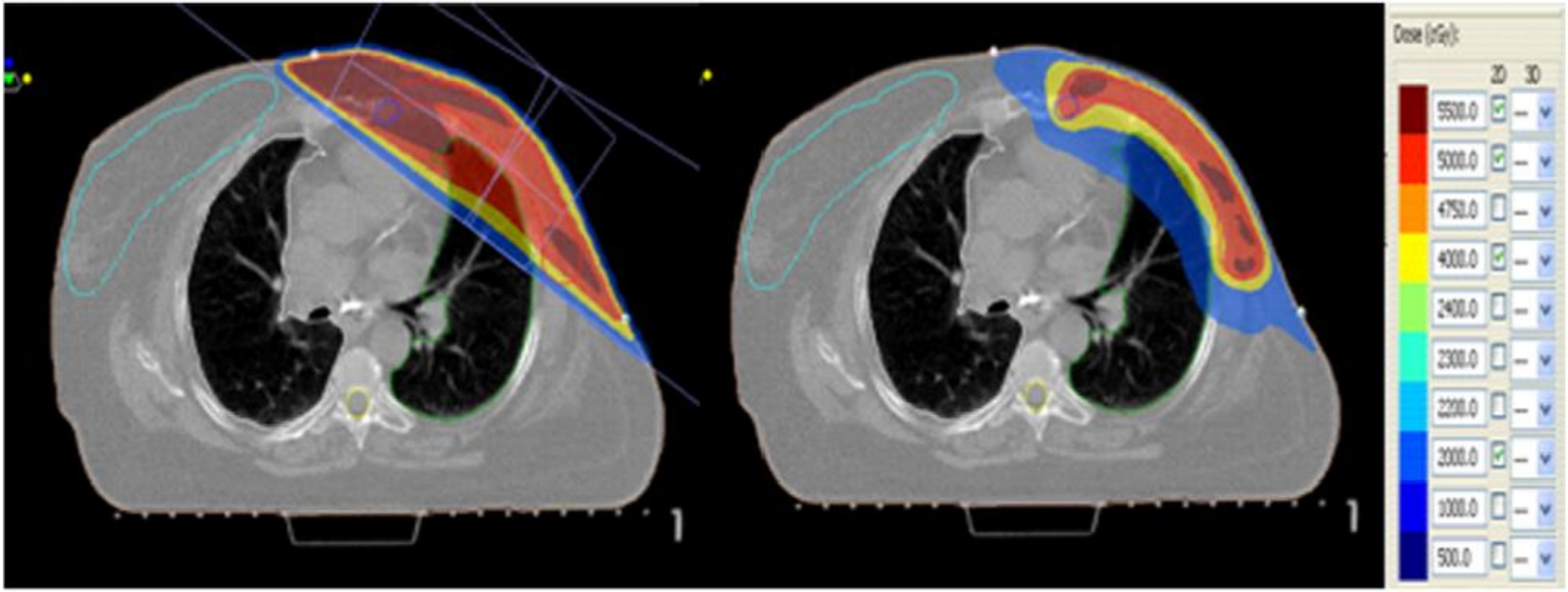
More advanced planning techniques in breast cancer patients

Aim: Reduction of RT-induced toxicity

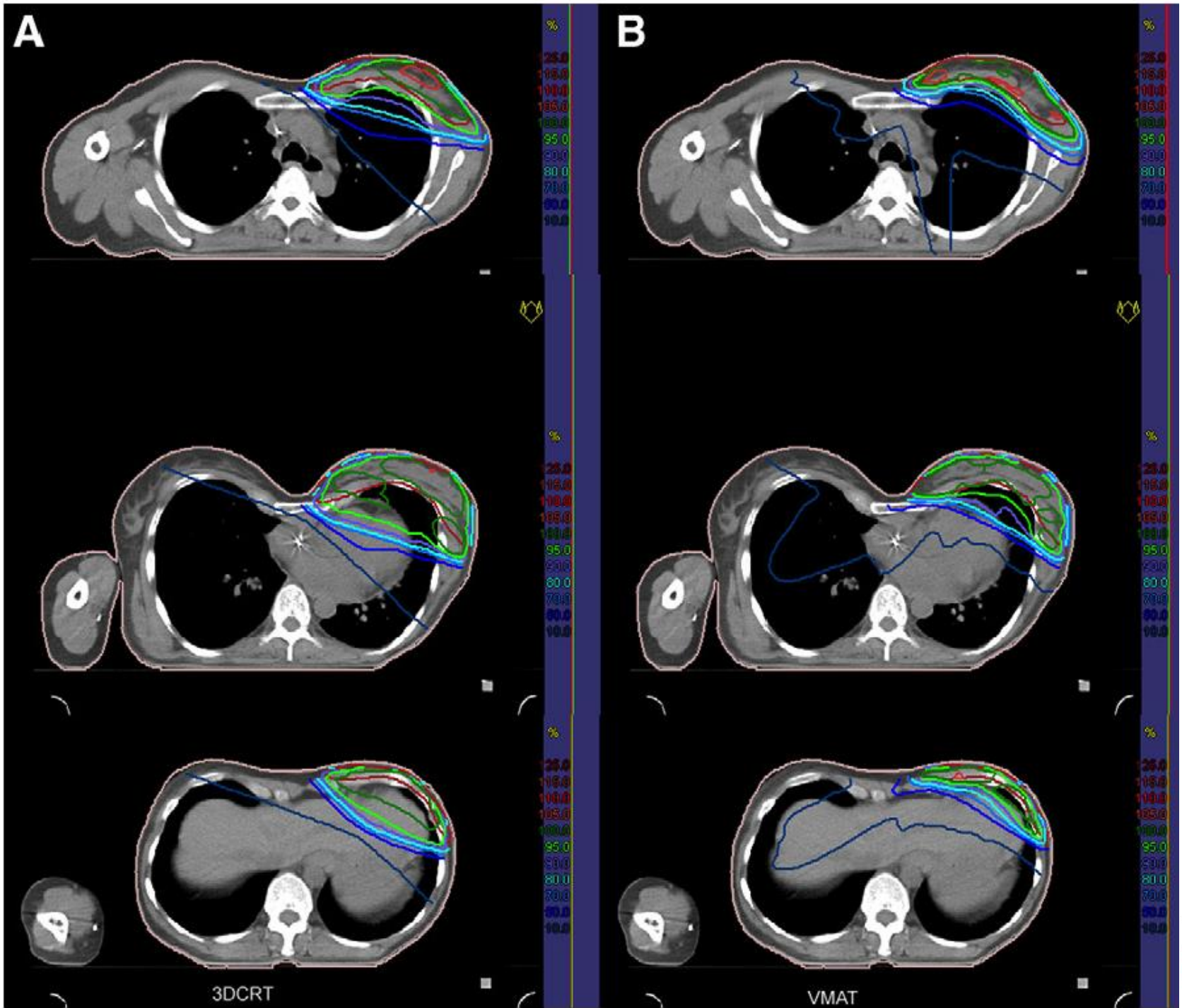
- IMRT and VMAT (instead of 3DCRT / f-IMRT)
  +/- breath-hold technique

3D-CRT compared with VMAT



3D-CRT VMAT

Funnel chest – Heartl 2014



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Introduction of IMRT and VMAT
Breast cancer radiotherapy

- Improved dose conformity (compared with 3D-CRT or forward-IMRT)
- Reduction in dose to heart and coronary arteries, lowest in combination with breath hold technique

Sakka 2017, Osman RO 2014, Popescu IJROBP 2010, Qi Med Dosimetry 2014

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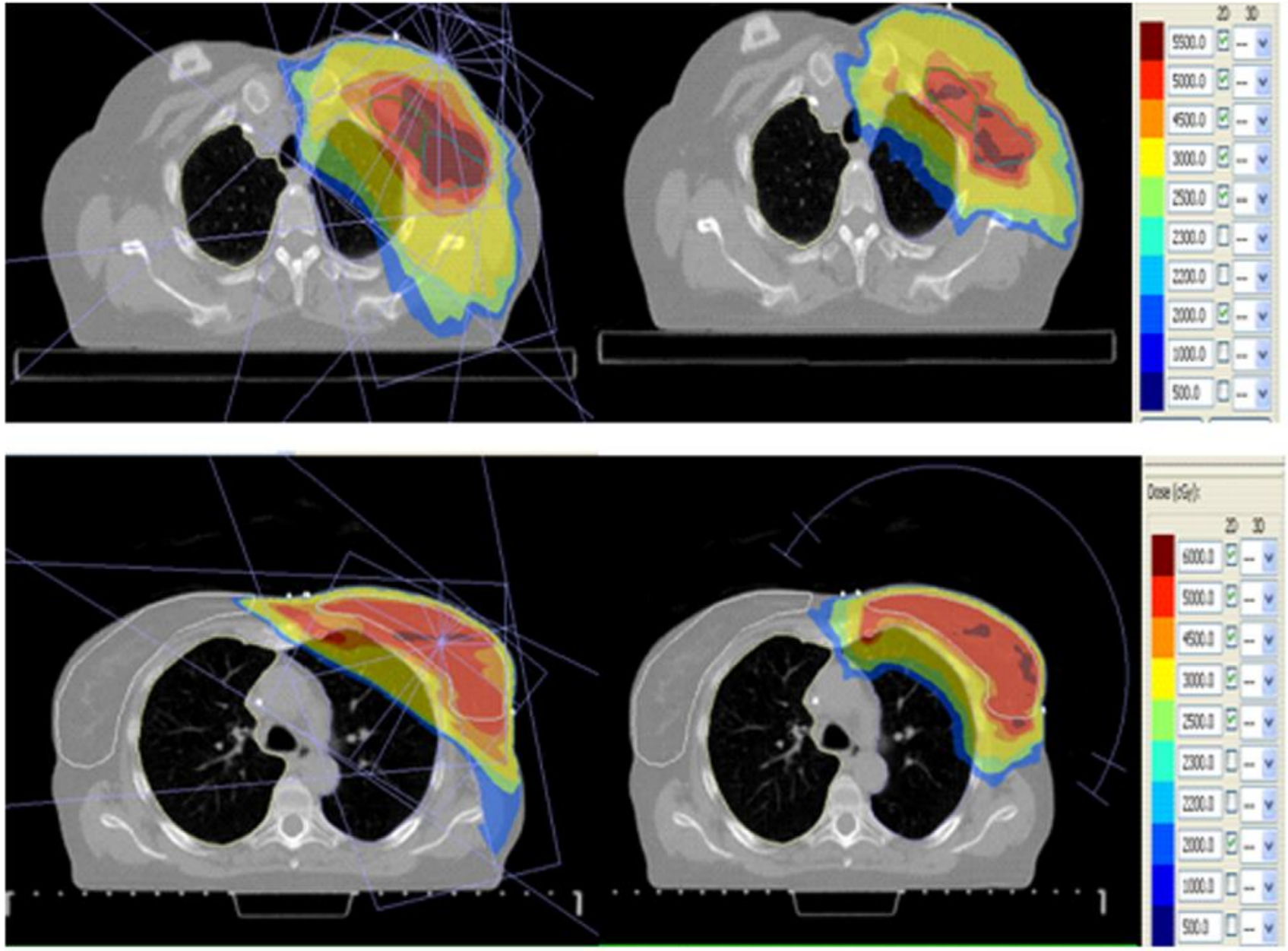
Multibeam-IMRT compared with VMAT



Qi Med Dosimetry 2014

Comparison of IMRT and VMAT
local / locoregional RT

- VMAT compared to IMRT:
  - Shorter delivery time
  - Reduced number of monitor units in VMAT compared to IMRT

Sakka 2017, Osman RO 2014, Popescu IJROBP 2010, Qi Med Dosimetry 2014

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Conclusions – Innovations in breast RT planning

Focus on reduction of radiotherapy-induced toxicity:

- Hypofractionation
- Breath-hold technique
- (Accelerated) partial breast RT
- IMRT / VMAT with Breath hold technique

Hypofractionation and APBI →
Shorter duration of overall treatment time

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Thank you for your attention!

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WWW.ESTRO.ORG/SCHOOL

Case 1: Breast

ESTRO Athens
September 2018

Introduction case 1:
Breast and regional lymph nodes
(including internal mammary nodes)

Mrs V, 61 years old

- May 2017: Screening for breast cancer → referred to hospital
- Medical history: Hypertension, stenosis carotid artery (left)

Mrs V, 61 years old

- May 2017: Screening for breast cancer → referred to hospital
- Medical history: Hypertension, stenosis carotid artery (left)
- Physical examination:

  Left breast: tumor 2x2 cm

  Left axilla: palpable lymph node

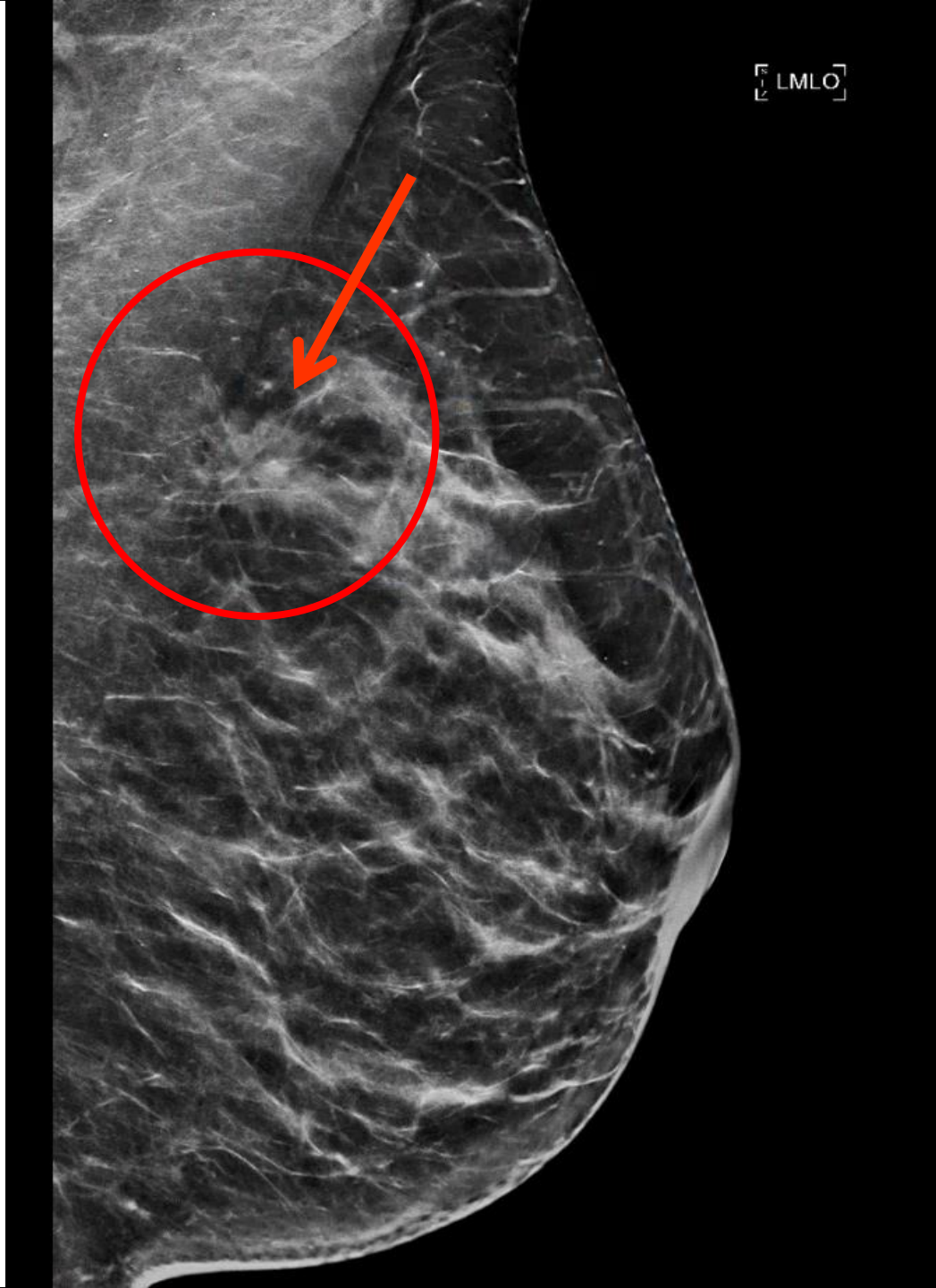
Mrs V, 61 years old

- Medical history: Hypertension, stenosis carotid artery (left)
- May 2017: Screening for breast cancer → referred to hospital

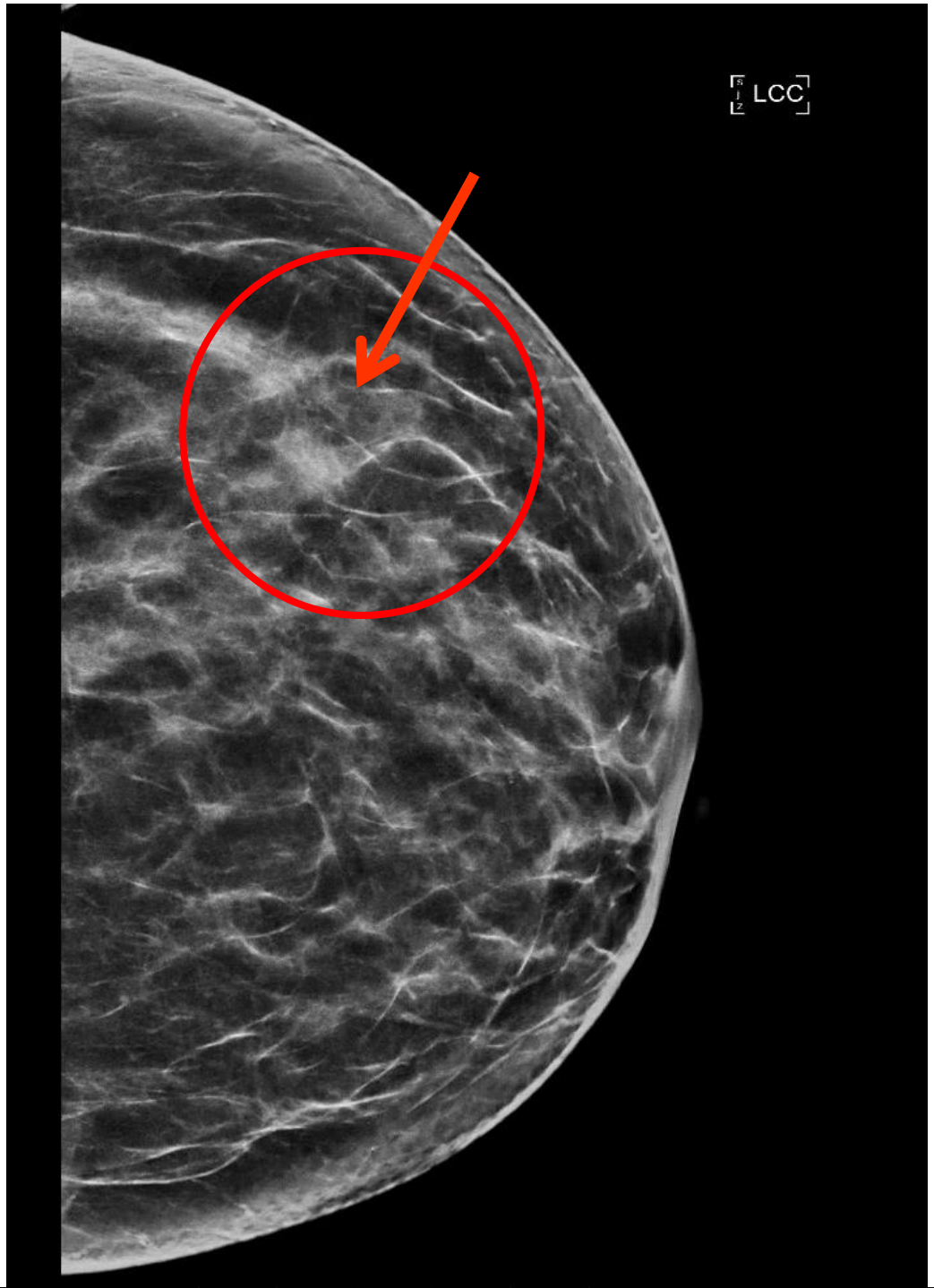
- Physical examination:
  - Left breast: tumor 2x2 cm
  - Right axilla: palpable lymph node

- Mammography:
  - Lesion in left breast
  - In upper-outer quadrant
  - 19 mm

Mammography
Mediolateral oblique view



Mammography
- Craniocaudal view



Mrs V, 61 years old

- Medical history: Hypertension, stenosis carotid artery (left)
- May 2017: Screening for breast cancer → referred to hospital

- Physical examination:
  - Left breast: tumor 2x2 cm
  - Right axilla: palpable lymph node

- Mammography:
  - Lesion in left breast, in upper-outer quadrant, 19 mm
  - Birads-IV

BI-RADS: Breast Imaging-reporting and data system

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

BI-RADS classification

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

Mrs V, 61 years old - Diagnostics

- Ultrasound: 1 pathologically enlarged lymph nodes in right axilla

- Ultrasound-guided biopsy left breast

  Histology left breast: infiltrating ductal carcinoma, grade 2, ER100%, PR80%, HER2 negative

- Fine needle aspiration (FNA) left axilla: metastasis

- MRI:

  Tumor in left breast, 2x2 cm

  BIRADS-6

MRI - BI-RADS classification

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

Mrs V, 61 years old

- Ultrasound: 1 pathologically enlarged lymph nodes in right axilla
- Ultrasound-guided biopsy left breast

  Histology left breast: infiltrating ductal carcinoma, grade 2, ER100%, PR80%, HER2 negative
- Fine needle aspiration (FNA) left axilla: metastasis
- MRI:

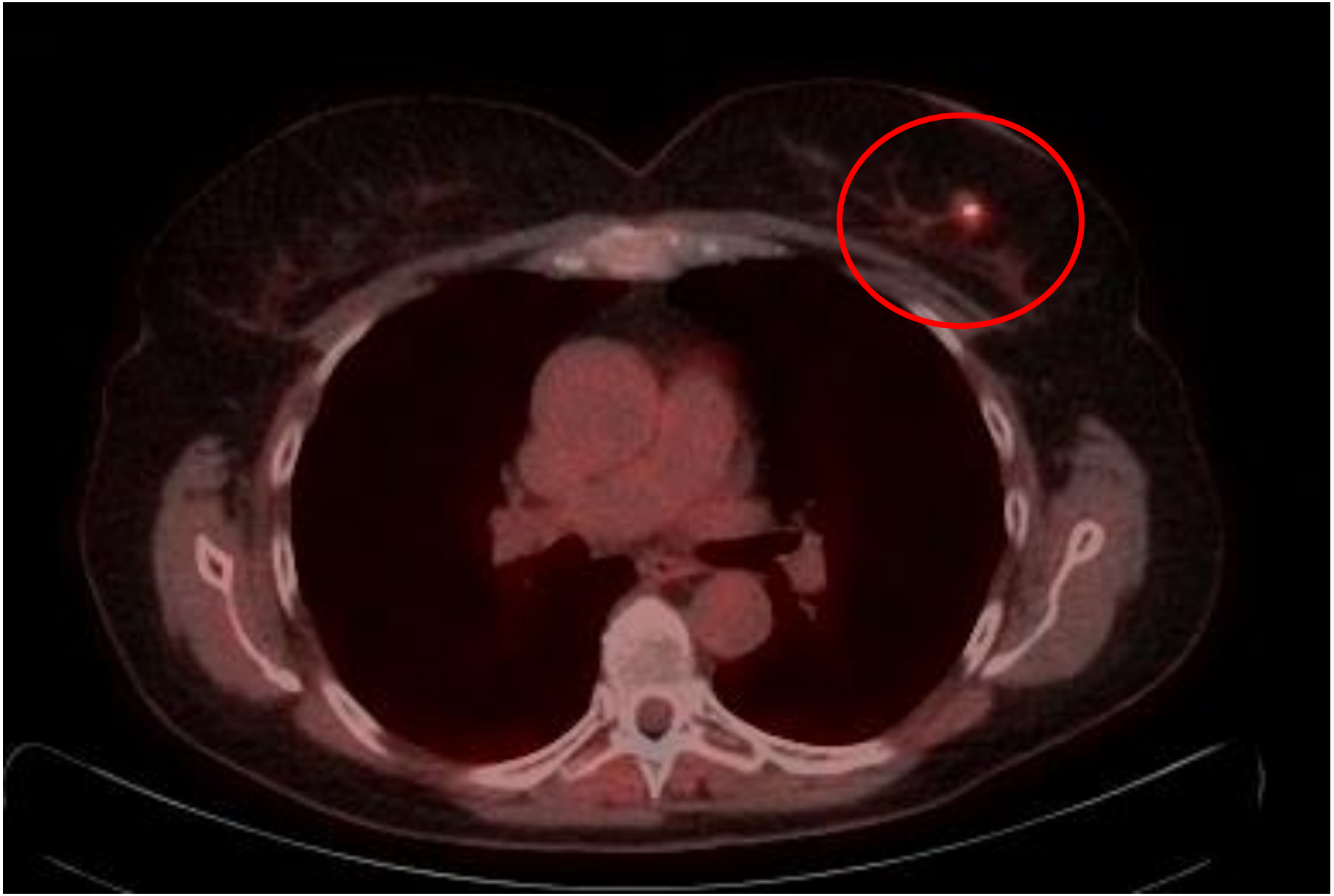
  Tumor in left breast, 2x2 cm

  BIRADS-6
- ^{18}FDG-PET-CT

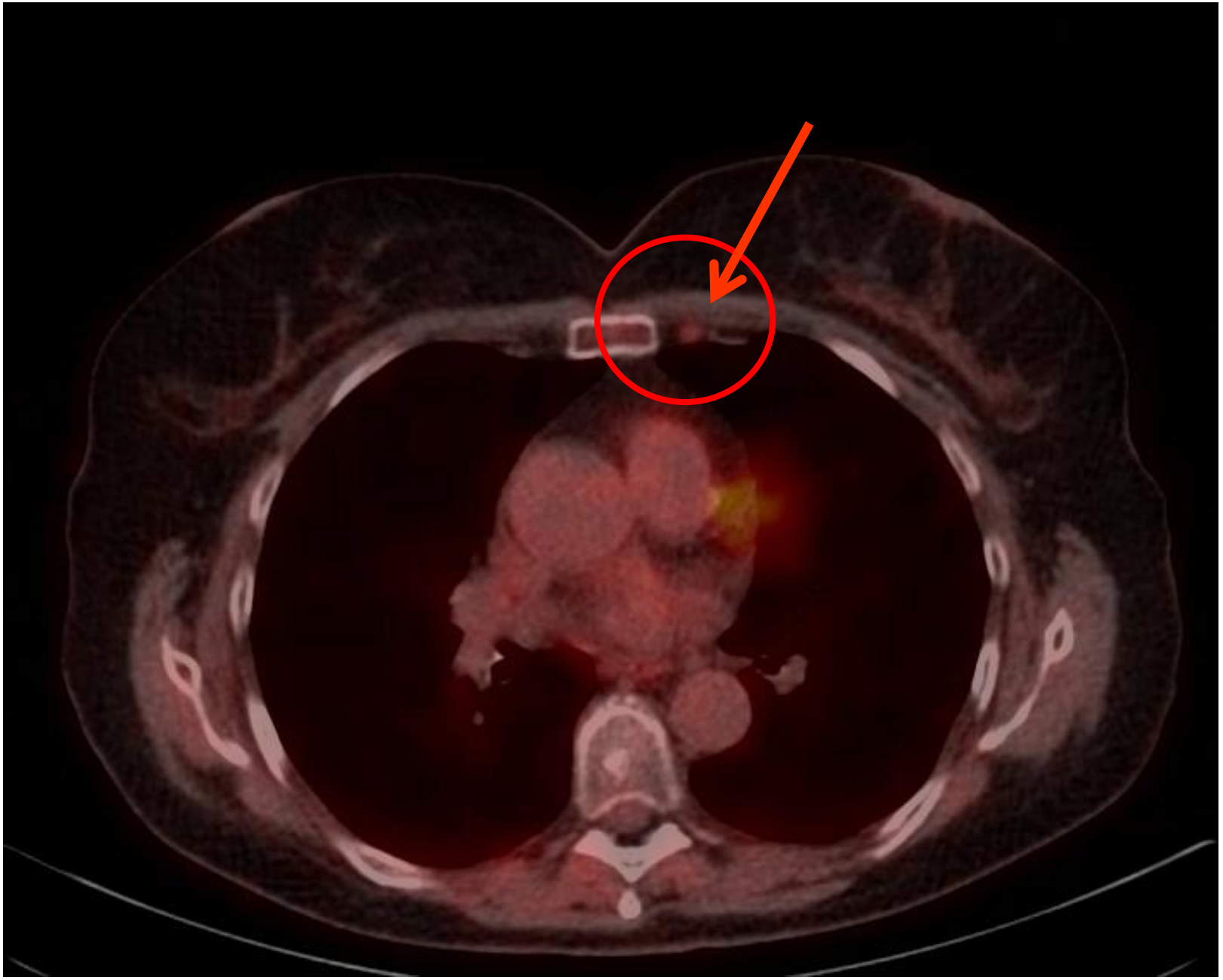
Mrs V, 61 years old – ^{18}FDG-PET-CT

- uptake:
  - In tumor left breast
  - In 6 lymph nodes:
    - axillary lymph nodes levels I and II
    - internal mammary lymph nodes
  - No distant metastases

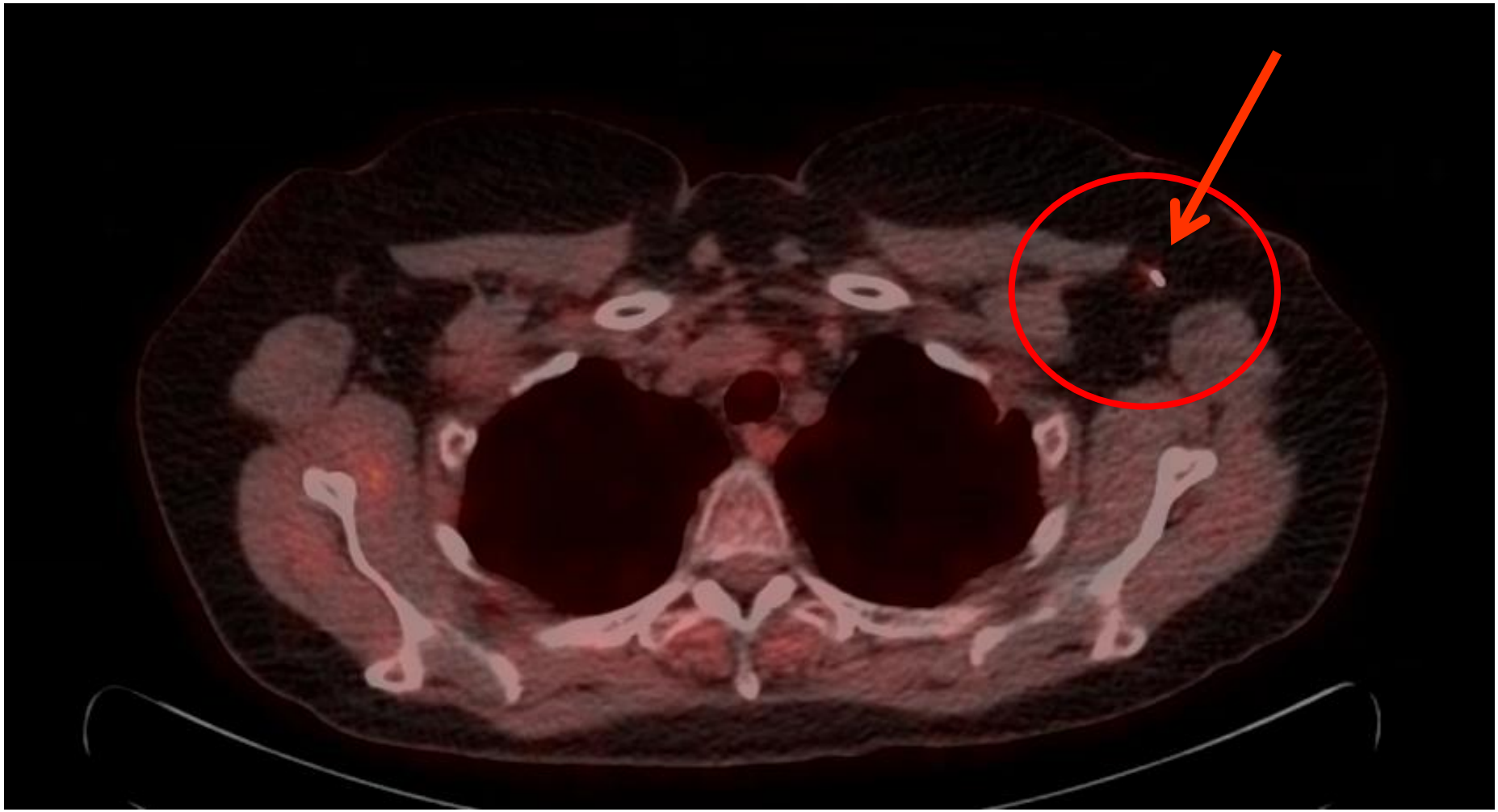
^{18}FDG-PET-CT



^{18}FDG-PET-CT



^{18}FDG-PET-CT



Mrs V, 61 years old – Clinical stage

- ^{18}FDG-PET-CT, uptake:
  - In tumor left breast
  - In 6 lymph nodes:
    - axillary lymph nodes levels I and II
    - internal mammary lymph nodes
  - No distant metastases

Clinical stage: cT1N3bM0 left-sided breast cancer

Mrs V, 61 years old - Treatment

- **Neo-adjuvant chemotherapy**
  until October 2017

- Imaging **after** neo-adjuvant chemotherapy:
  MRI: decreased enhancement of tumor, diameter15 mm

  ^{18}FDG-PET-CT: residual uptake in breast tumor, lymph nodes

  → No new lesions

Mrs V, 61 years old - Treatment

- **Neo-adjuvant chemotherapy** until Oktober 2017

- **Breast-conserving surgery including targeted axillary dissection**
  Microscopy: no response, tumor diameter 1.5 cm
  1 lymph nodes: tumorpositive

- **Axillary lymph node dissection:** 12/27 tumorpositive nodes

→ Breast cancer cT1N3b → ypT1cpN3

Mrs V, 61 years old - Treatment

Breast cancer cT1N3b → ypT1cpN3

Post-operative treatment:

- Locoregional radiotherapy
  - Breast + boost
  - Axilla level I I–IV (Level IV = supraclavicular region)
  - Internal mammary nodes + boost

Mrs V, 61 years old - Treatment

Breast cancer cT1N3b → ypT1cpN3

Post-operative treatment:

- Locoregional radiotherapy – SIB and breath hold technique

  Breast + boost 21x2.66 Gy → converted to 23 fractions: **23x2.57 Gy**

  Axilla level II –IV: **23x2.03 Gy**

  Internal mammary nodes + boost: **23x2.66 Gy**

Mrs V, 61 years old - Treatment

Breast cancer cT1N3b → ypT1cpN3

Post-operative treatment:

- Locoregional radiotherapy – SIB and breath hold technique
  - Breast + boost: 23x2.57 Gy
  - Axilla level I –IV: 23x2.03 Gy
  - Internal mammary nodes + boost: 23x2.66 Gy

- Adjuvant endocrine therapy, biphosphonates

Breast planning – session objectives

- Target volumes

  Breast + **boost:** 21x2.66 Gy → converted to 23 fractions **23x2.57 Gy**

  Axilla level II –IV: **23x2.03 Gy**

  Internal mammary nodes + **boost: 23x2.66 Gy**

- Dmean 99%-101%, V95% PTV's > 99%, D2cc <107%
- Techniques:
  - 3D CRT / Forward IMRT /
  - VMAT / IMRT /
  - Tomotherapy /
  - Hybrid technique

Locoregional RT – Organs at risk

Organ at risk	Acute toxicity	Late toxicity	Dose constraint
Skin	radiation dermatitis	Teleangiectasia	ALARA*
(Contralateral) breast	oedema	tumor induction, teleangiectasia, fibrosis	ALARA* *< 1 Gy if age ≤ 40 year* *< 5 Gy if age > 40 year*
Heart	pericarditis	valvular dysfunction cardiomyopathy atherosclerosis	V10Gy < 5% V5Gy < 10% mean heart dose < 3 Gy (V25Gy < 10%)
Lungs	radiation pneumonitis	lung fibrosis	Mean lung dose < 7 Gy
Esophagus	radiation esophagitis	stenosis, fistula	ALARA* (Dmean < 45 Gy)
Spinal cord		myelopathy	Dmax 50 Gy (α/β 2)
Brachial plexus		plexopathy (paralysis)	Dmax 66 Gy (α/β 2)
Upper extremity (musculature)	Pain, limited mobility, oedema		ALARA*

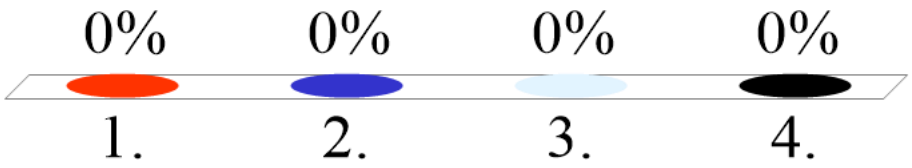
*ALARA: As Low As Reasonably Achievable

Which is the most important part PTV in this patient?

1. Breast
2. Tumor bed
3. Internal mammary lymph nodes
4. Axillary lymph nodes

www.responseware.eu

ID: ATP18

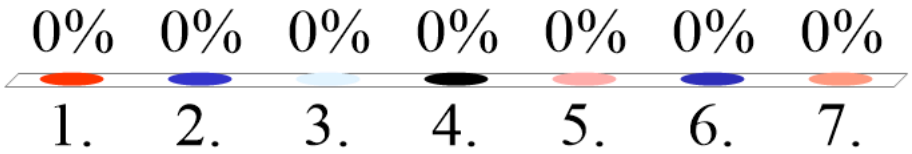


Which is the most important normal tissue in this patient?

1. Brachial plexus
2. Chest wall
3. Contralateral breast
4. Heart
5. Ipsilateral breast
6. Left lung
7. Esophagus

www.responseware.eu

ID: ATP18



Planning – breast case

- VMAT
  - 1st arc: 0-270 degrees
  - 2nd arc: 270-180 degrees
  - 3rd arc: 180-90 degrees

Planning – breast case

- VMAT
  - 1st arc 0-270 degrees
  - 2nd arc 270-180 degrees
  - 3rd arc: 180-90 degrees

- Breath-hold technique; small beams to optimize heart sparing
  - 14 breath holds (without treatment verificiation)

Planning – breast case

- VMAT
  - 1st arc 0-270 degrees
  - 2nd arc 270-180 degrees
  - 3rd arc: 180-90 degrees

- Breath-hold technique; small beams to optimize heart sparing
  - 14 breath holds (without treatment verificiation)

- Adaptation of the PTV internal mammary lymph nodes (imn)
  → PTV imn evaluation, i.e. PTV imn minus lung

Planning – breast case

- Autoflash 2.5 cm → contour changes (e.g. breast oedema)

- Robustness of the plan: shiftplan

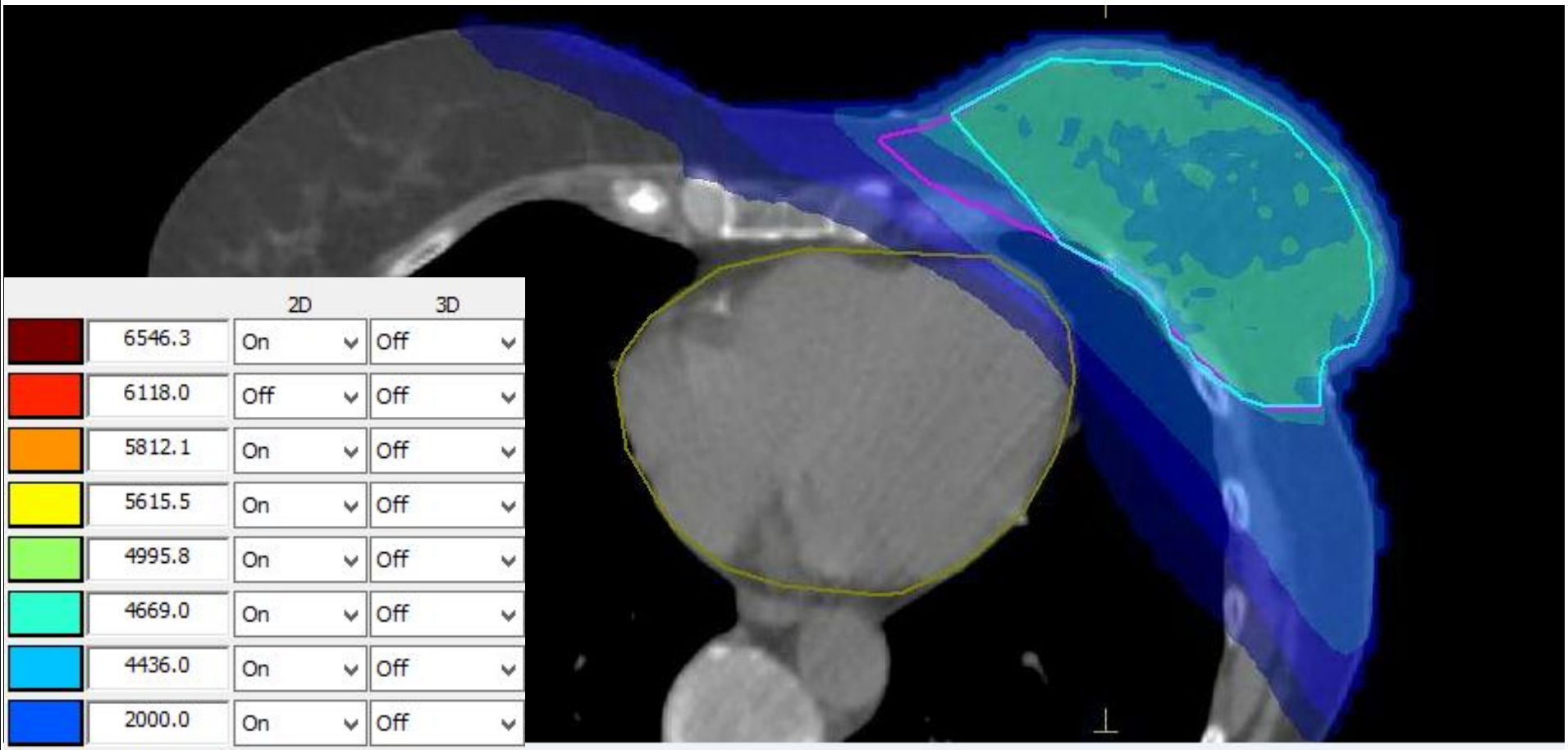
  Isocenter was shifted (5 mm)

Planning – breast case

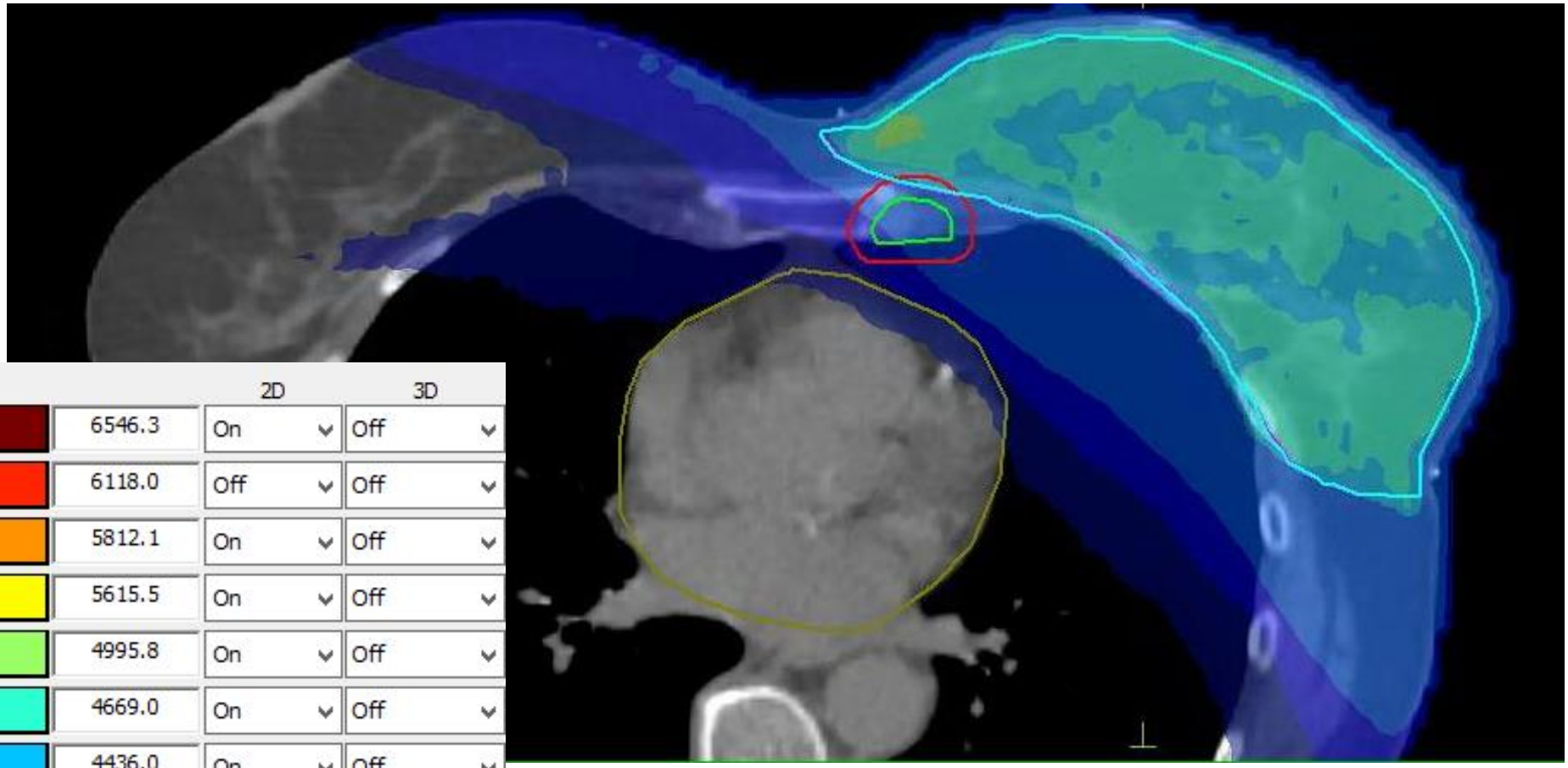
- First plan: heart dose was too high

- Compromise:
- ‘Elective fields’
  - internal mammary lymph nodes
  - caudal part of the breast

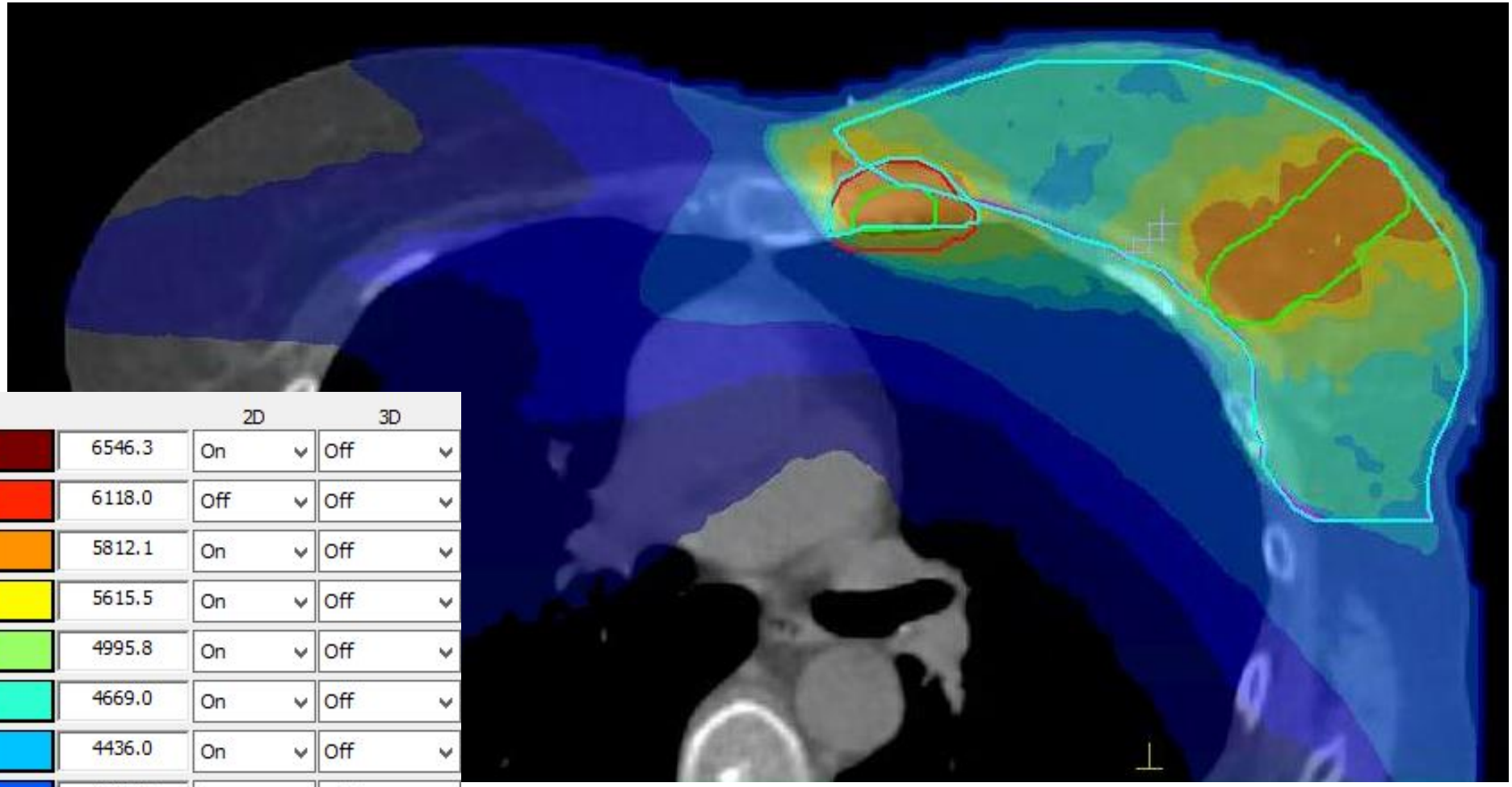
Breast planning – cropped breast



Breast planning – cropped IMN



Breast planning – cropped IMN (II)



Happy Planning!

Treatment delivery and verification – breast case

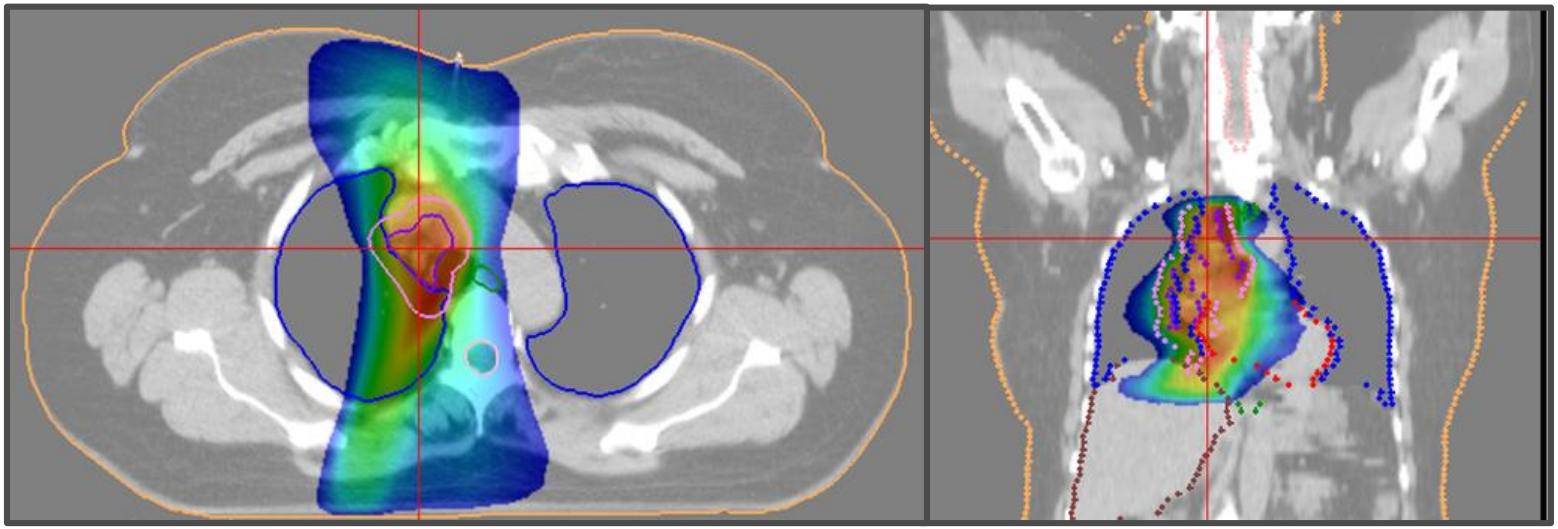
- 1,050 MU

  delivery time 164 seconds

ESTRO School

Kliniken Maria Hilf
Mönchengladbach

UNIVERSITÄTS KLINIKUM FREIBURG

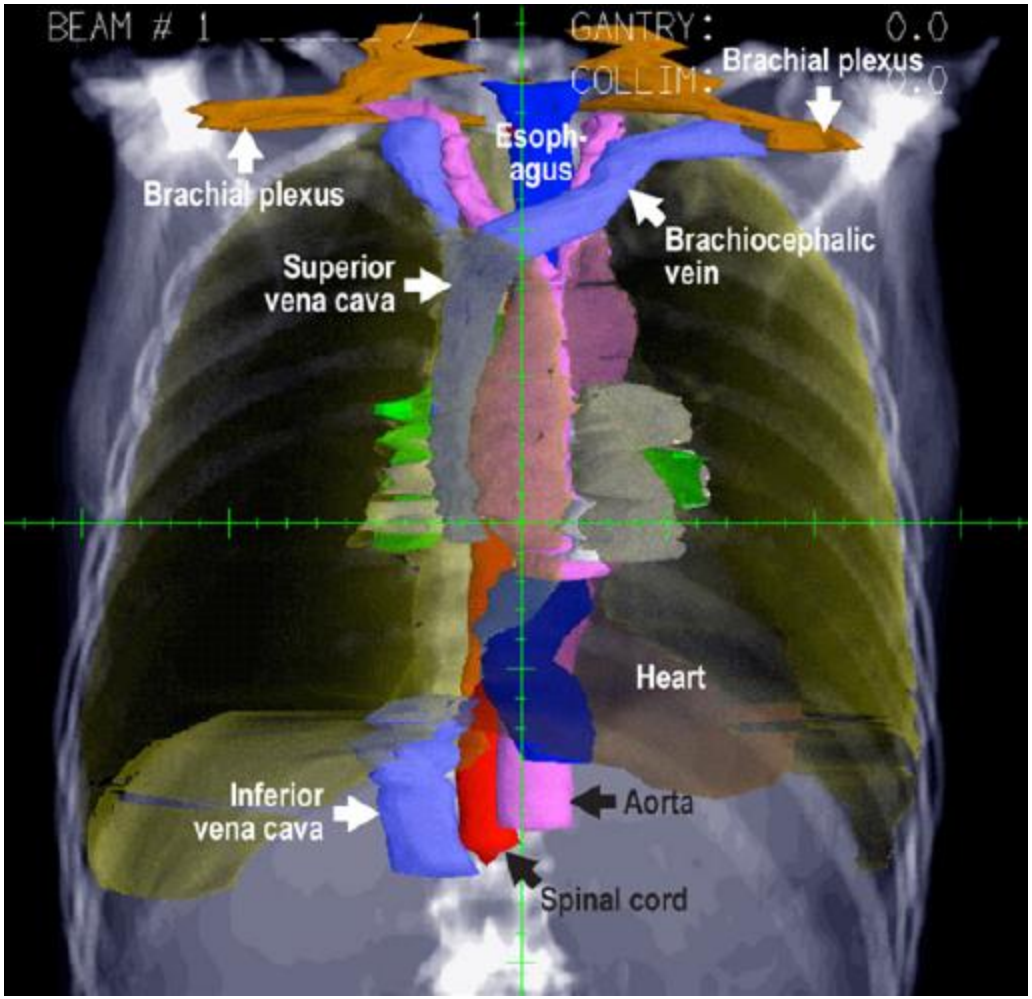


Relationships between 3D dose distributions and clinical toxicities - Chest

Prof. Dr. med Ursula Nestle

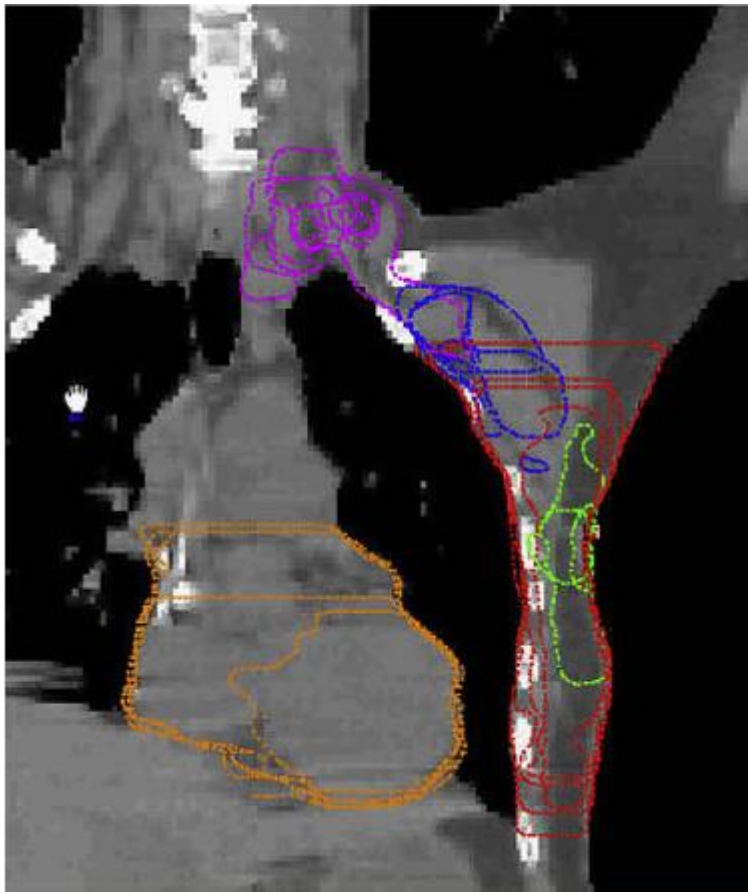
KMH Mönchengladbach
and UK Freiburg, Germany

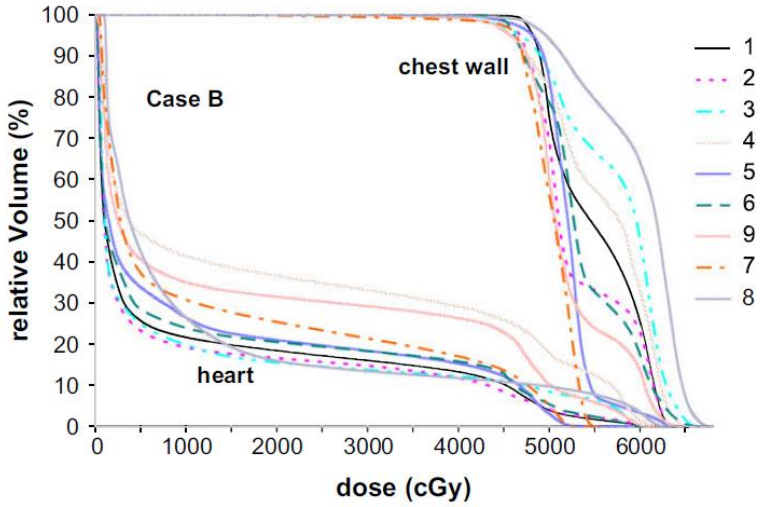
Normal tissues in the chest

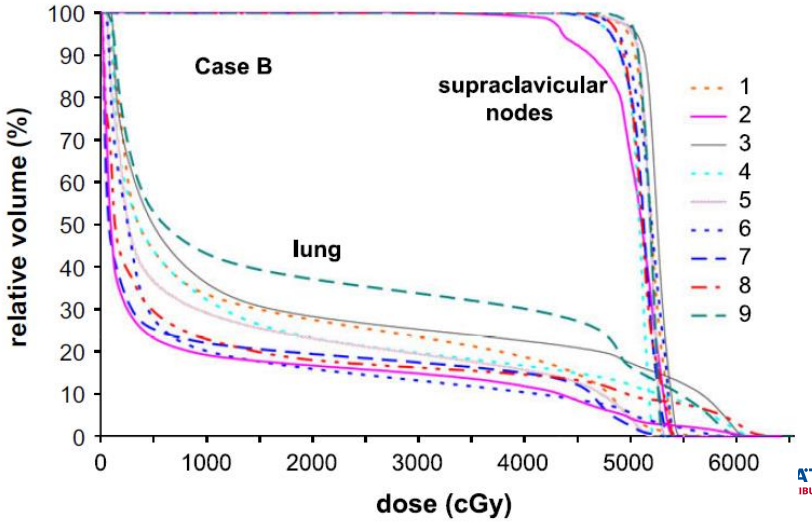


Kong, IJROBP 2011; 81(5); 1442-57

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







Kliniken Maria Hilf Mönchengladbach

Li, IJROBP 2009; 73(3); 944-51

Dose limits for normal tissues in the chest

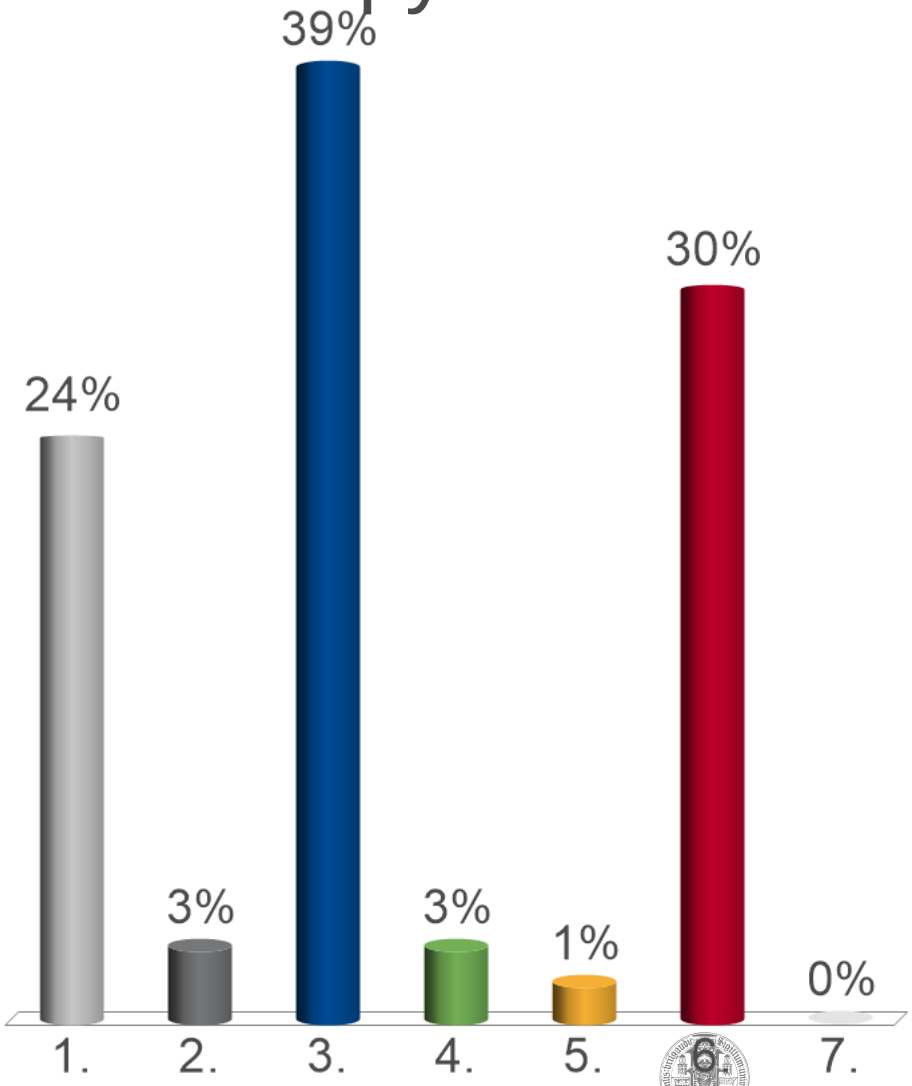
Table 1. Dosimetric limits for thoracic organs at risk

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

Q1: What do you consider the most critical normal tissue for chest radiotherapy?

1. lung
2. esophagus
3. spinal cord
4. brachial plexus
5. thoracic wall
6. heart
7. central bronchi

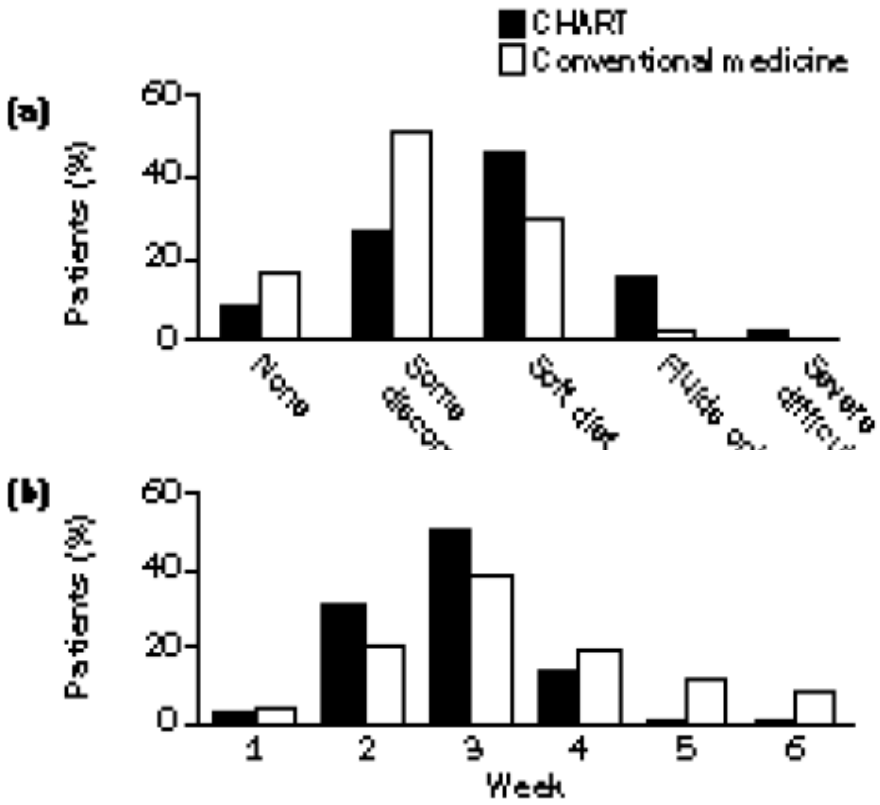


Esophagus: acute reactions

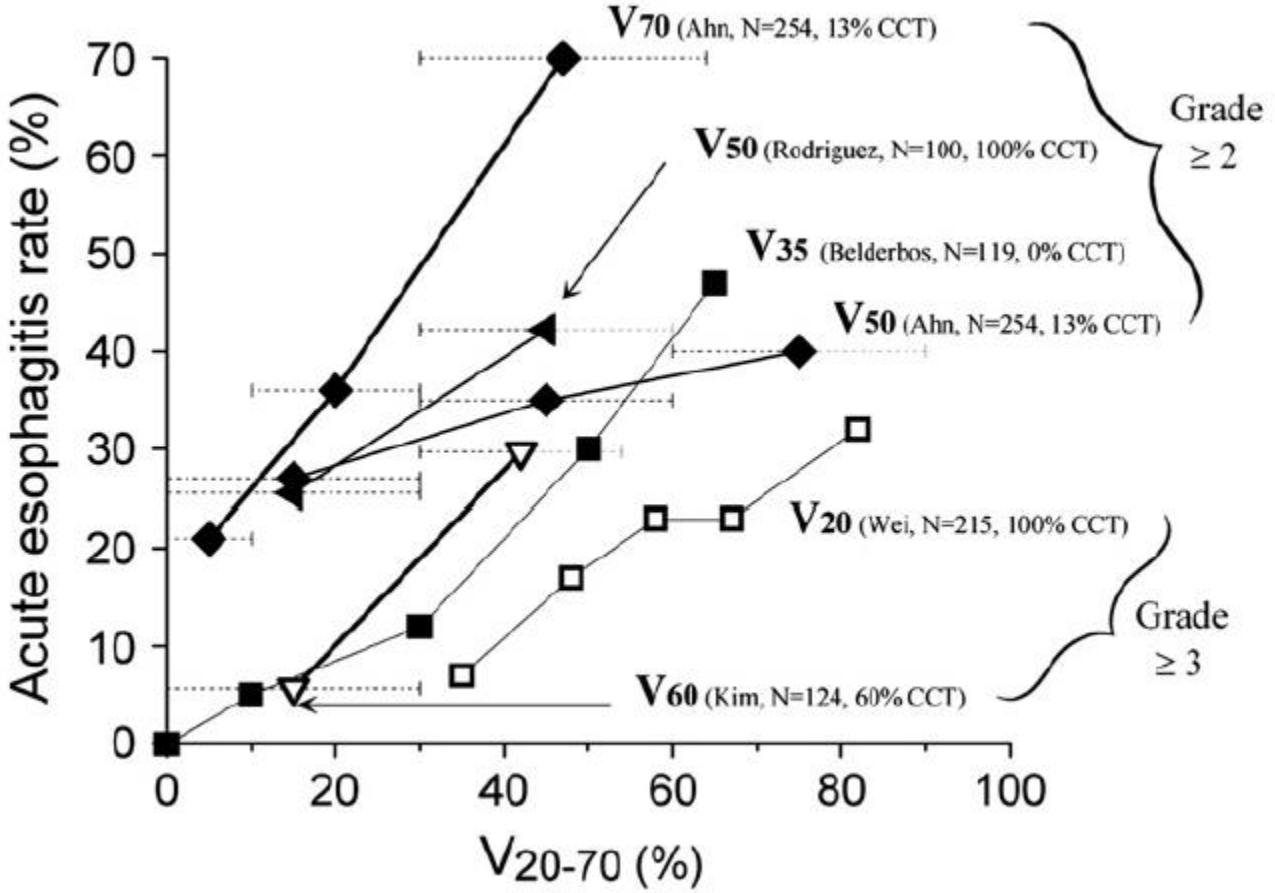
Acute esophagitis
- from ca. 30 Gy/2 Gy
- ca. 3%/ 60 Gy fluid only

Influencing factors:
- Dose
- Fractionation
- Chemotherapy

Therapy:
- symptomatic



Acute esophagitis: dose/volume effects



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

Esophagus: late reactions

Fibrosis

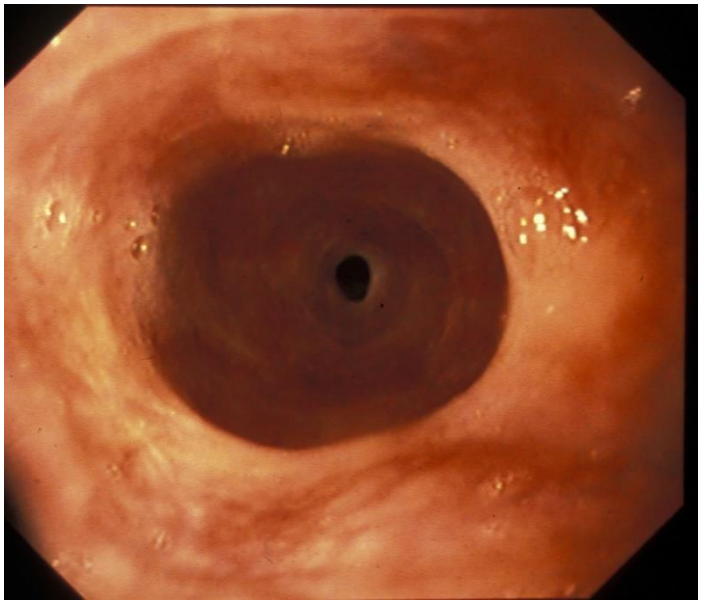
Stricture < 2% < 60 Gy

Influence factors:

- Dose
- Fractionation
- Volume

Therapy:

symptomatic



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

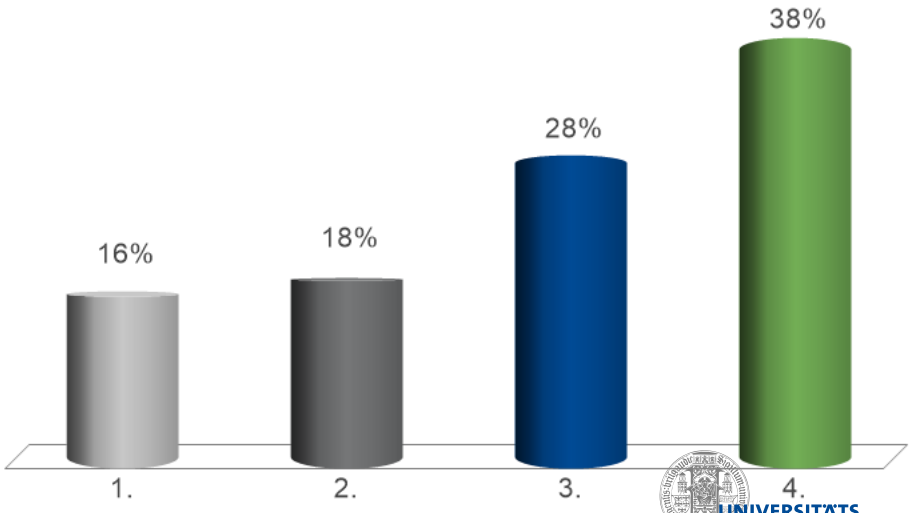
SBRT

Rosel-trial:

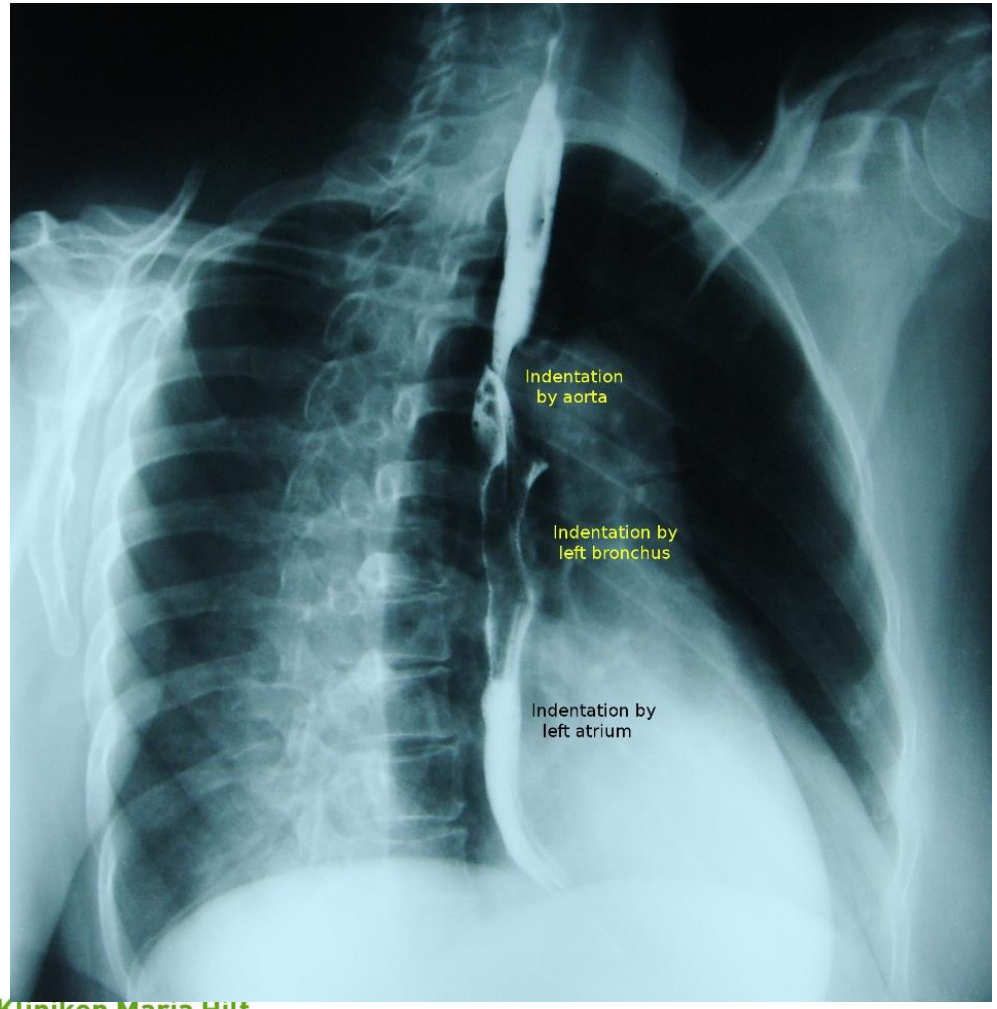
maximum dose: 24Gy/3fr or 27Gy/5fr

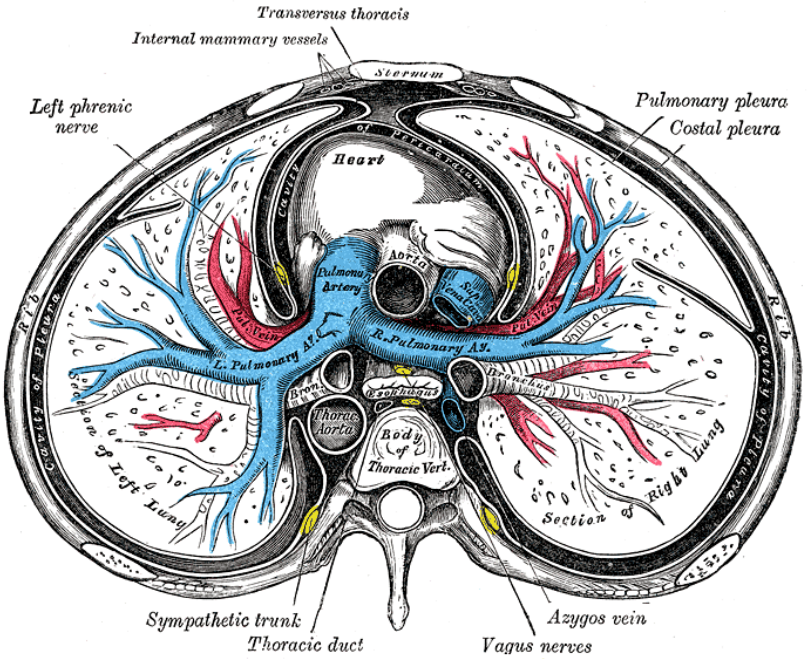
Q2: What about contouring the esophagus? In our department,

1. I am contouring ☹, it is easy ☺
2. I am contouring ☹, it is a challenge ☹
3. Others are contouring ☺, it is easy ☹
4. Others are contouring ☺, it is a challenge ☺



Esophagus: anatomy





Wikipedia

Esophagus: contouring

- contour whole organ including its filling from cricoid cartilage to gastroesophageal junction

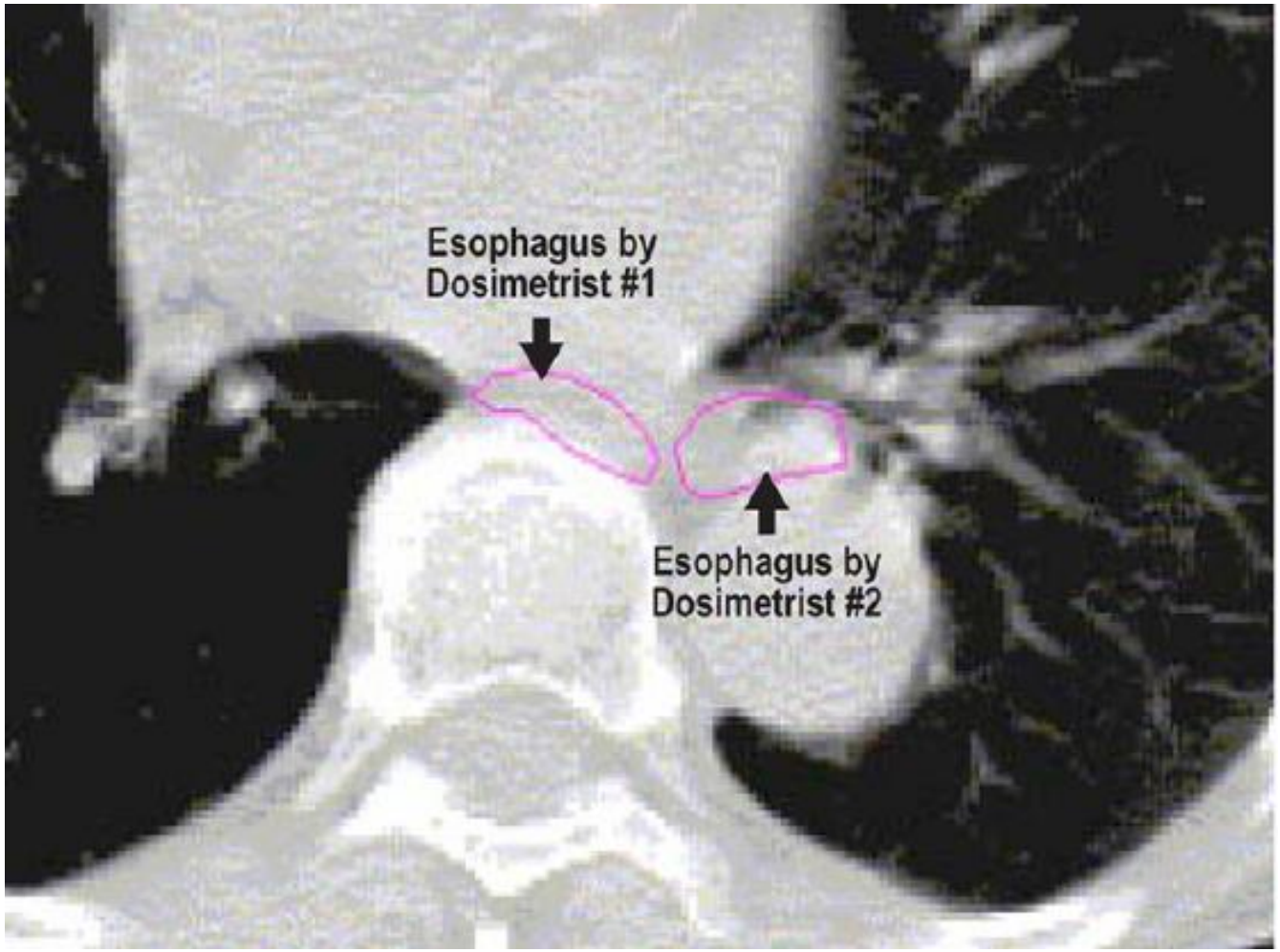
Challenges:

may be difficult to find (search for air)

varying filling

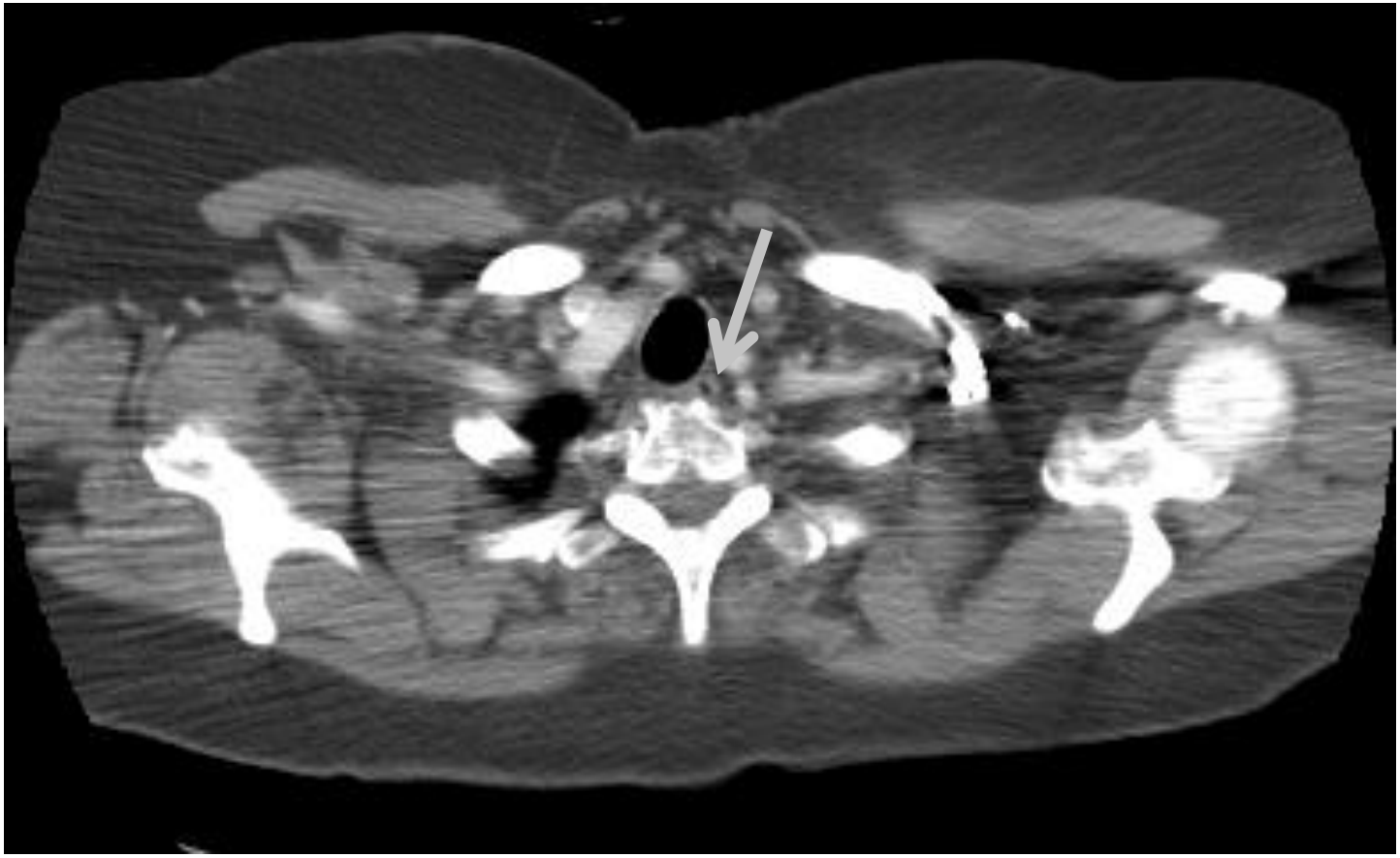
often collapsed (barium swallow or interpolation may help)

Esophagus: geographic miss

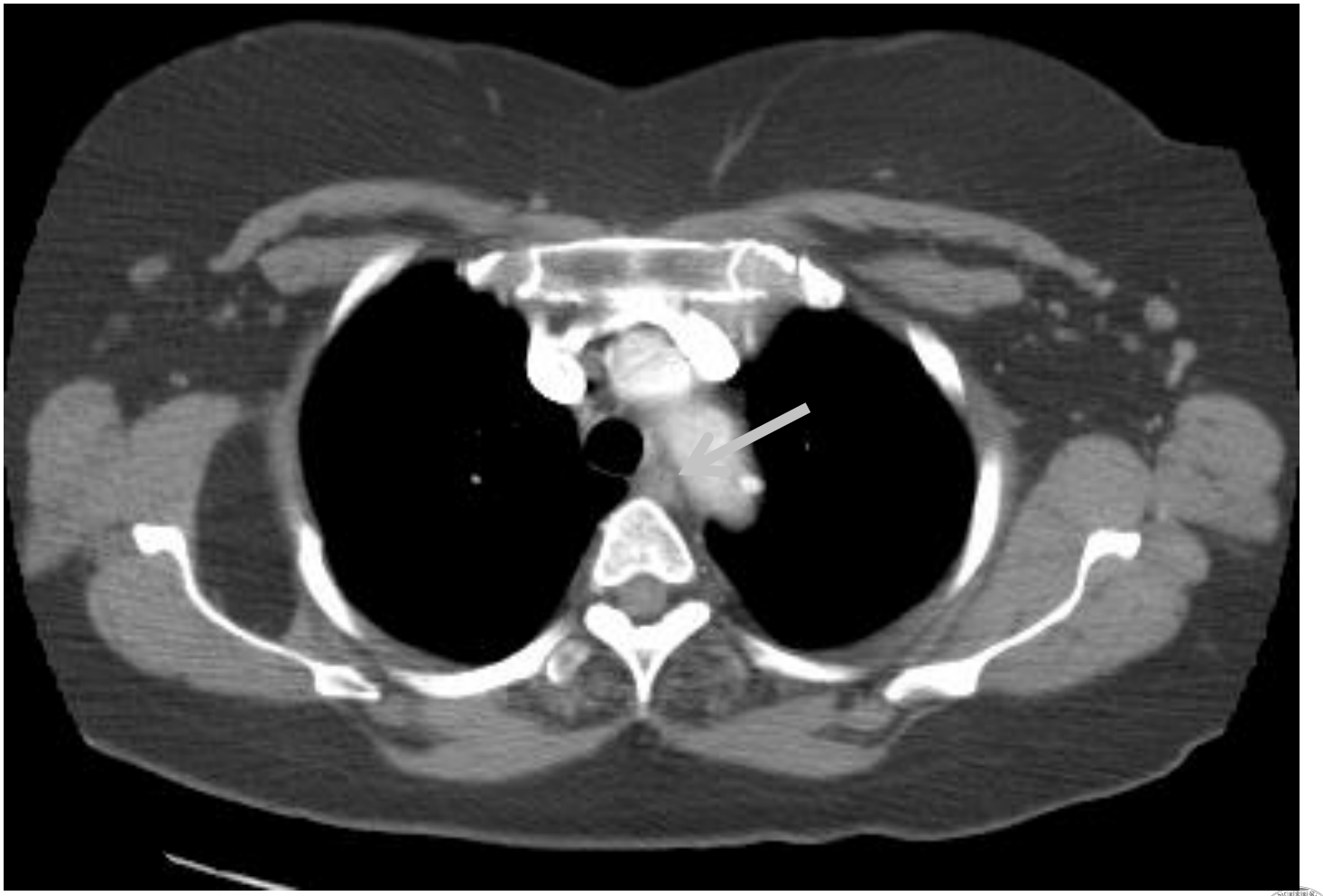


Collier 2003 JACMP 4; 17-24

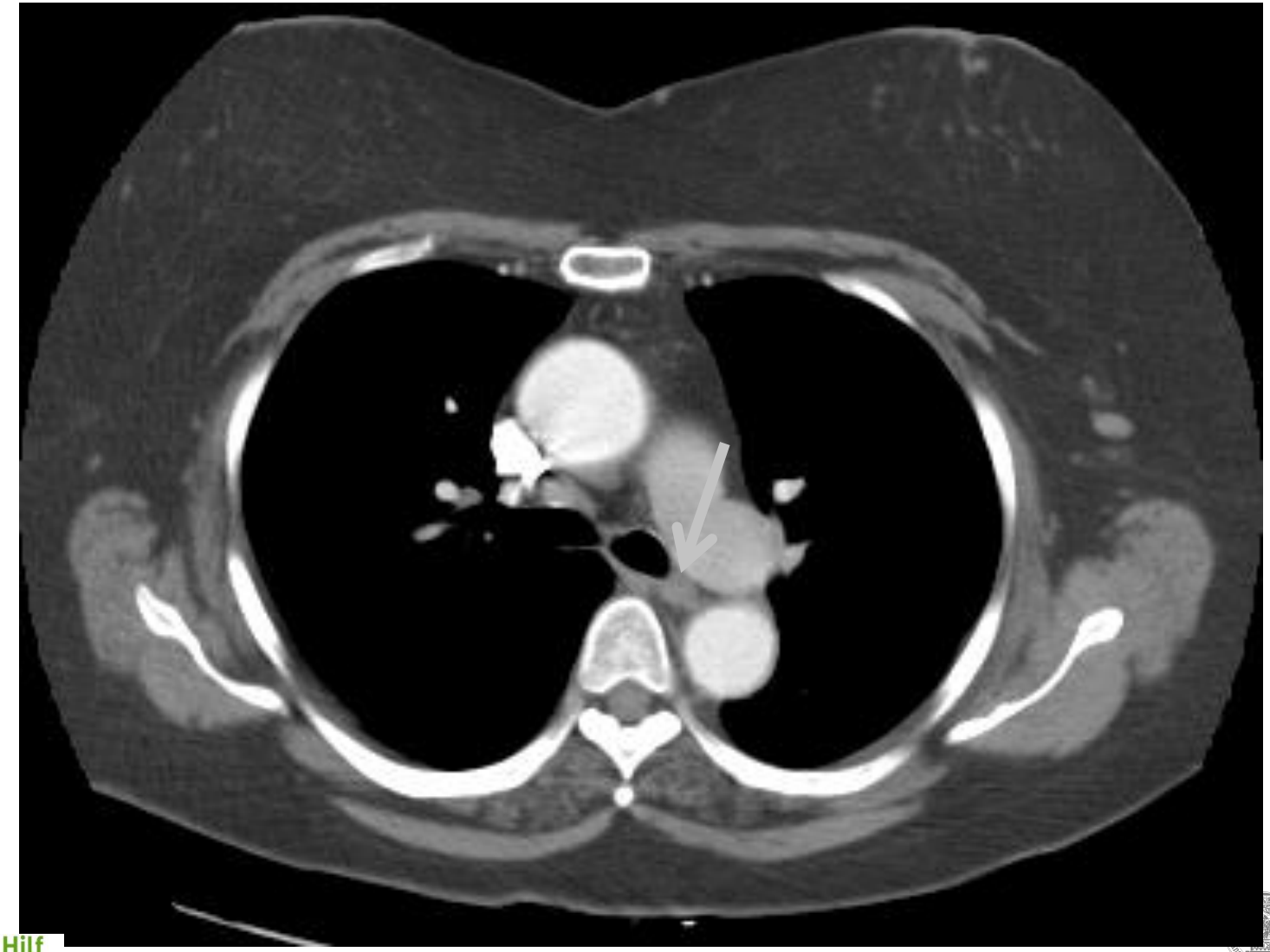
Find the esophagus



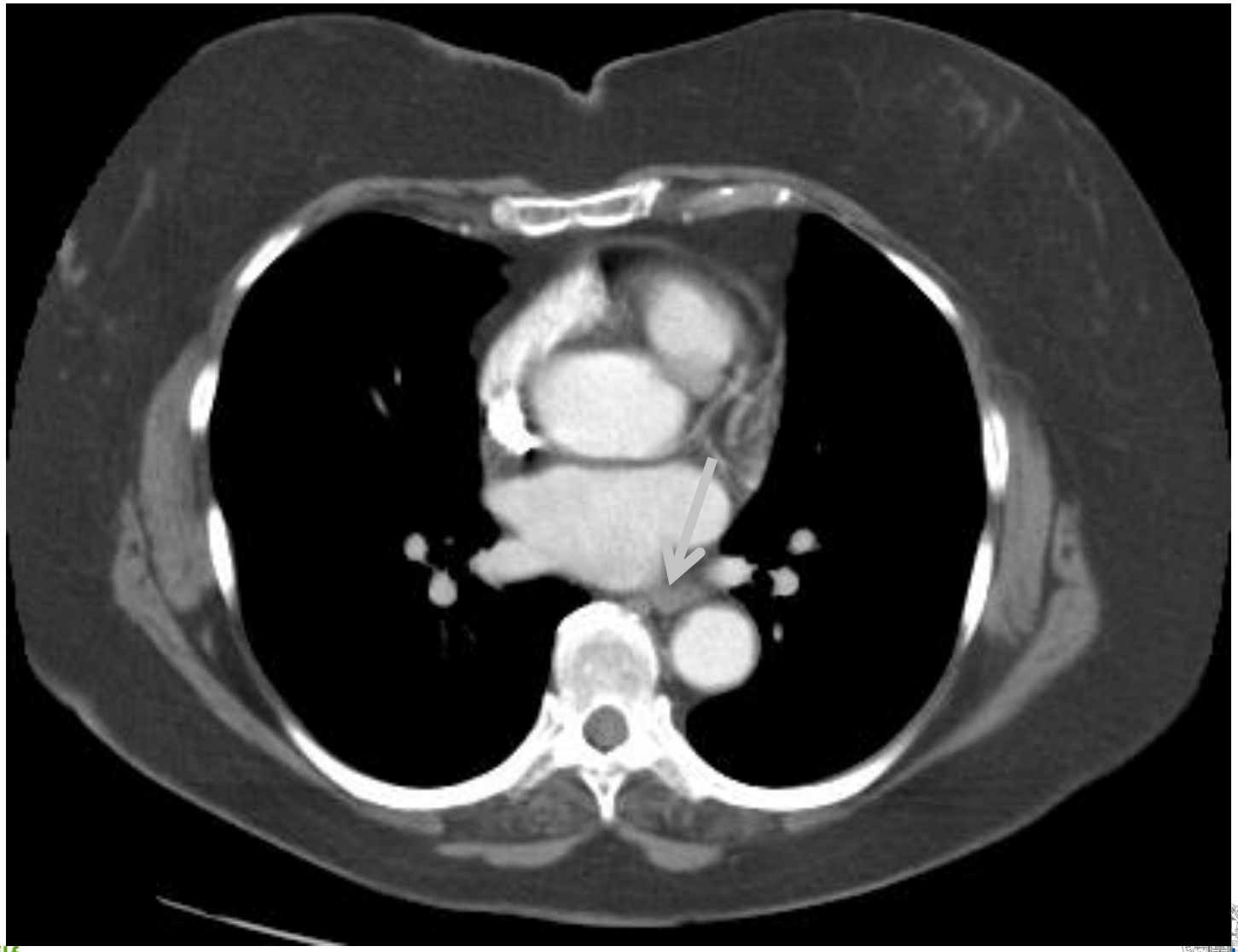
Find the esophagus



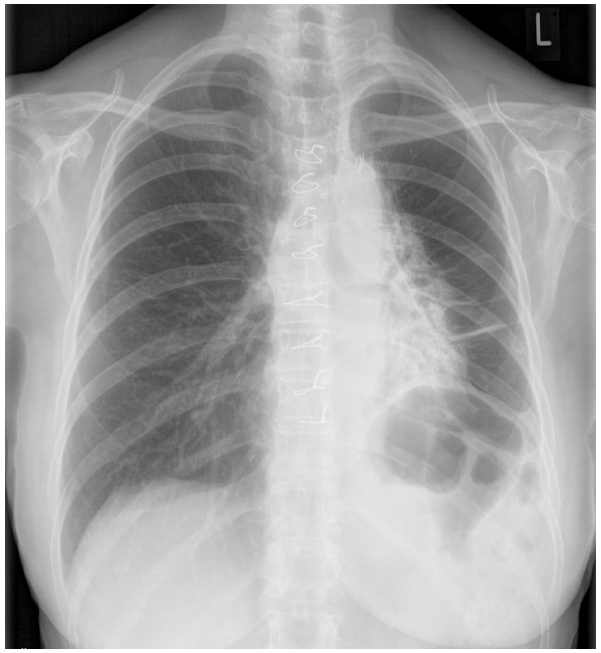
Find the esophagus



Find the esophagus

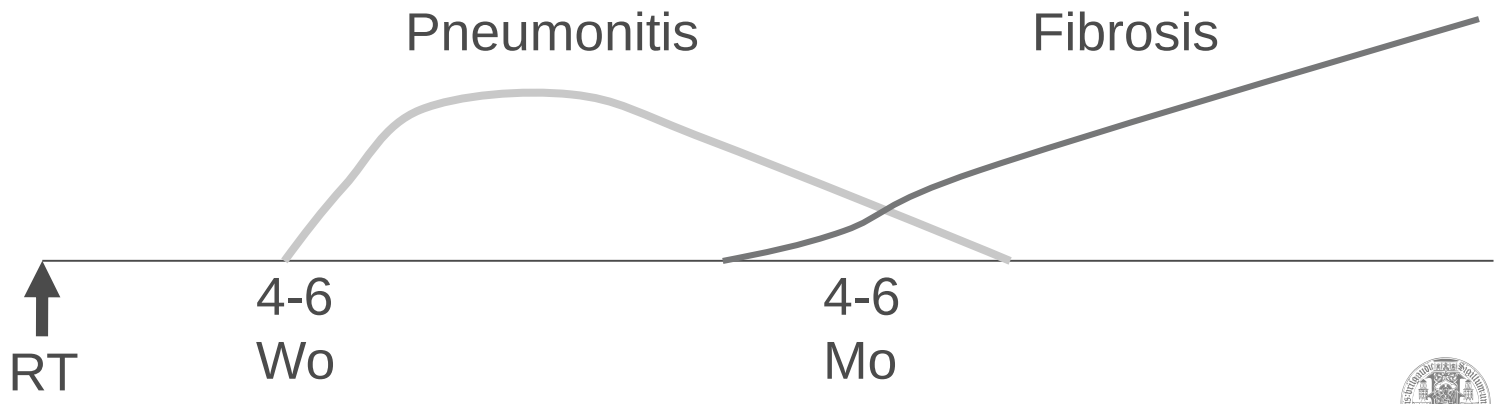


Lung (RILD)



1. acute radiogenous Pneumonitis
   (cough, fever, dyspnea)
   Treatment: Corticoids

2. focal radiogenous fibrosis
   symptoms depending on volume involved
   treatment: none
   prophylaxis: treatment planning



RILD: influence factors

Total dose: clear dose-response relation; tolerance < 25 Gy/2 Gy

clear fractionation effect

Influence factors: old age, smoking, chemotherapy

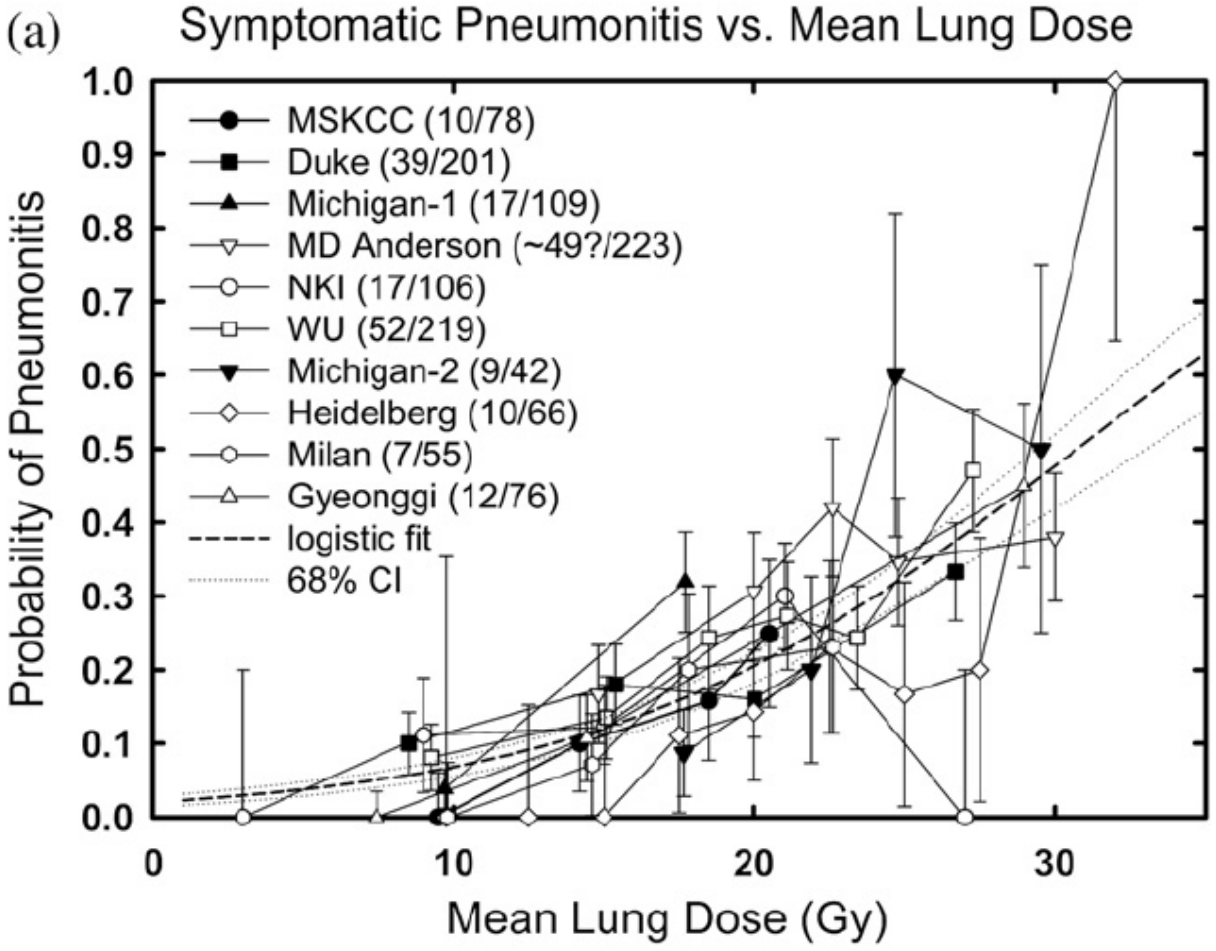
Graham et al. IJROBP1999:

V20 single best predictor of acute pneumonitis (cave: 3D-CRT)

Table 6. Correlation between V_{20} and severity of pneumonitis

V_{20} (%)	Grade 2 (%)	Grade 3–5 (%)
<22	0	0
22–31	8	8
32–40	13	5 (1 fatal)
>40	19	23 (3 fatal)

RILD: corelation between MLD and probability of symptomatic pneumonitis



Marks, IJRBOP 76(3) S70-S76 2010

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.

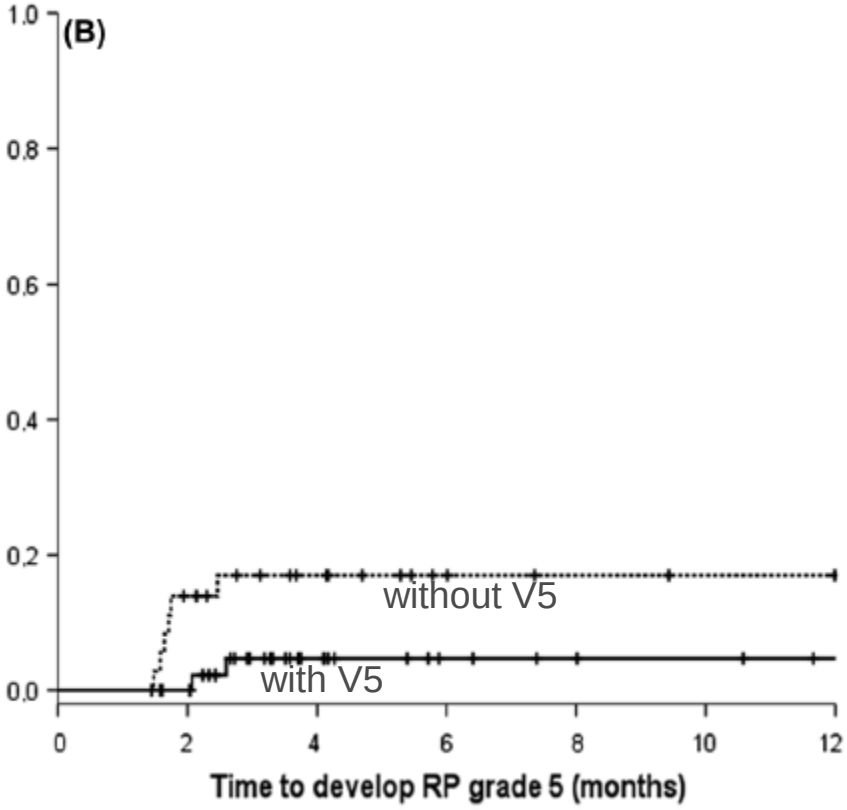
Lung: what about low doses?

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.

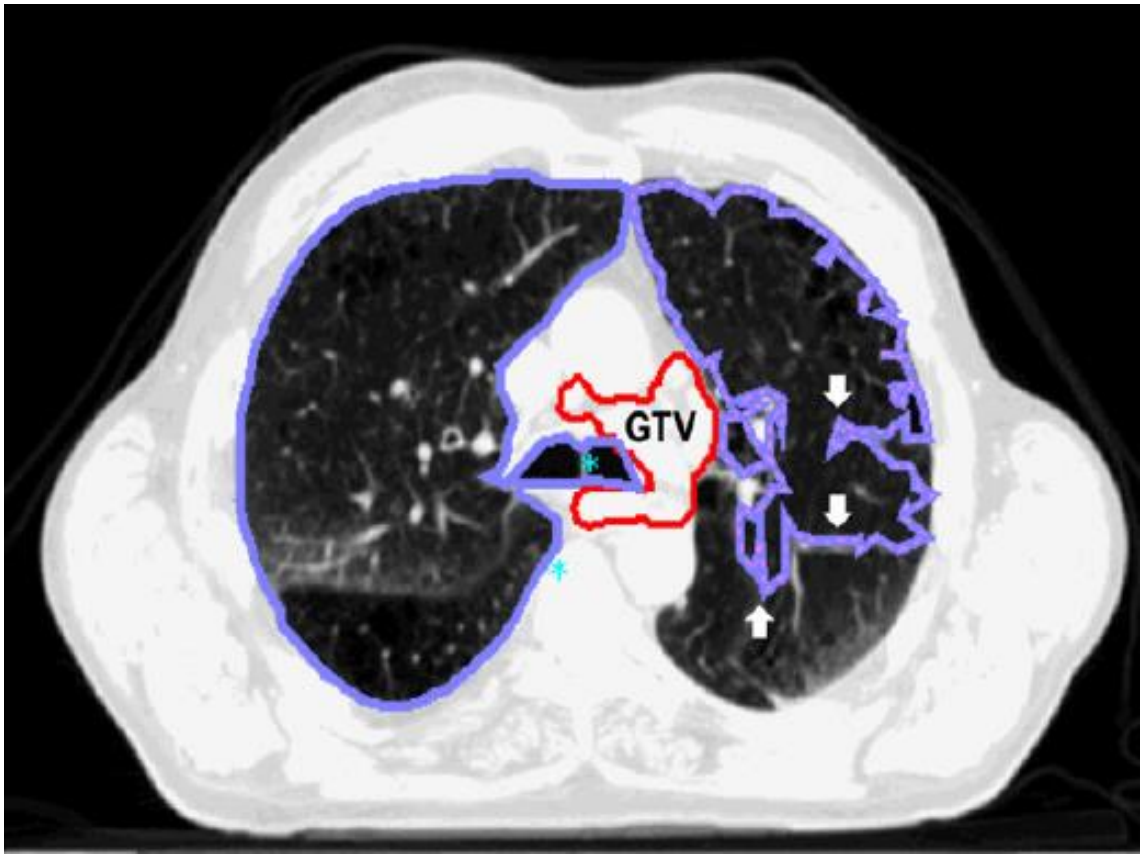
Lung: planning constraints II

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



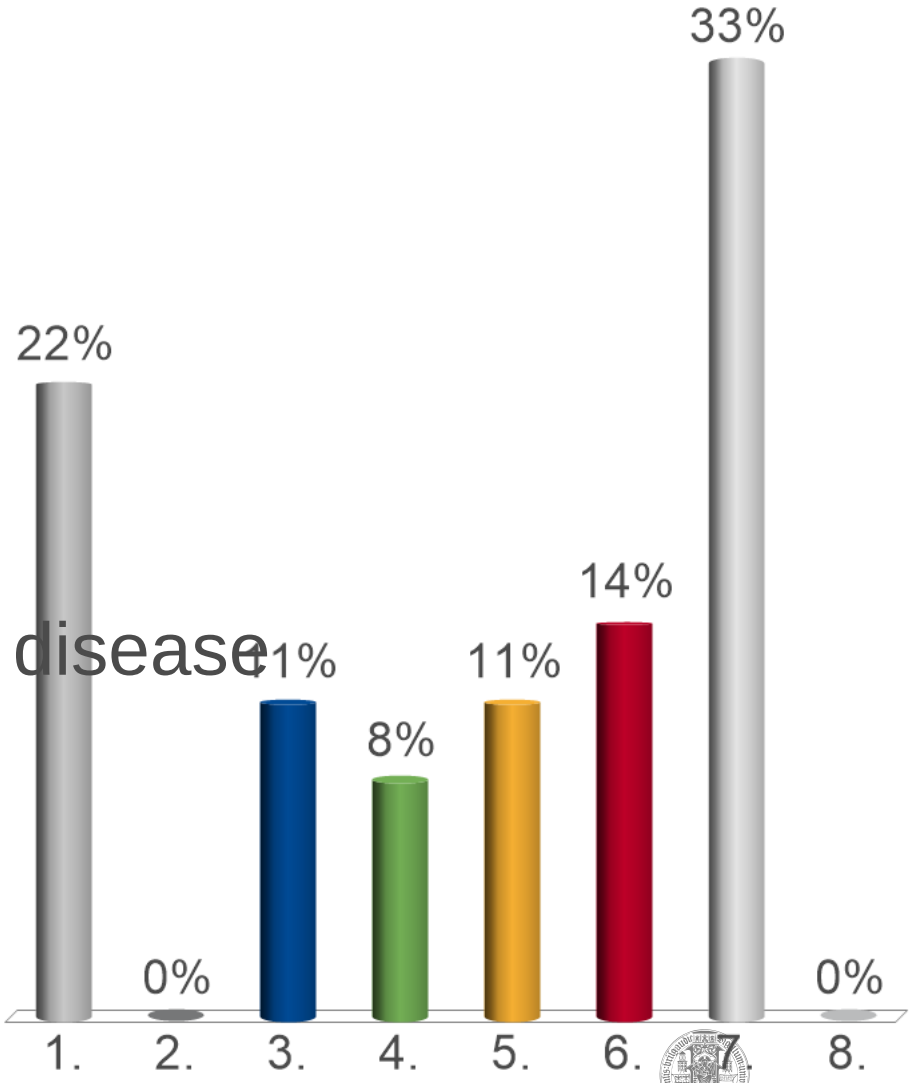
Check complete volume after automatic contouring!

exclude bronchi, bullae, non-lung air

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

Q3: have you / your department ever seen clinical cases with any of those radiation induced late effects:

1. Severe lung injury
2. Paraparesis
3. Brachial plexus paresis
4. Osteoradionecrosis
5. Radiation induced heart disease
6. Bronchial necrosis
7. Several of the above
8. All of the above



Spinal cord

Late effect: Myelitis

Incidence:

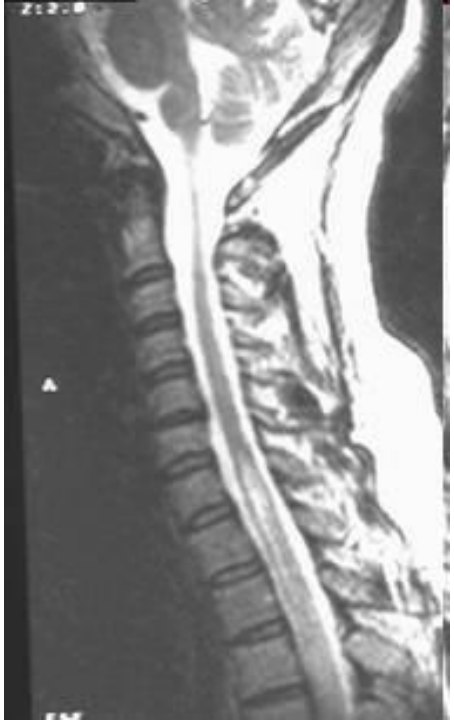
1% @ 2 years after 50-55 Gy/2

Influence factors

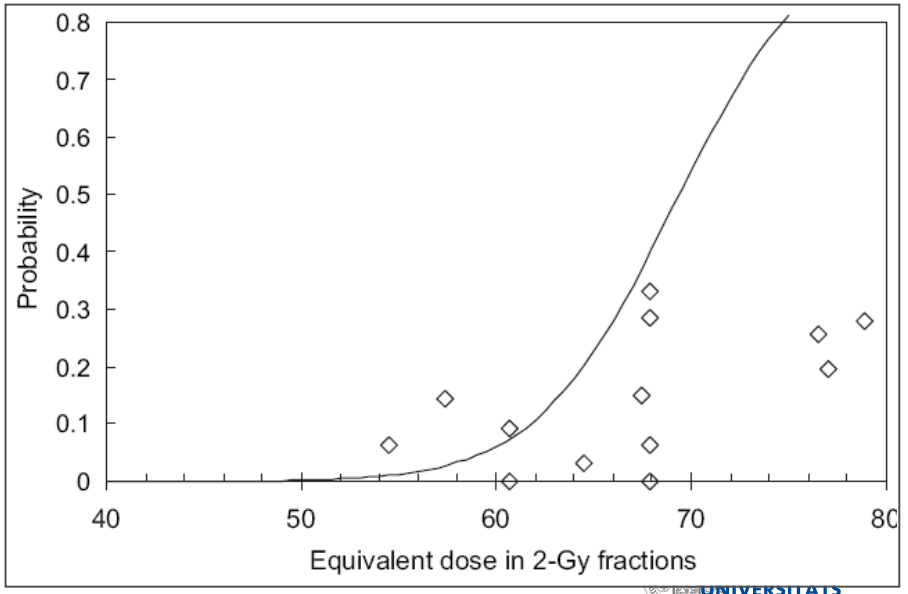
- Dose
- Fractionation
- Volume

Therapy: symptomatic

Prophylaxis: RT-Planning



Tersteeg, Cancer Therapy 2004



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.

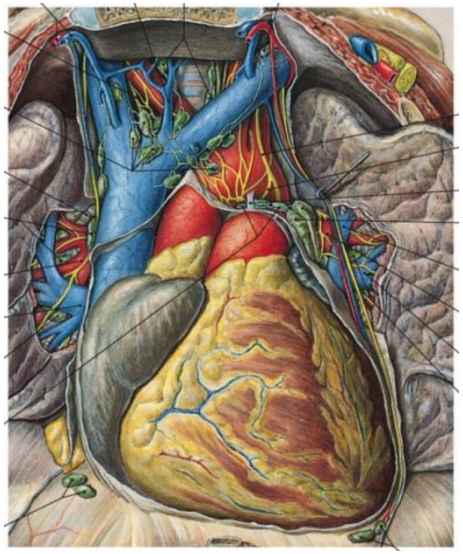
Kong, IJROBP 2011; 81(5); 1442-57

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)

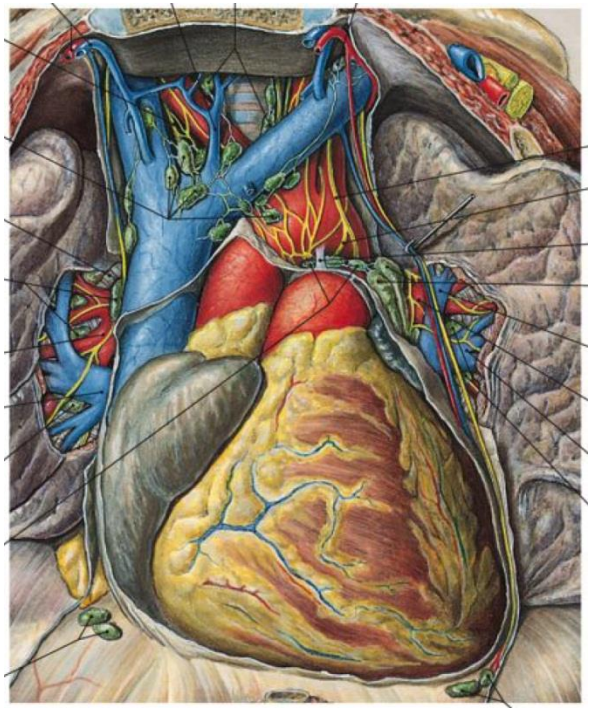


OAR: whole myocardium, coronary arteries, Pericardium…

Gagliardi, IJROBP 2010

Heart

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

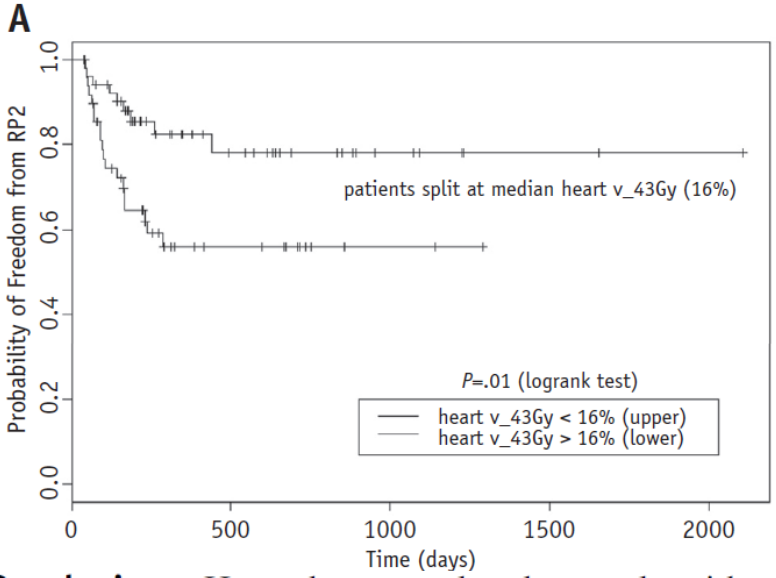


Darby (breast cancer patients):
no threshold
7%/Gy increased risk

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%.

Kliniken Maria Hilf
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

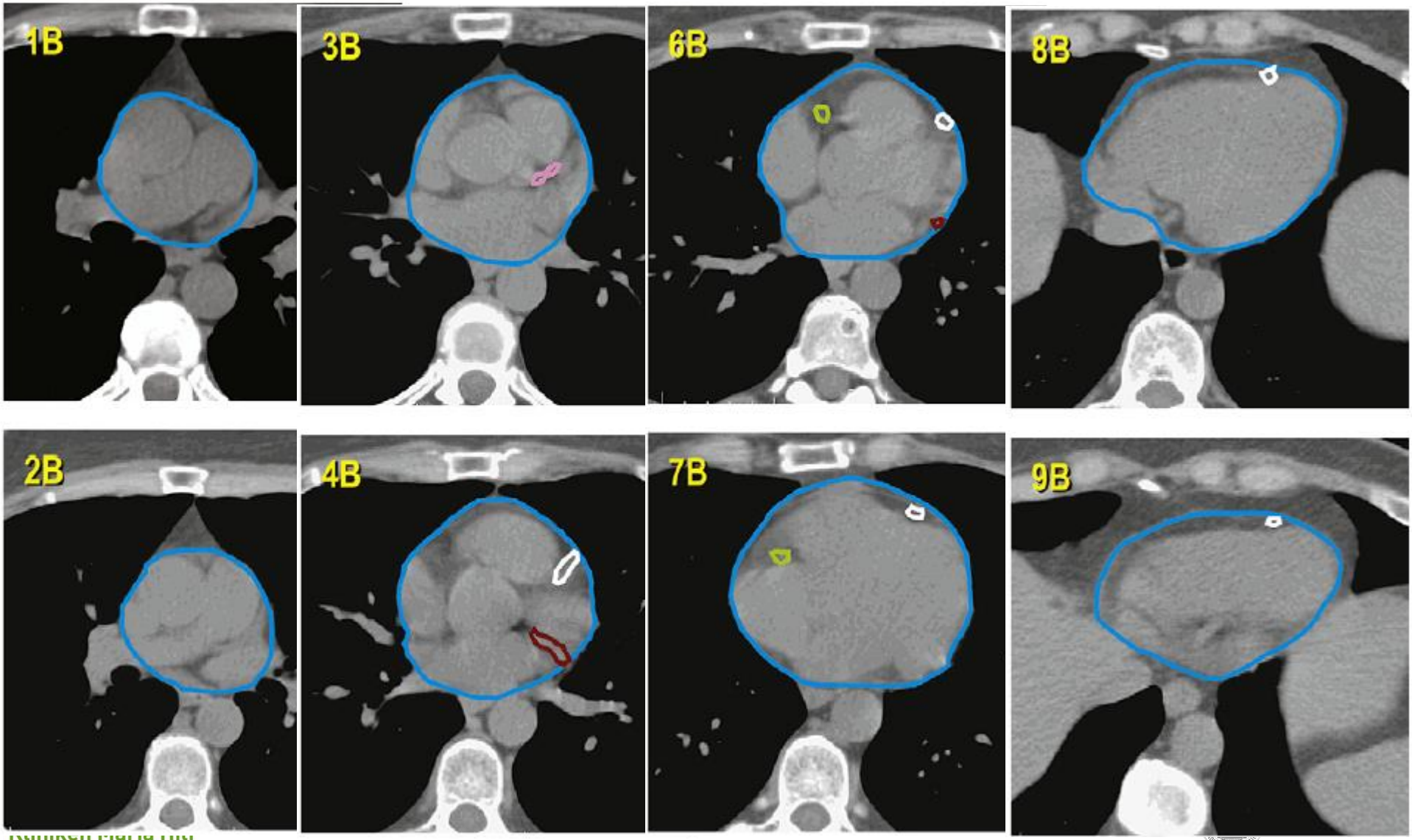
problem: no subvolumes available for further optimisation

Heart: recommended 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



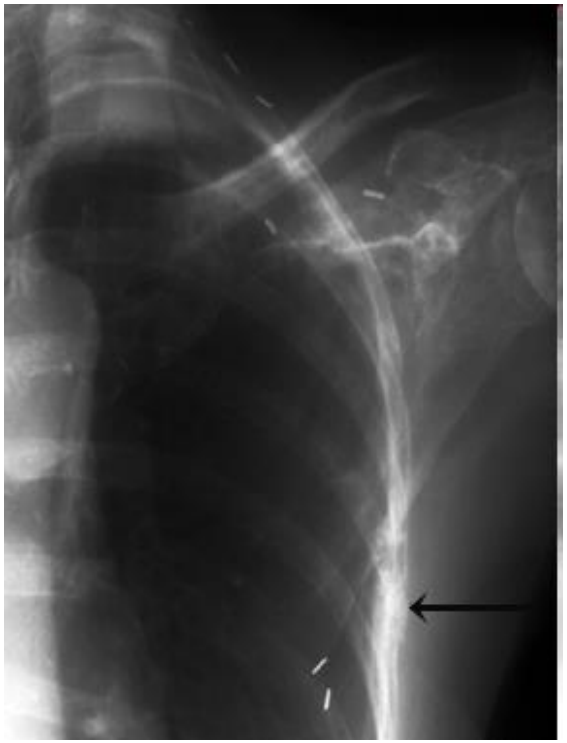
Feng IJRBOP 2011 79(1) 10-18

Bone

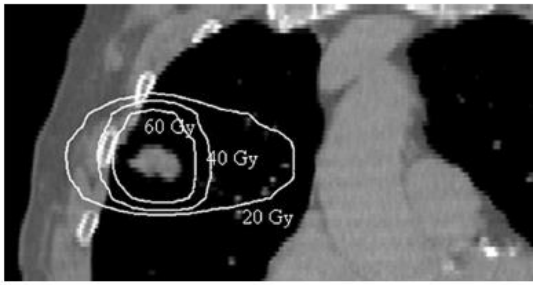
late effect
    Osteoradionecrosis

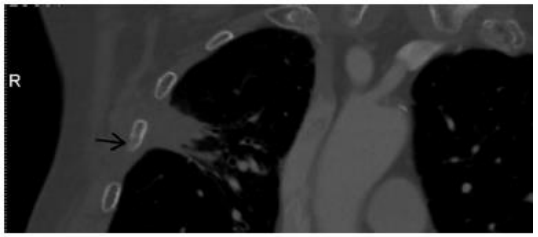
Tolerance dose
    ca. 60 Gy/2 Gy

treatment:
    symptomatic



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





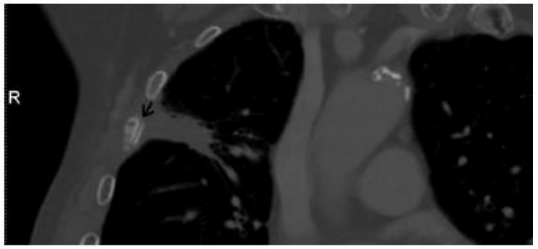


Table 5 Univariate and multivariate analysis on predictors for rib fractures (repeated measures have been taken into consideration)

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

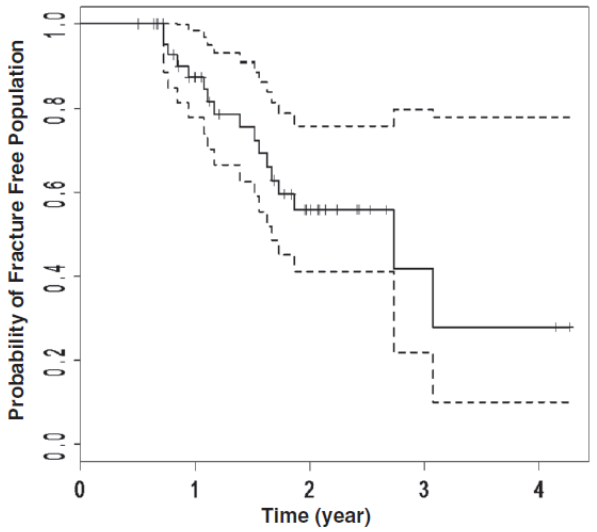


Figure 2 Kaplan Meier curve for fractured rib as an event (n = 46 patients). Dashed lines indicate 95% confidence intervals.

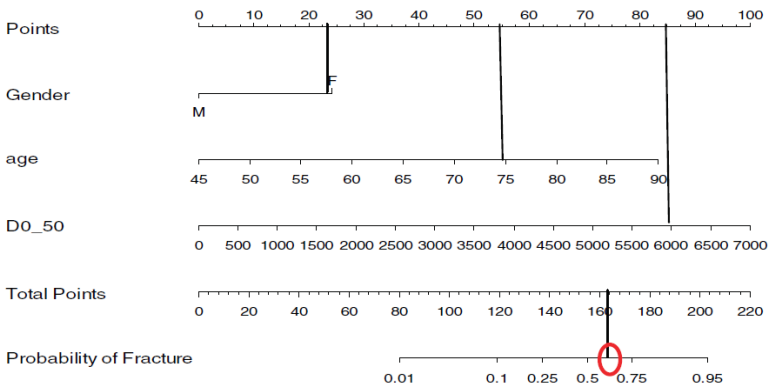
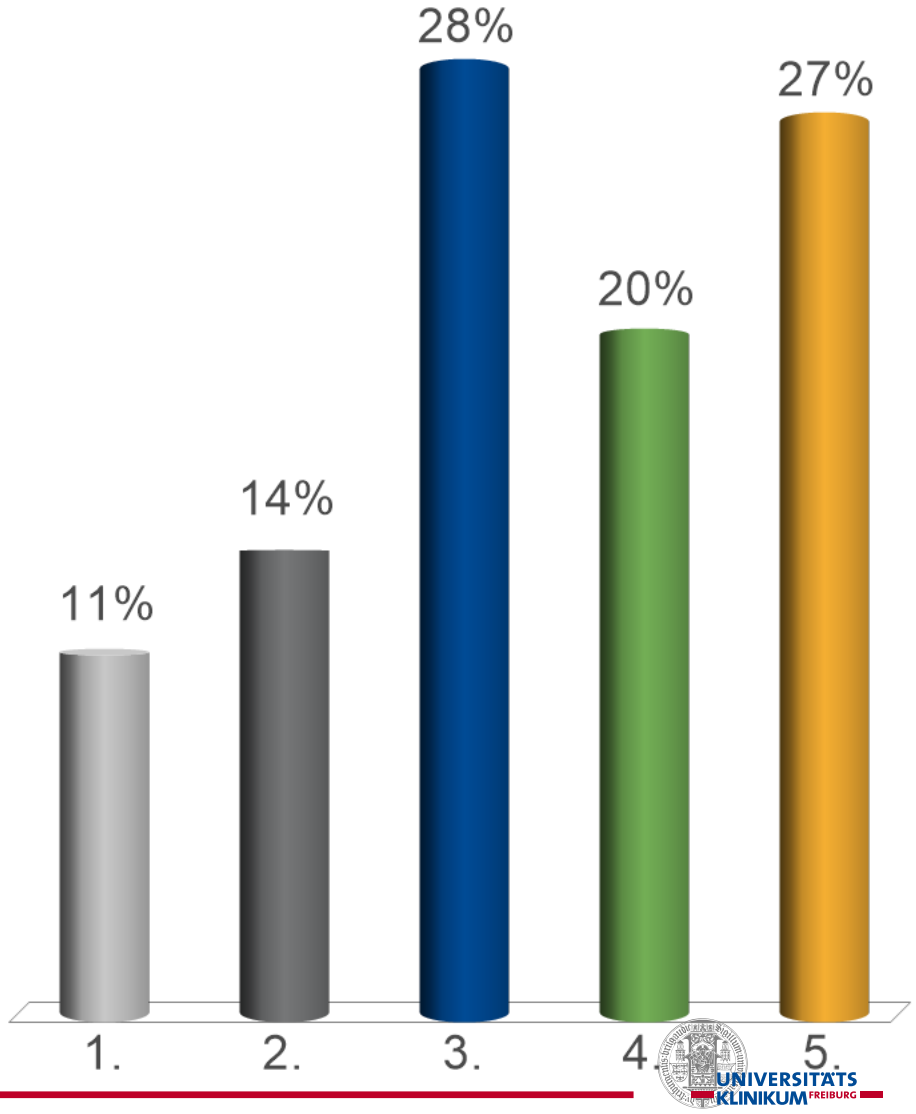


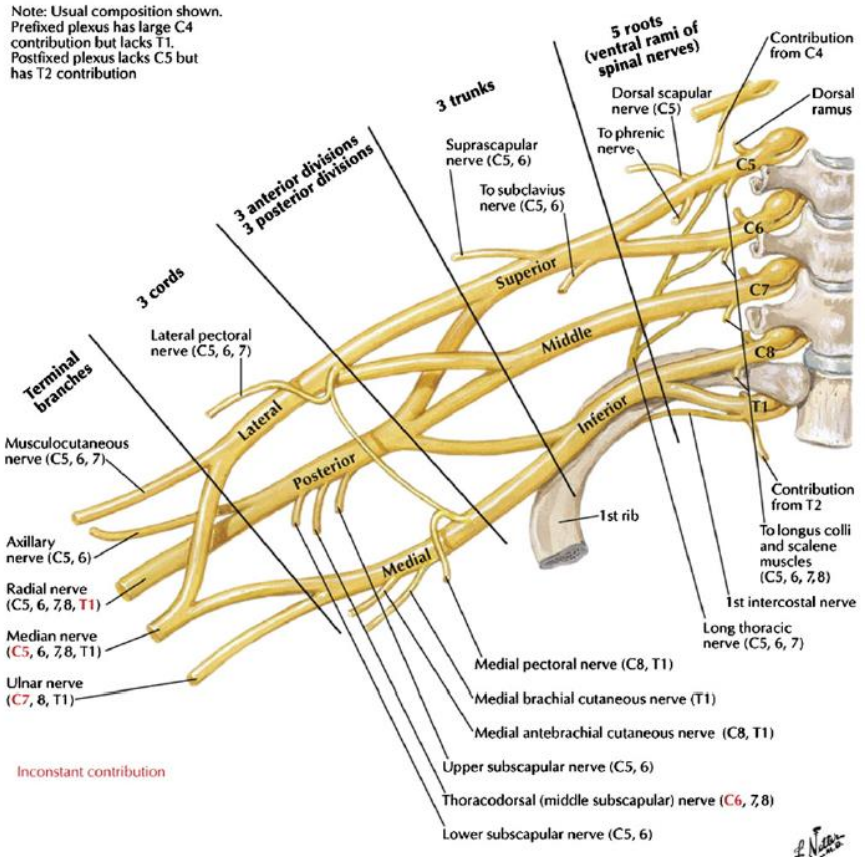
Figure 6 RIBI nomogram based on gender, age and $D_{0.5}$ in 46 patients treated with SBRT at Princess Margaret Hospital (Estimating risk of rib fracture at median follow up of 25 month). Risk of rib fracture in a 75 year old lady treated with 54 Gy in 3 fractions and D0.5 of 60 Gy (within a median FU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

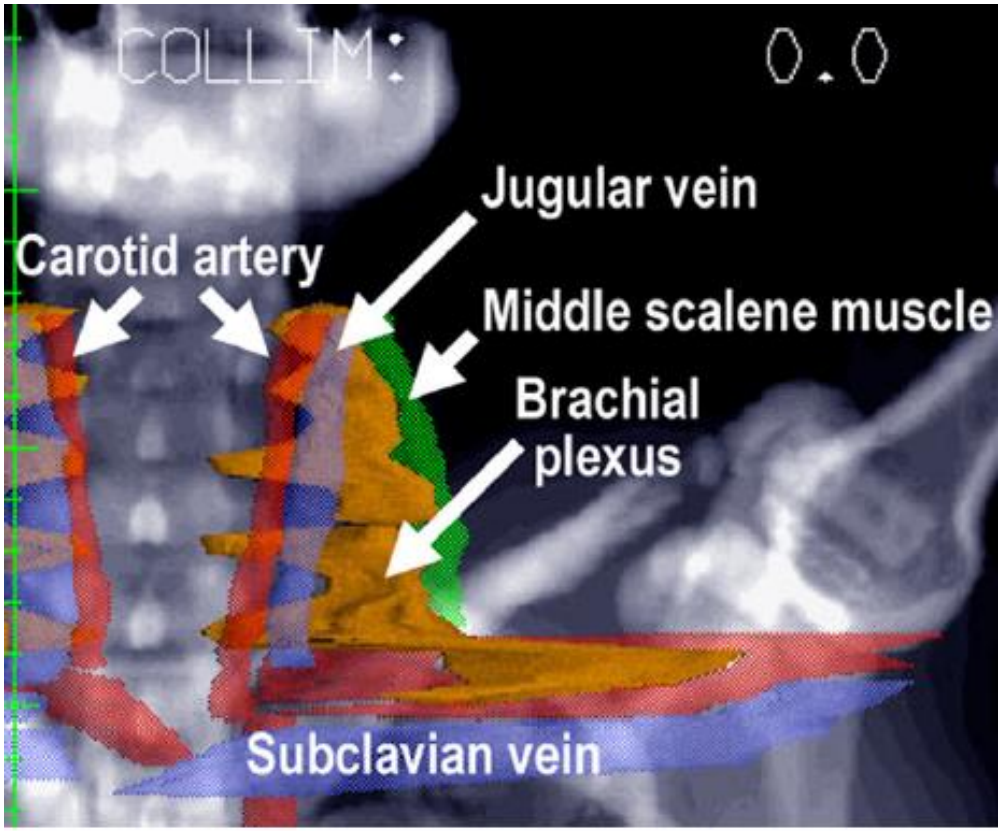
Q4: For which situations do you contour the brachial plexus as OAR most often?

1. routine RT for breast and/or lung cancer
2. high dose RT head & neck cancer
3. SBRT for apical lung cancer
4. reirradiation situations
5. we never contour the plexus



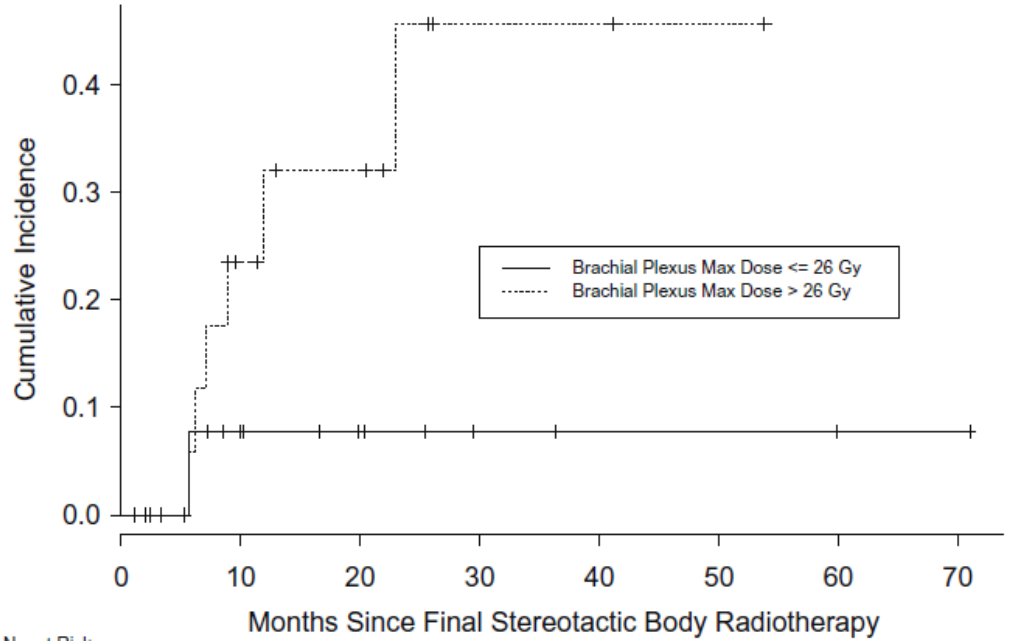
Brachial plexus

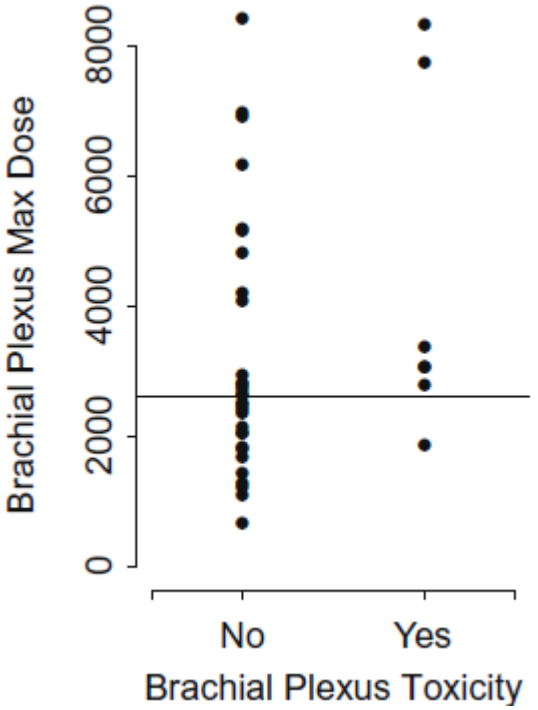




Kong, IJROBP 2011; 81(5); 1442-57

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.

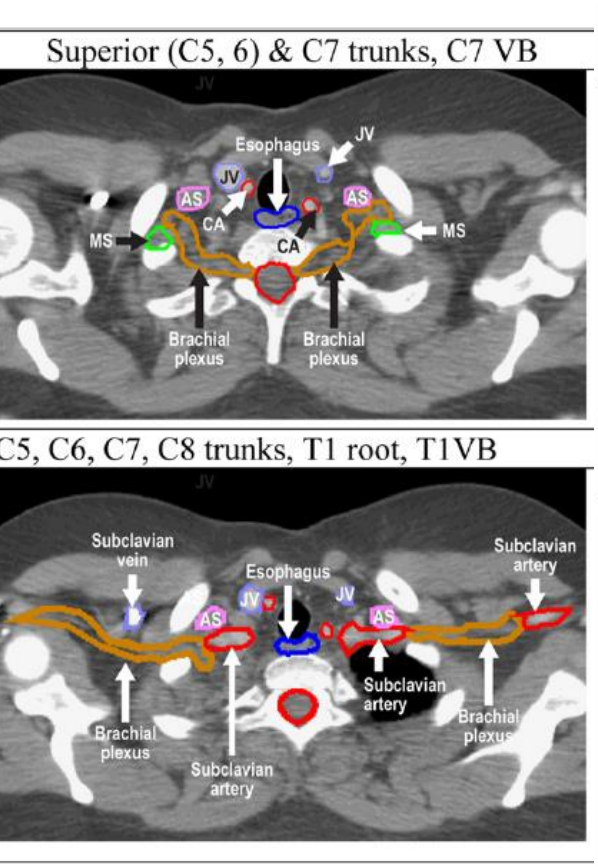
Forquer, R&O 2009; 93; 408-412

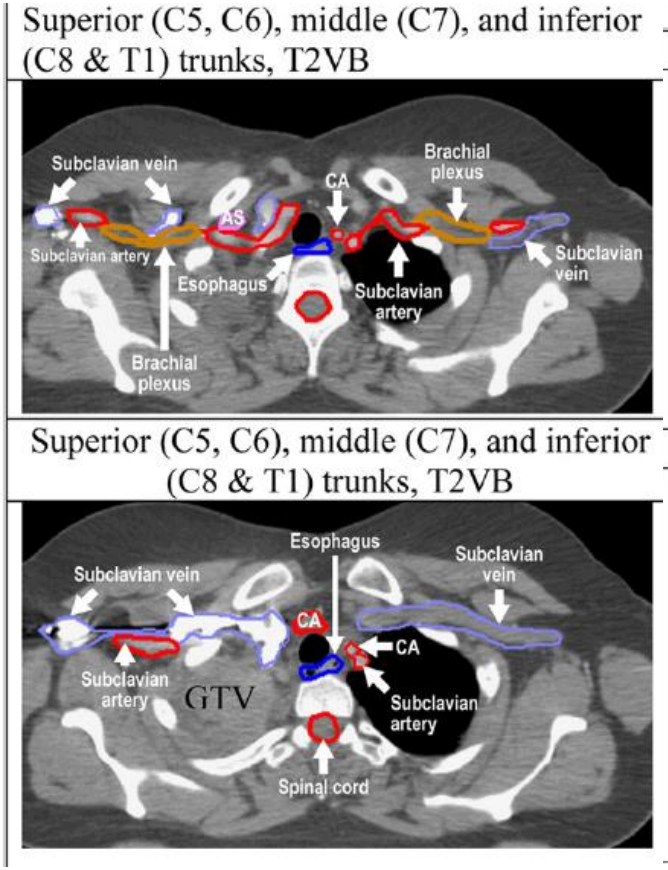
Contouring the brachial plexus

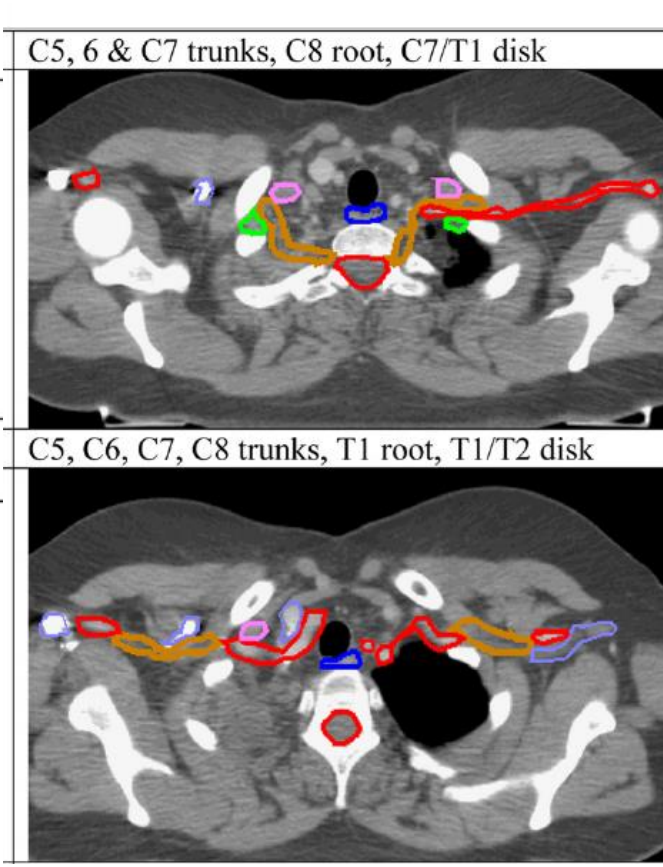
1. Locate the neural foramina at the C4-C5 and T1-T2 levels to identify the C5 and T1 roots, respectively
2. Locate the subclavian and axillary neurovascular bundle to identify the lateral aspect of the brachial plexus inferiorly
3. Locate the anterior and middle scalene muscles from the C5 vertebral 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



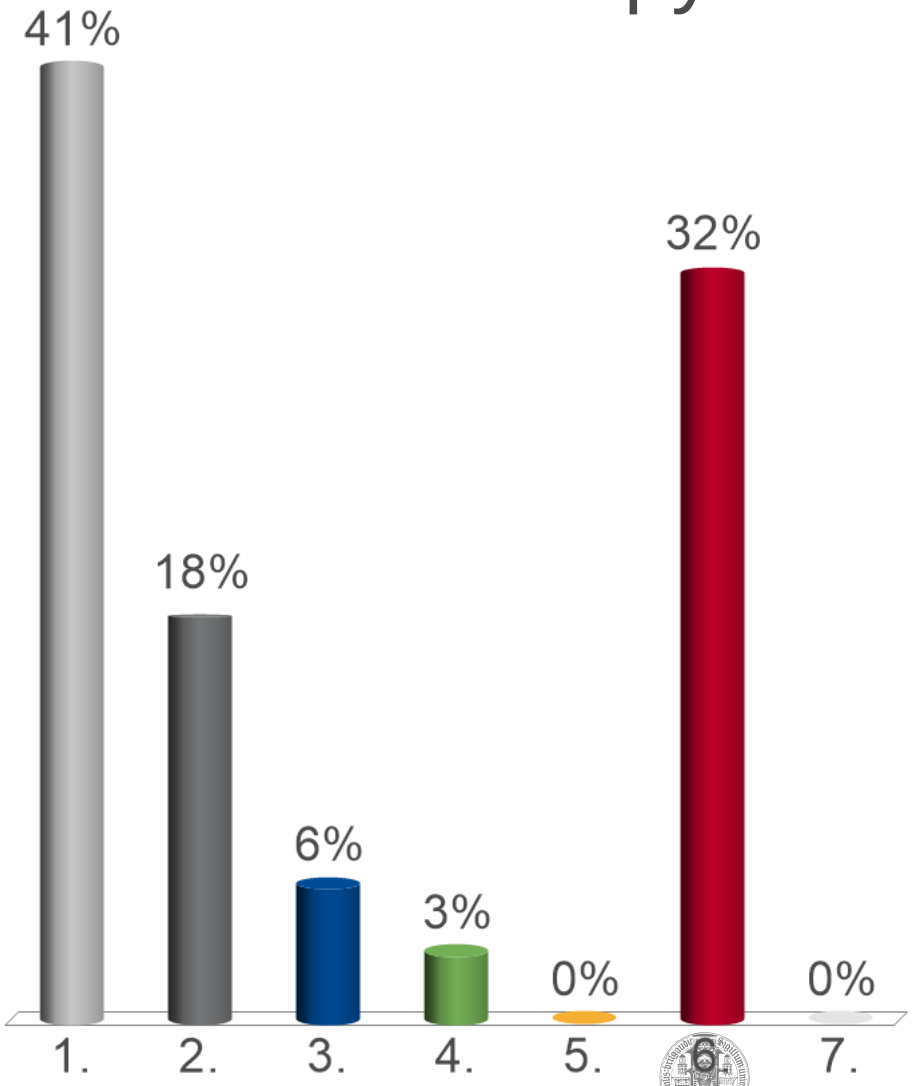




Kong, IJROBP 2011; 81(5); 1442-57

Q1 reloaded : What do you consider the most critical normal tissue for chest radiotherapy?

1. lung
2. esophagus
3. spinal cord
4. brachial plexus
5. thoracic wall
6. heart
7. central bronchi



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Corinne Faivre-Finn
Cecile Le Pechoux
Dirk DeRuysscher

RT Freiburg, PET-Plan Team:
Markus Stockinger
Andreas Thomsen

other places …
Michael Baumann
Matthias Guckenberger

IMRT treatment planning parameters

or

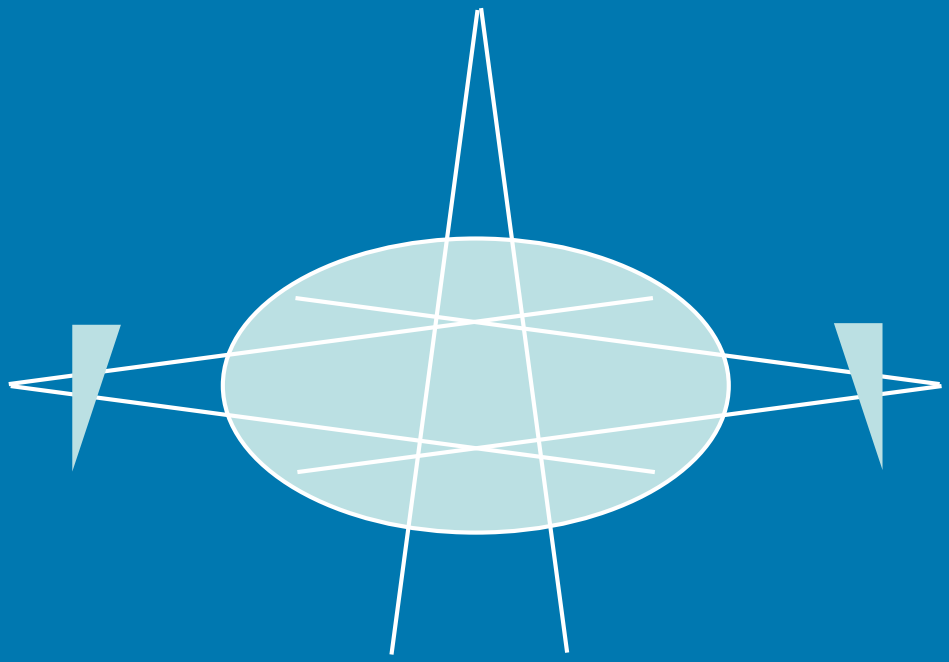
17 tips and tricks for happy IMRT planning

Gert Meijer

ESTRO
European Society for Therapeutic Radiology and Oncology

Optimalisation 3DCRT

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



5 degrees of freedom

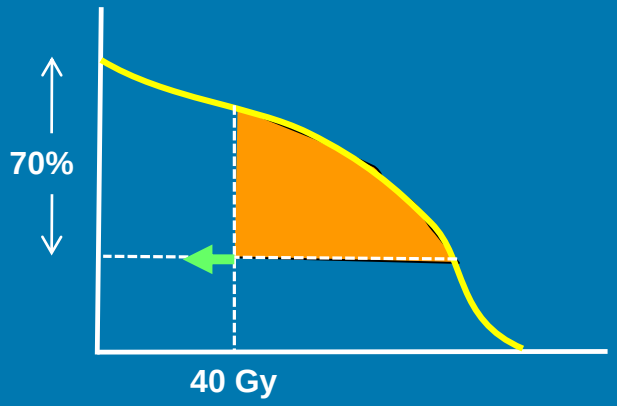
Optimalisatie IMRT

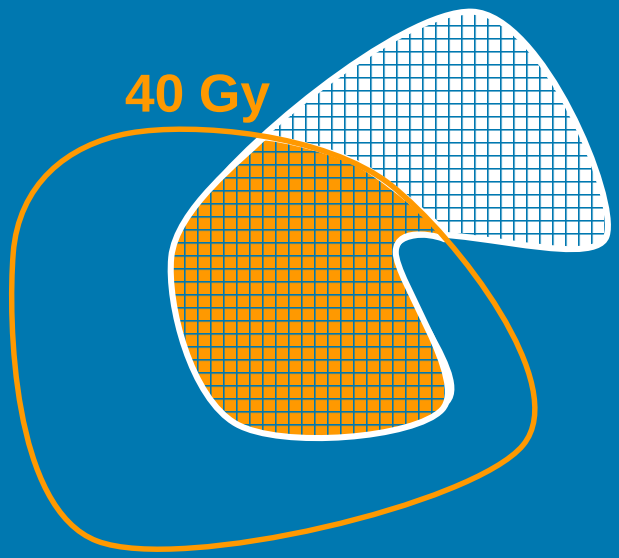
- ~~gantry angle~~
- beam weight
- ~~wedge~~
- ~~collimator angle~~
- ~~beam energie~~

- fluence profile

2000 degrees of freedom

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



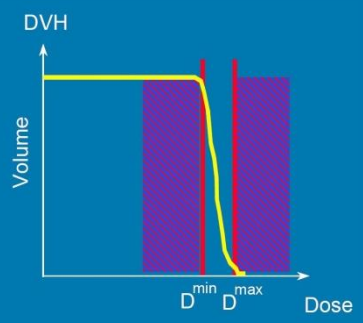


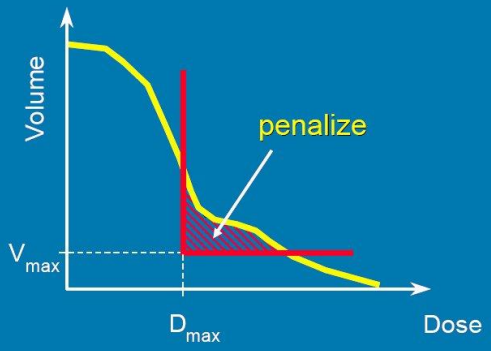
70% should receive 40 Gy or less

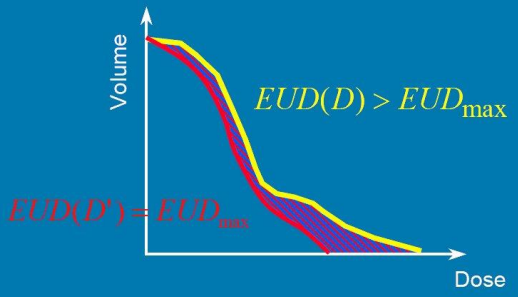
70%	33	0
	35	0
	36	0
	38	0
	39	0
	41	$1/7\times(1/40)^2$
	42	$1/7\times(2/40)^2$
30%	43	**$1/7\times5/1600$**
	49	

Optimization

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







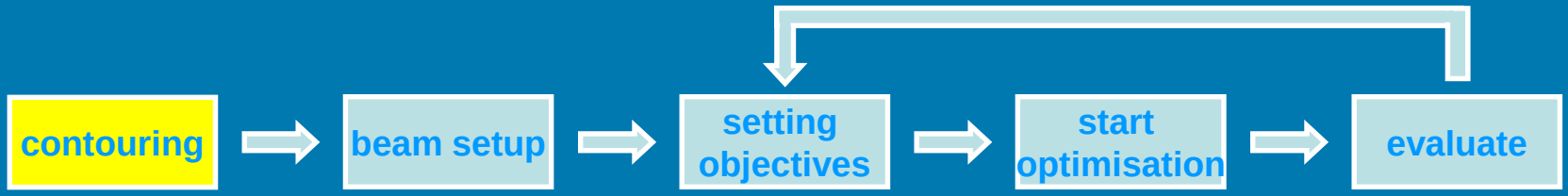
17 tips and tricks for happy IMRT planning

1

make sure your delineations are accurate

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

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



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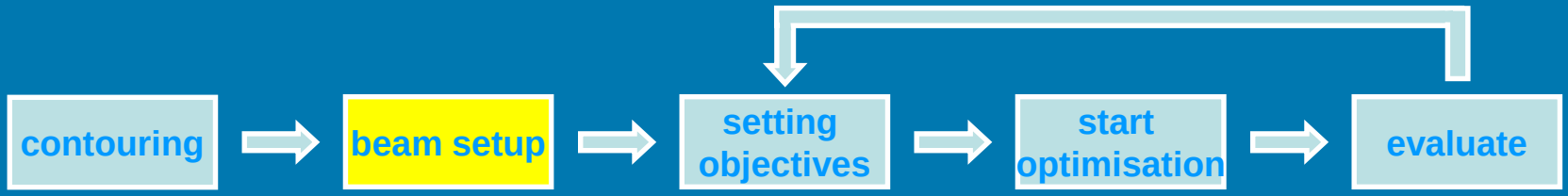
17 tips and tricks for happy IMRT planning

2

place your isocenter in the center of all PTVs

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



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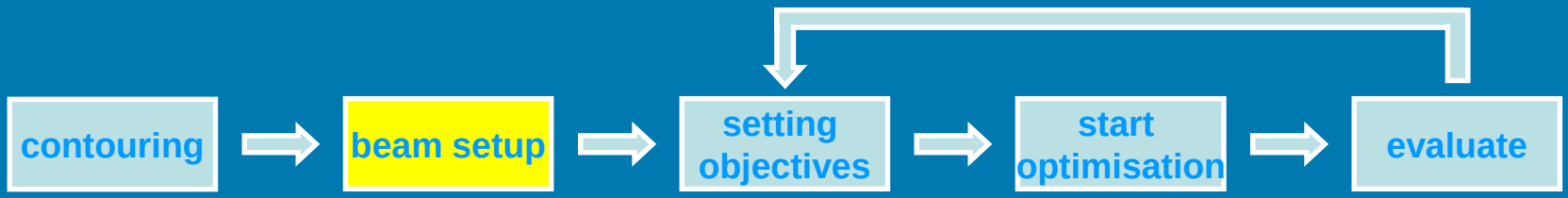
3

Bear in mind that steep dose gradients can **ONLY** be obtained perpendicular to beam axes just like in 3DCRT

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



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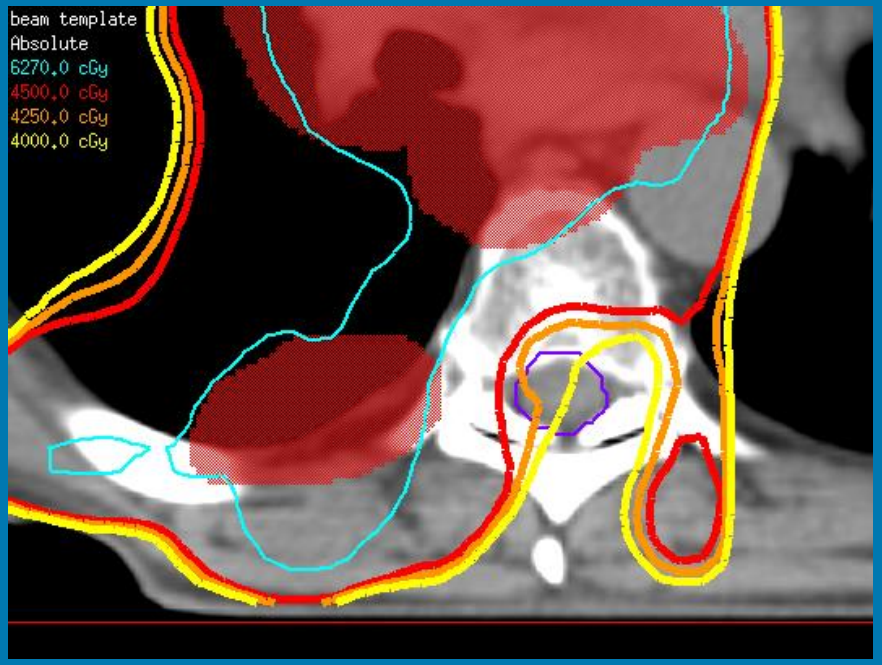

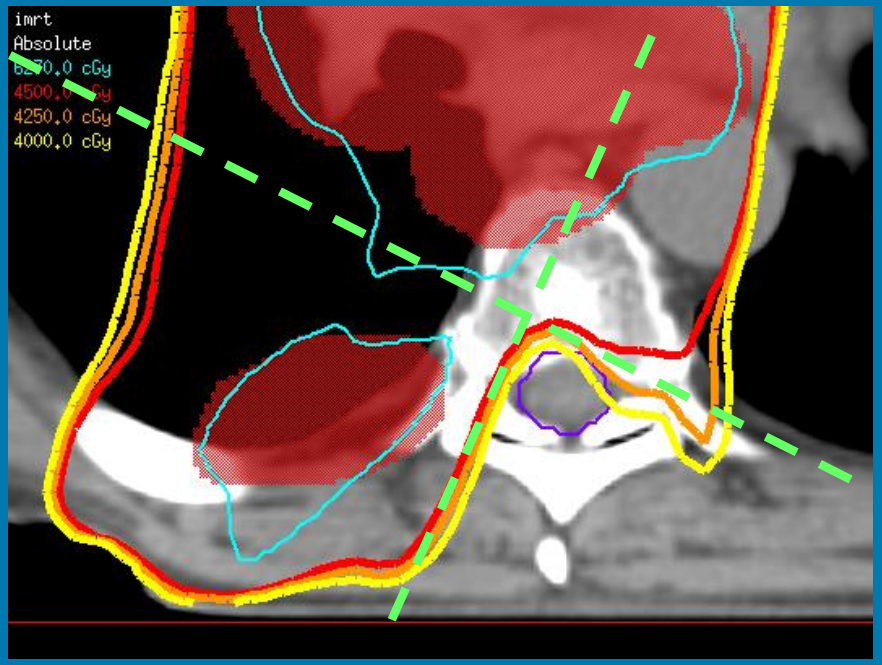

contouring → beam setup → setting objectives → start optimisation → evaluate

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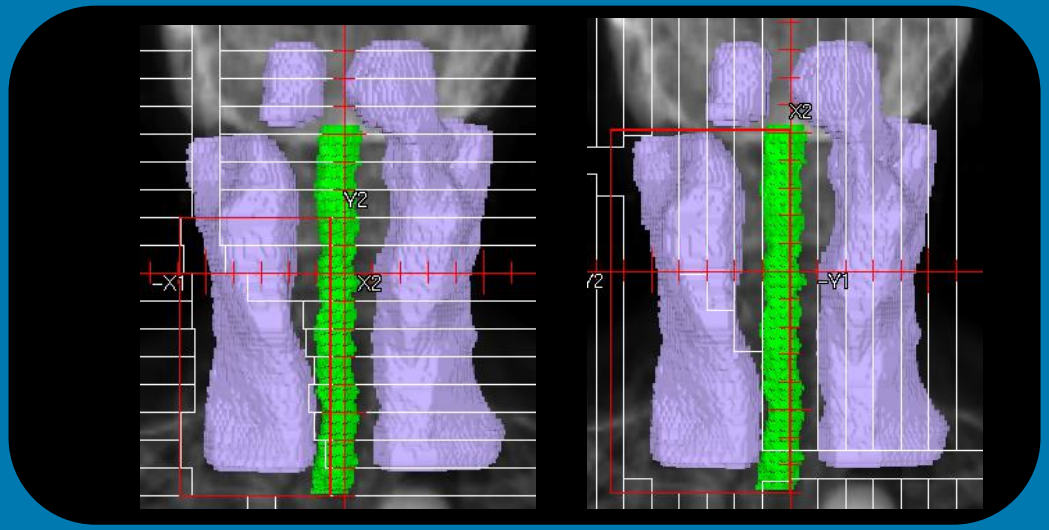
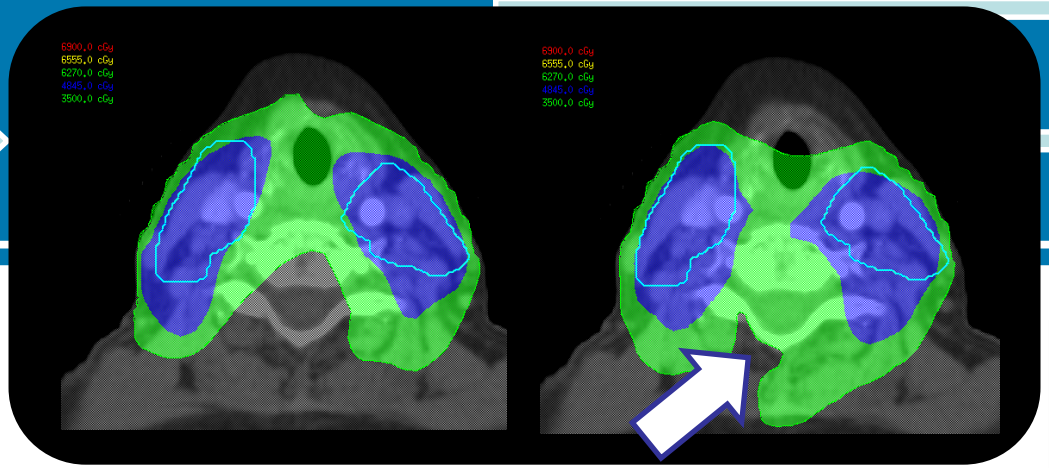
4

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



contouring →  → evaluate

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5

create optimisation structures next to evaluation structures

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

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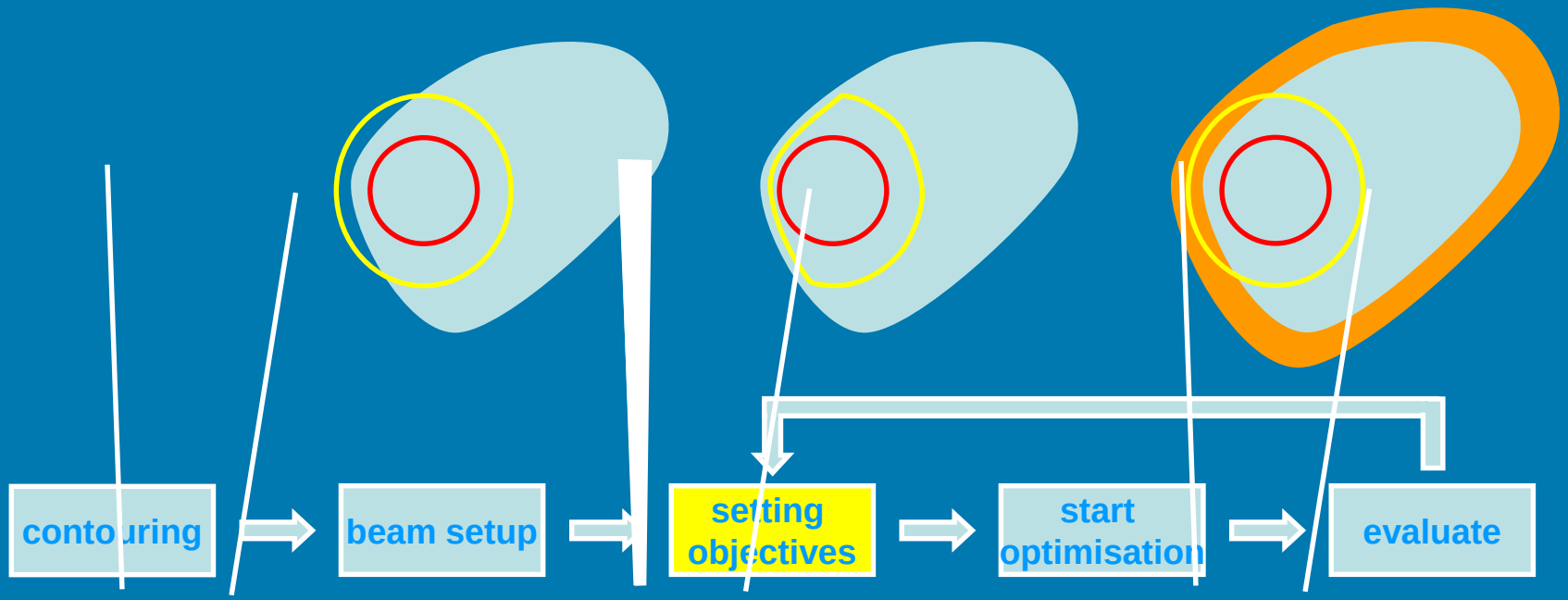
6

create optimisation structures next to evaluation structures



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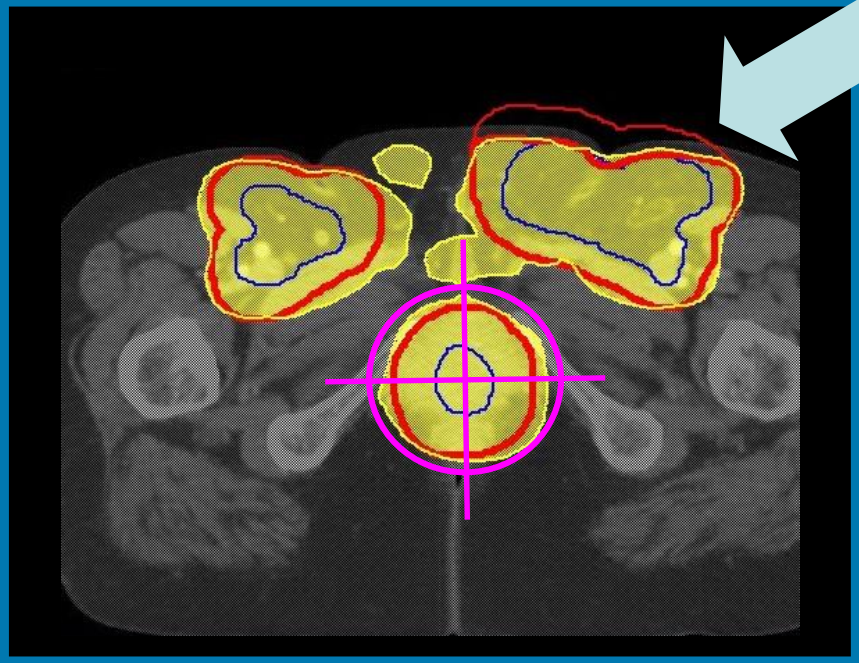
6



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

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

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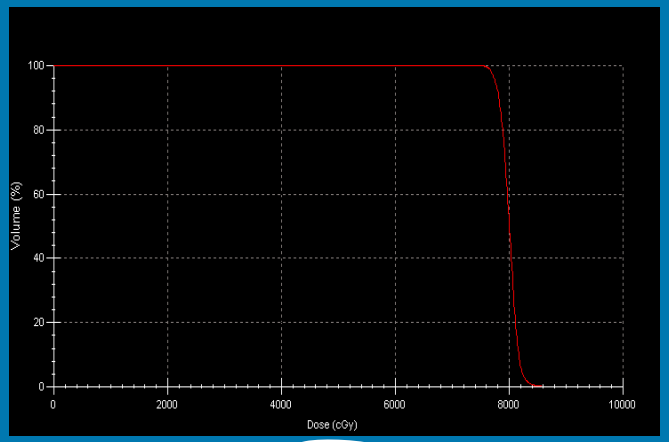
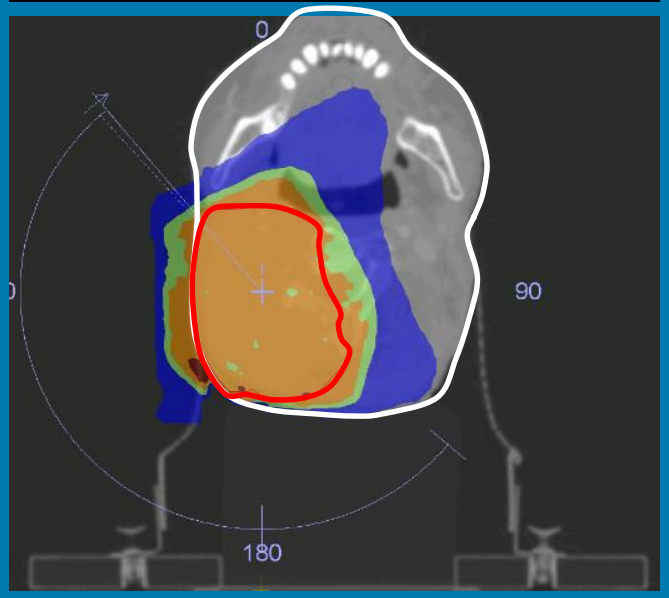
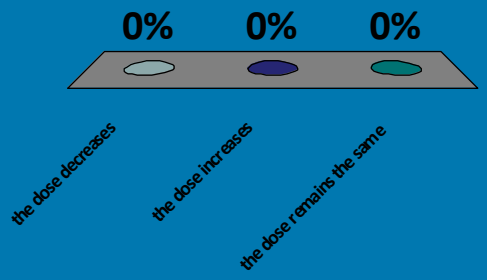
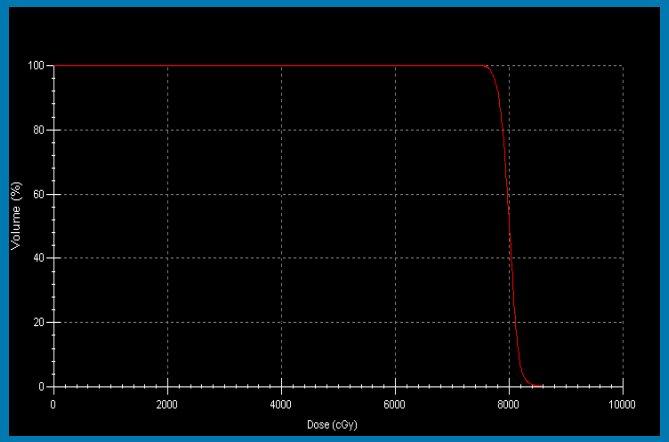


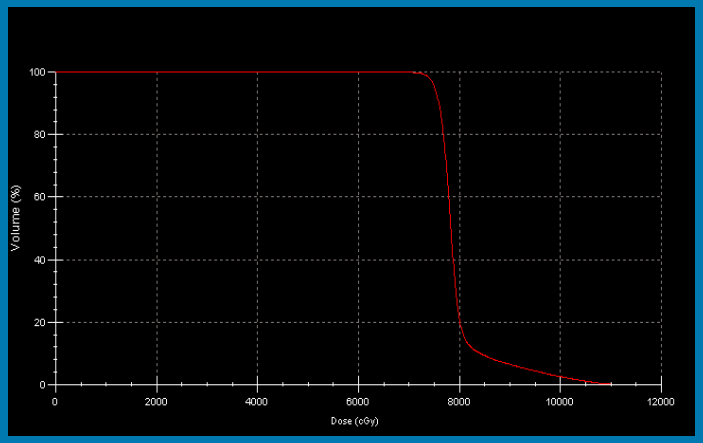


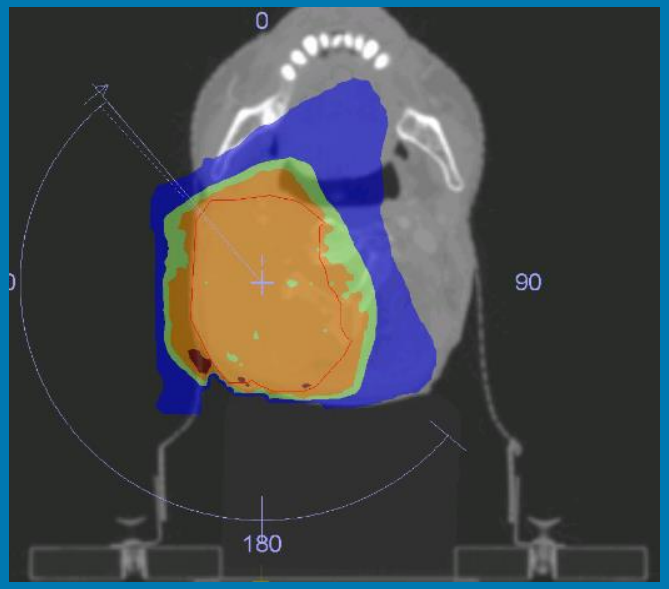
what happens to the dose in the posterior part of PTV when the patient is shifted 1 cm dorsally?

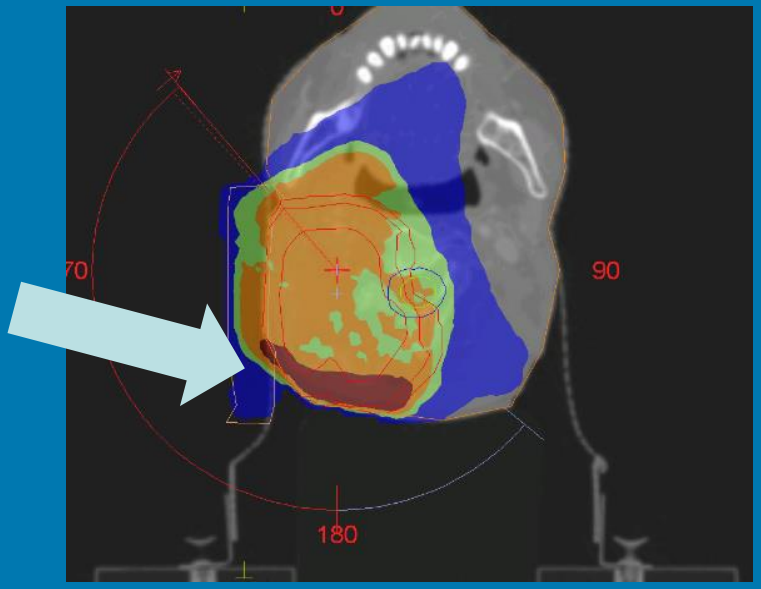
A. the dose decreases
B. the dose increases
C. the dose remains the same











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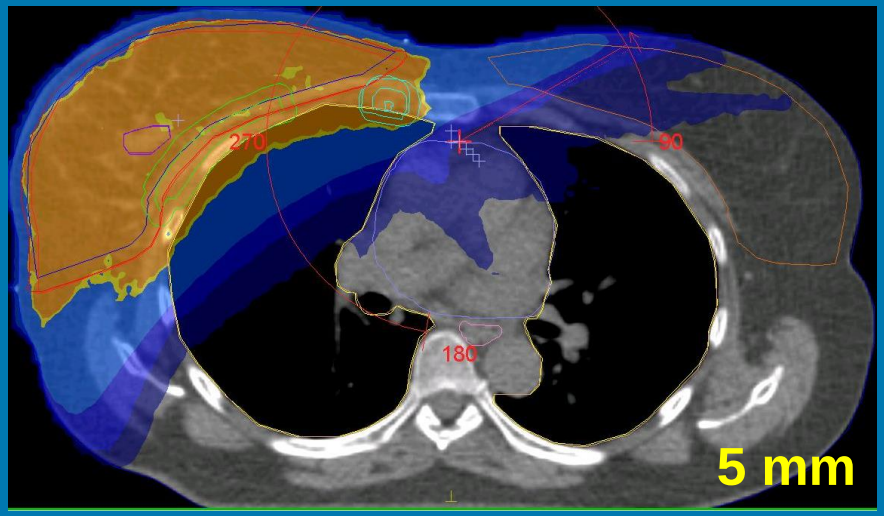

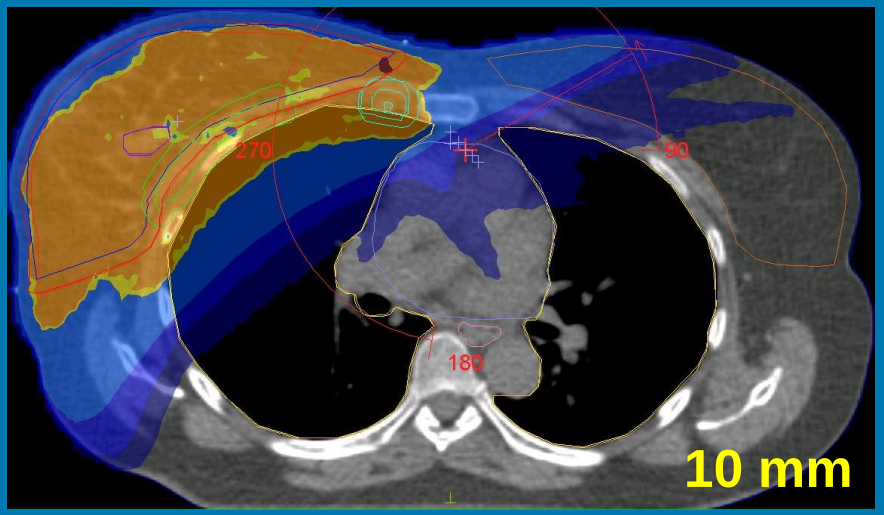

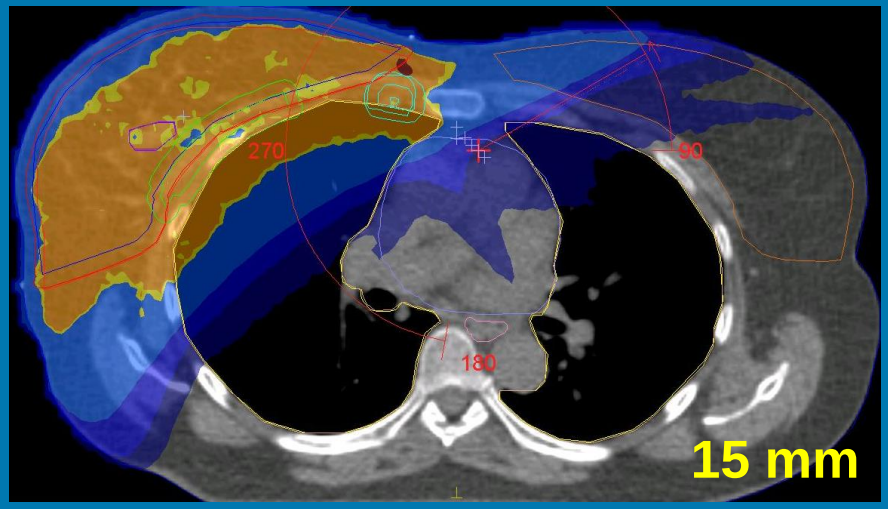

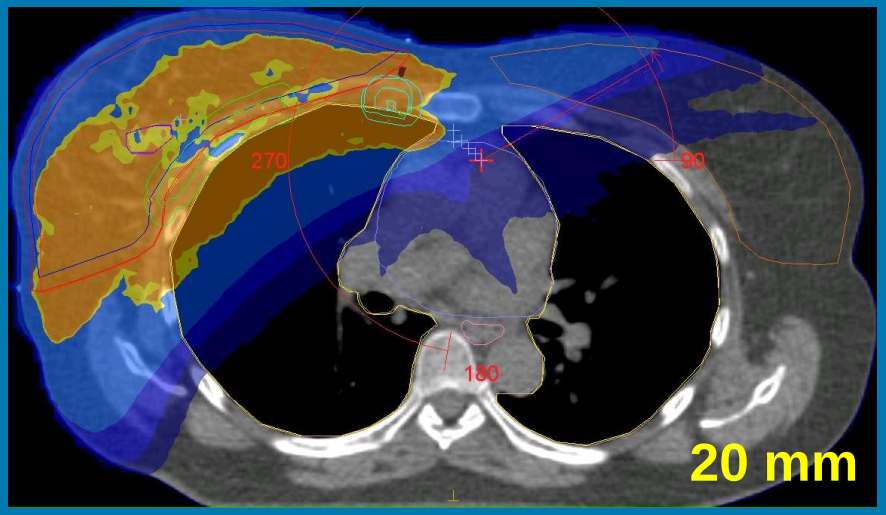

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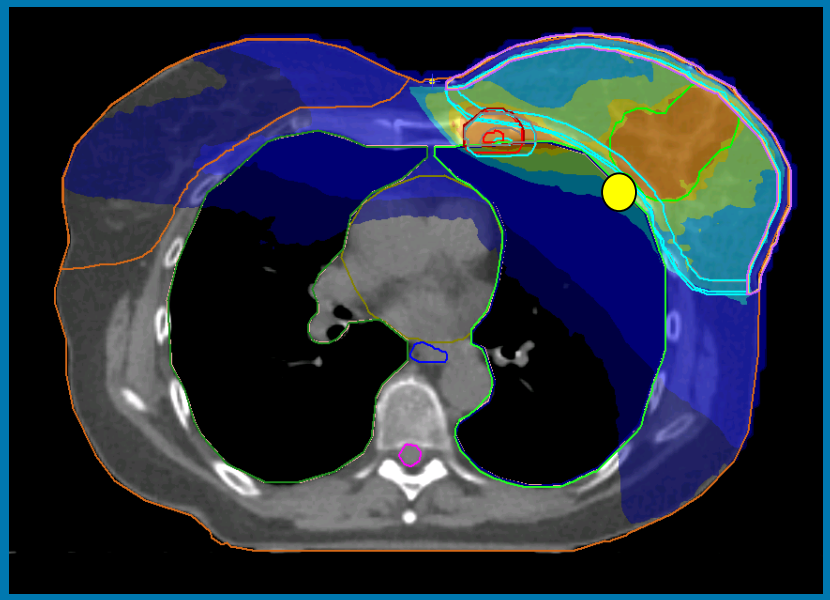

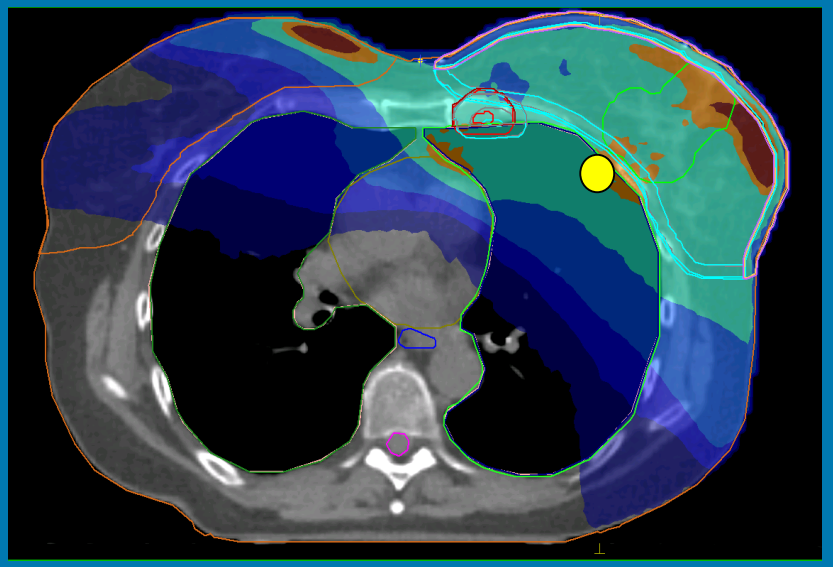

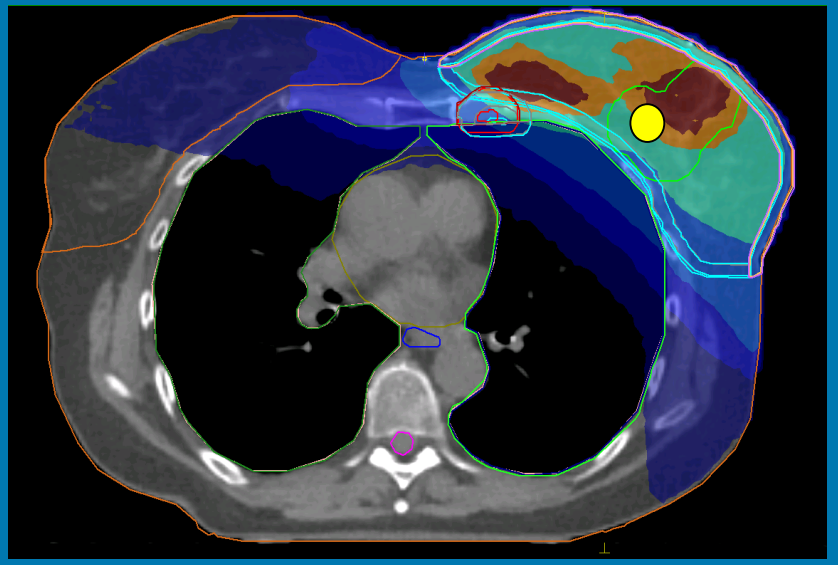

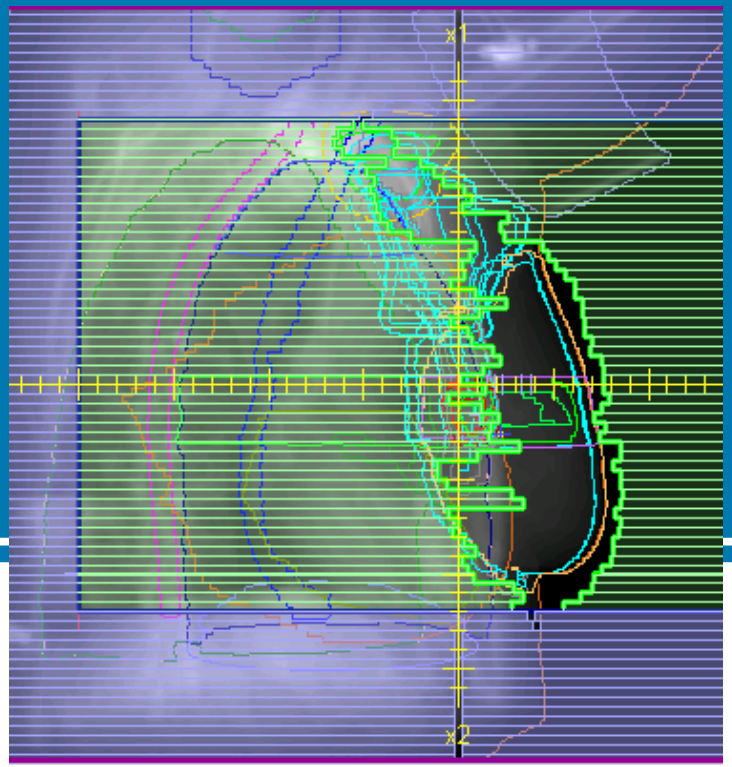

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7

avoid voxels with conflicting objectives

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

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

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

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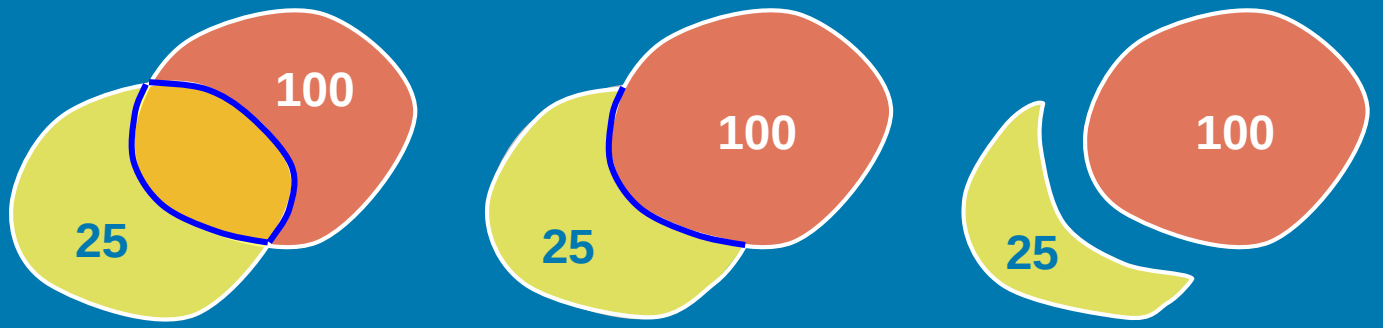
7

when target coverage has a higher priority than organ sparing



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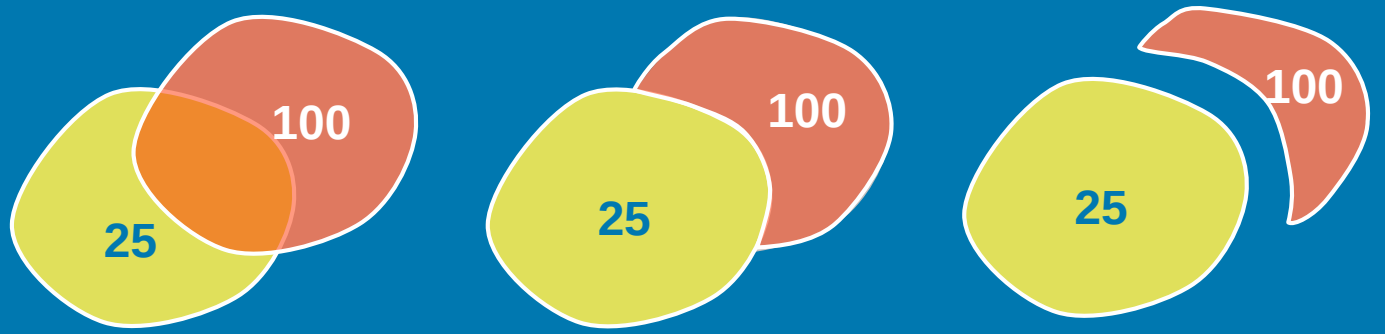
7

when organ function preservation has a higher priority than target coverage



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8

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

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

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9

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

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

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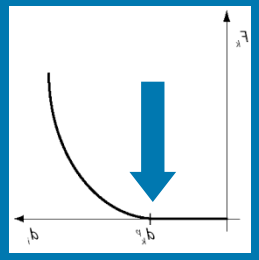
10

always set your IMRT objectives more stringent than your clinical objectives

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



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11

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

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

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

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

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

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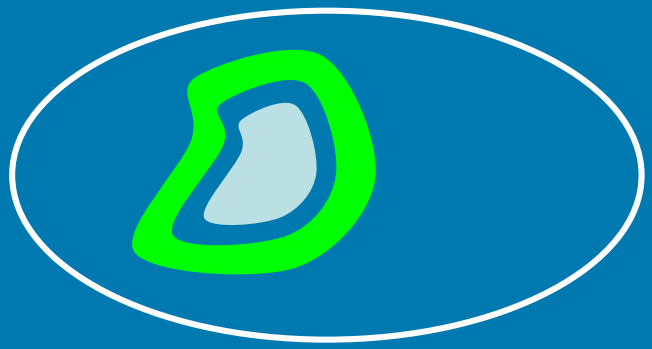

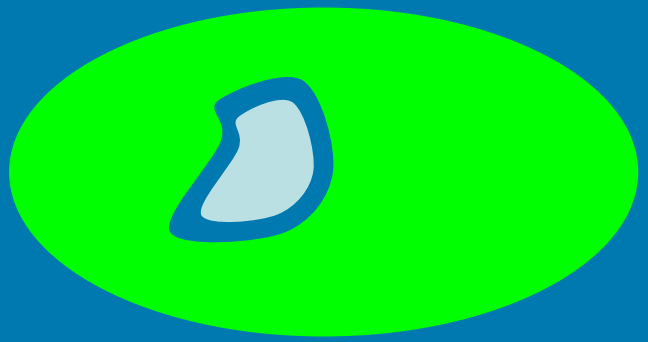

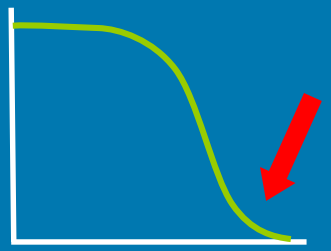

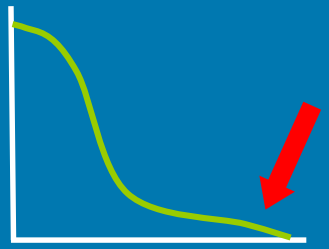

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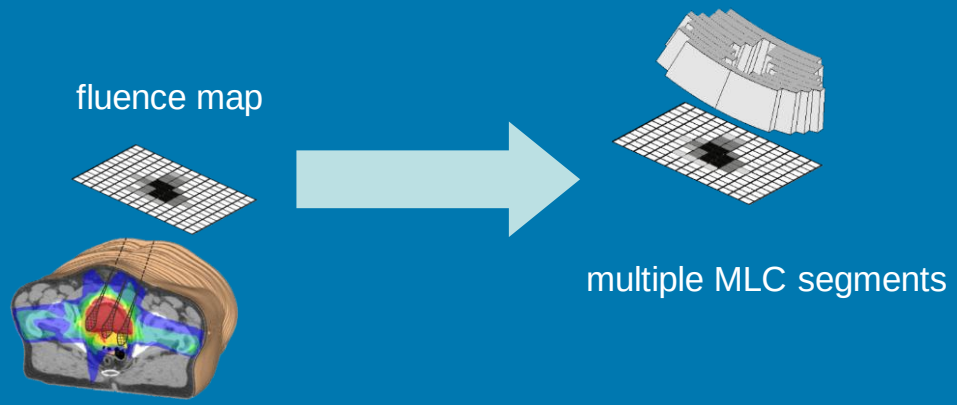

… and then at some point in our journey we need to convert the fluence map into MLC segments

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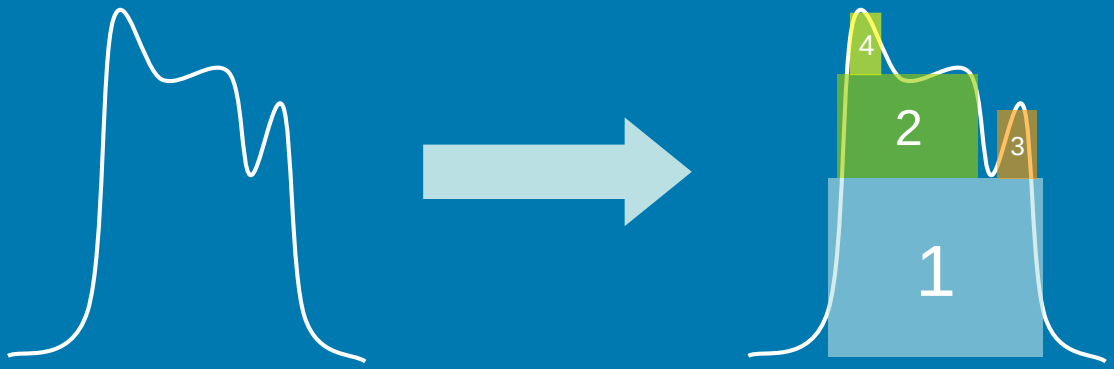

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close in

sliding window

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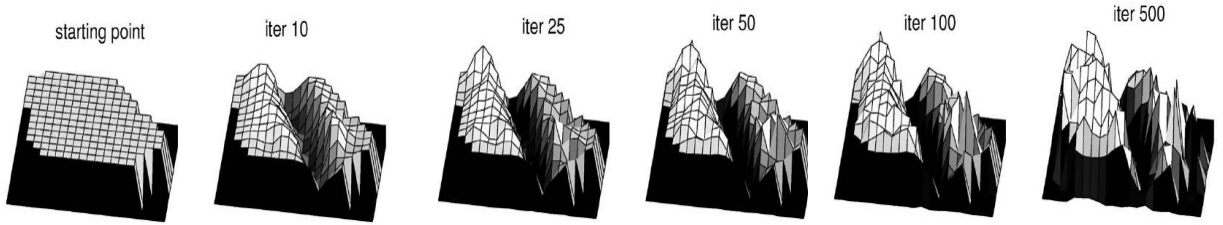
13

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



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

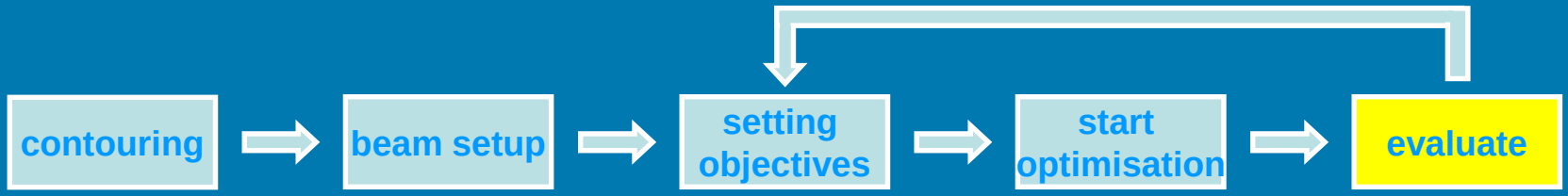
17 tips and tricks for happy IMRT planning

14

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

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

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



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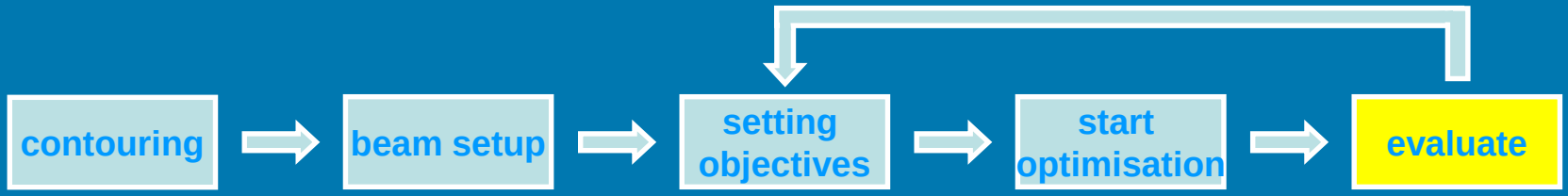
15

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

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

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



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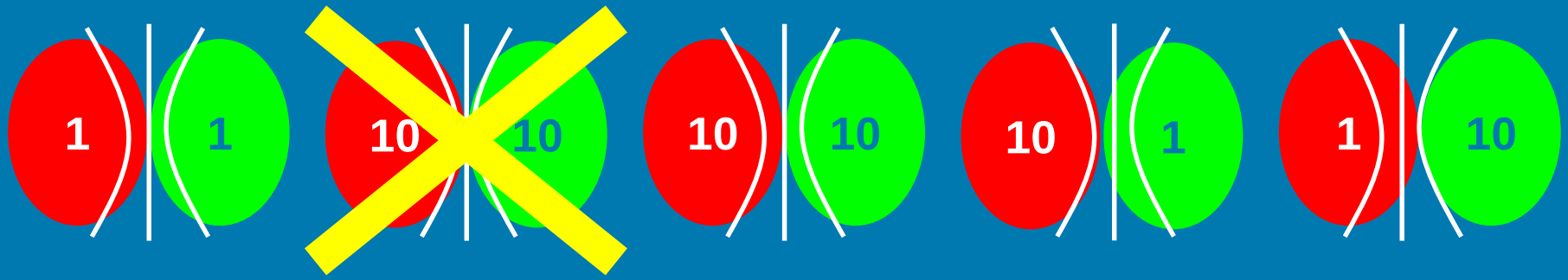
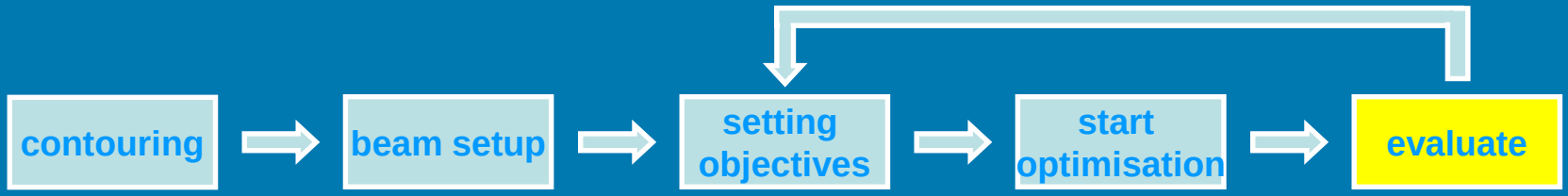
17 tips and tricks for happy IMRT planning

16

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





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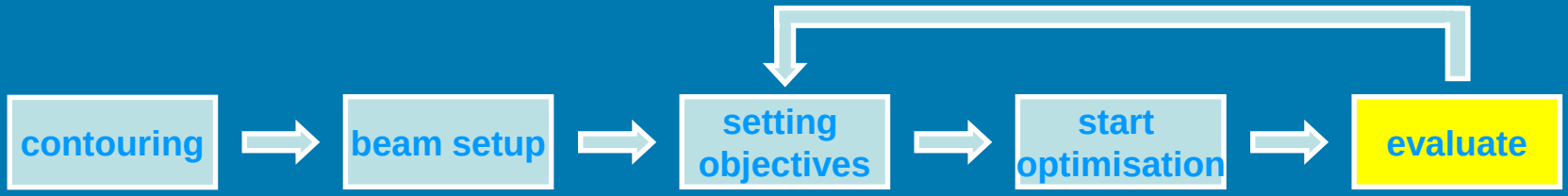
17 tips and tricks for happy IMRT planning

17

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

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



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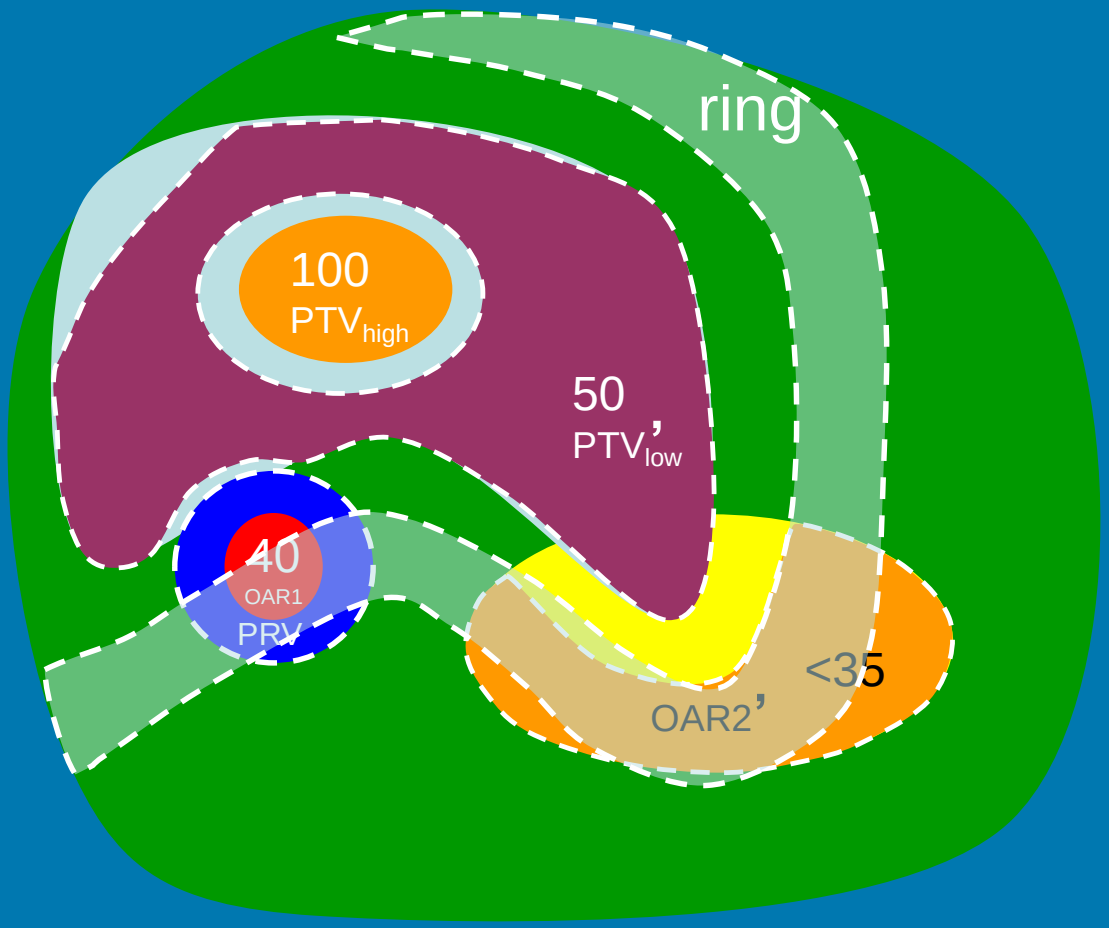

high priority

low priority

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

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Conclusions

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

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Practical aspects of IMRT planning part 2

Advanced Treatment Planning Course
23-27 September 2018 – Athens, Greece

Markus Stock

MedAustron
Ion Therapy Center

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!

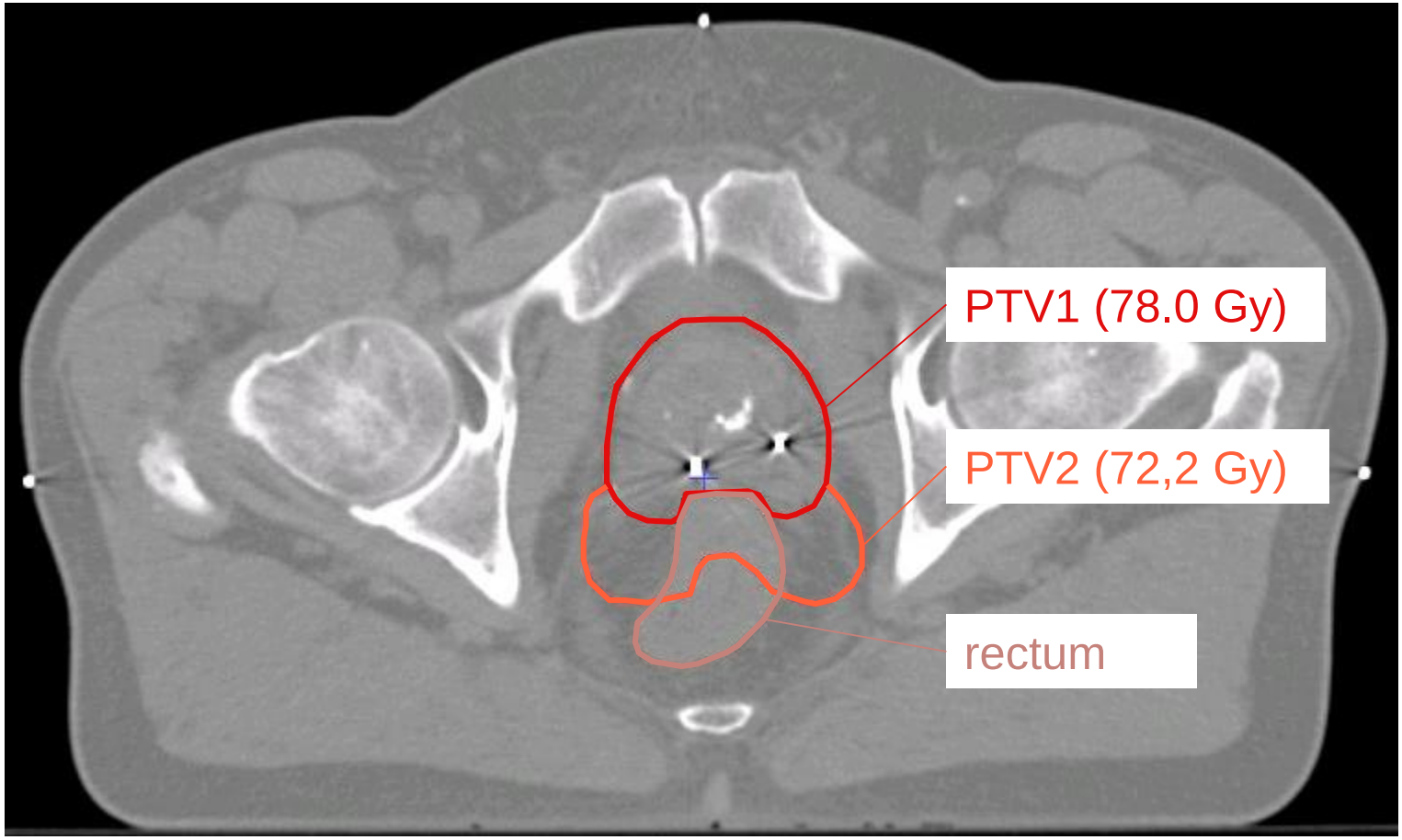
  more beams results in:

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

more beams will <u>not</u> automatically result in more treatment time!

prostate planning: 5 vs 7 beams

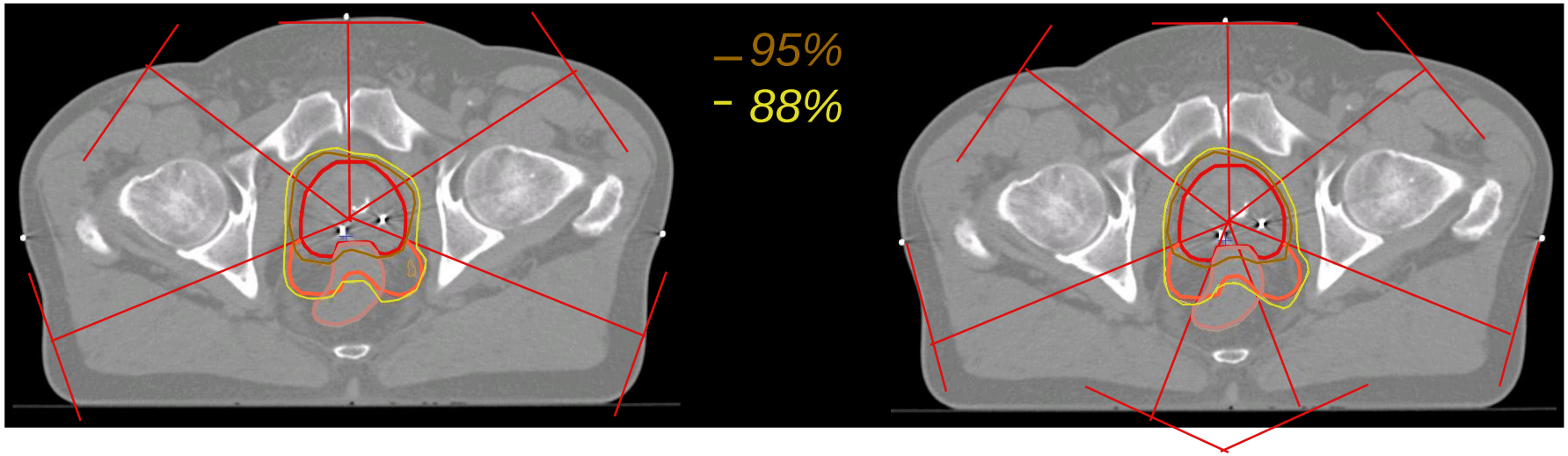
- SIB planning



prostate planning: 5 vs 7 beams

5 beams

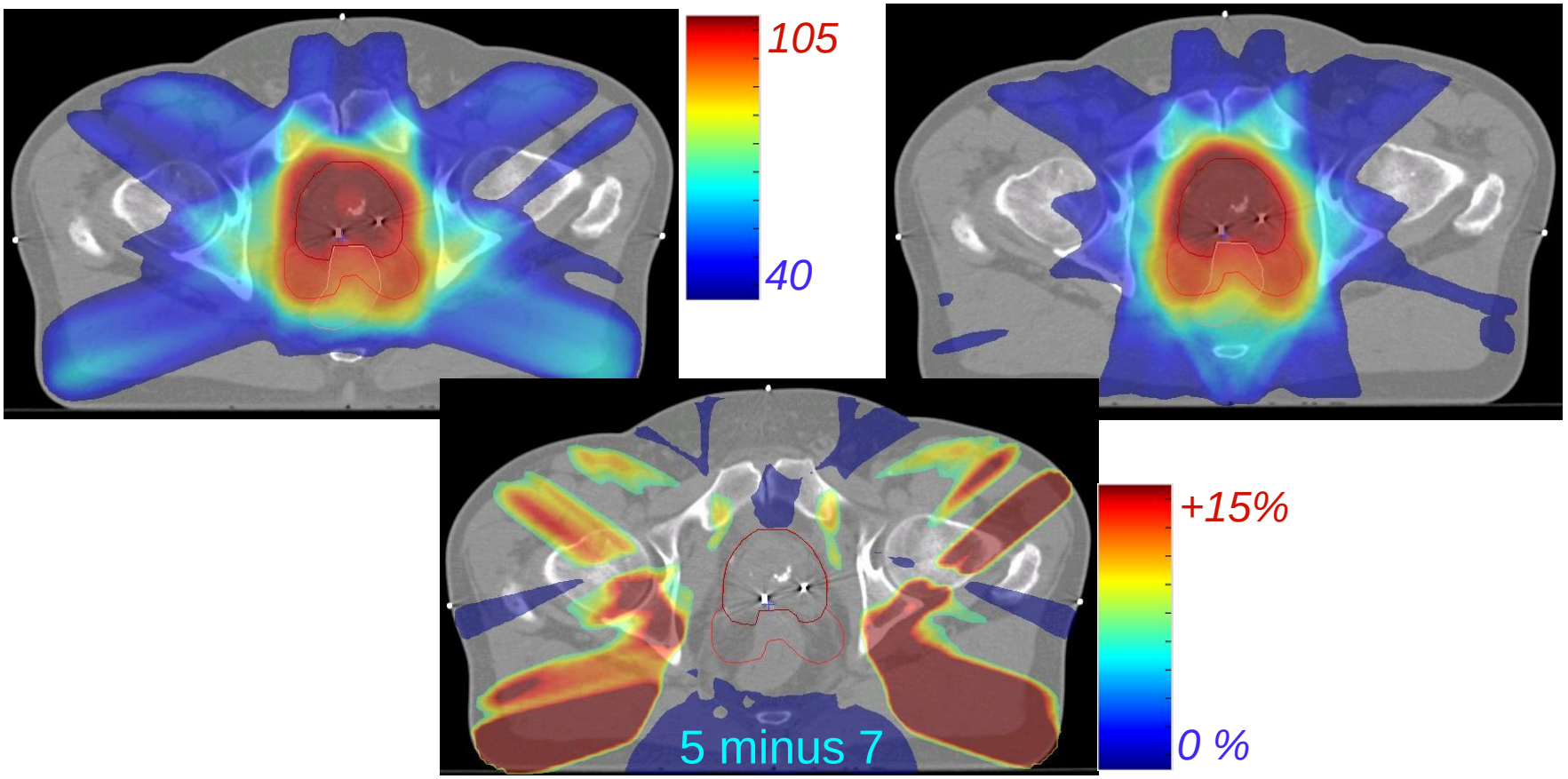
7 beams



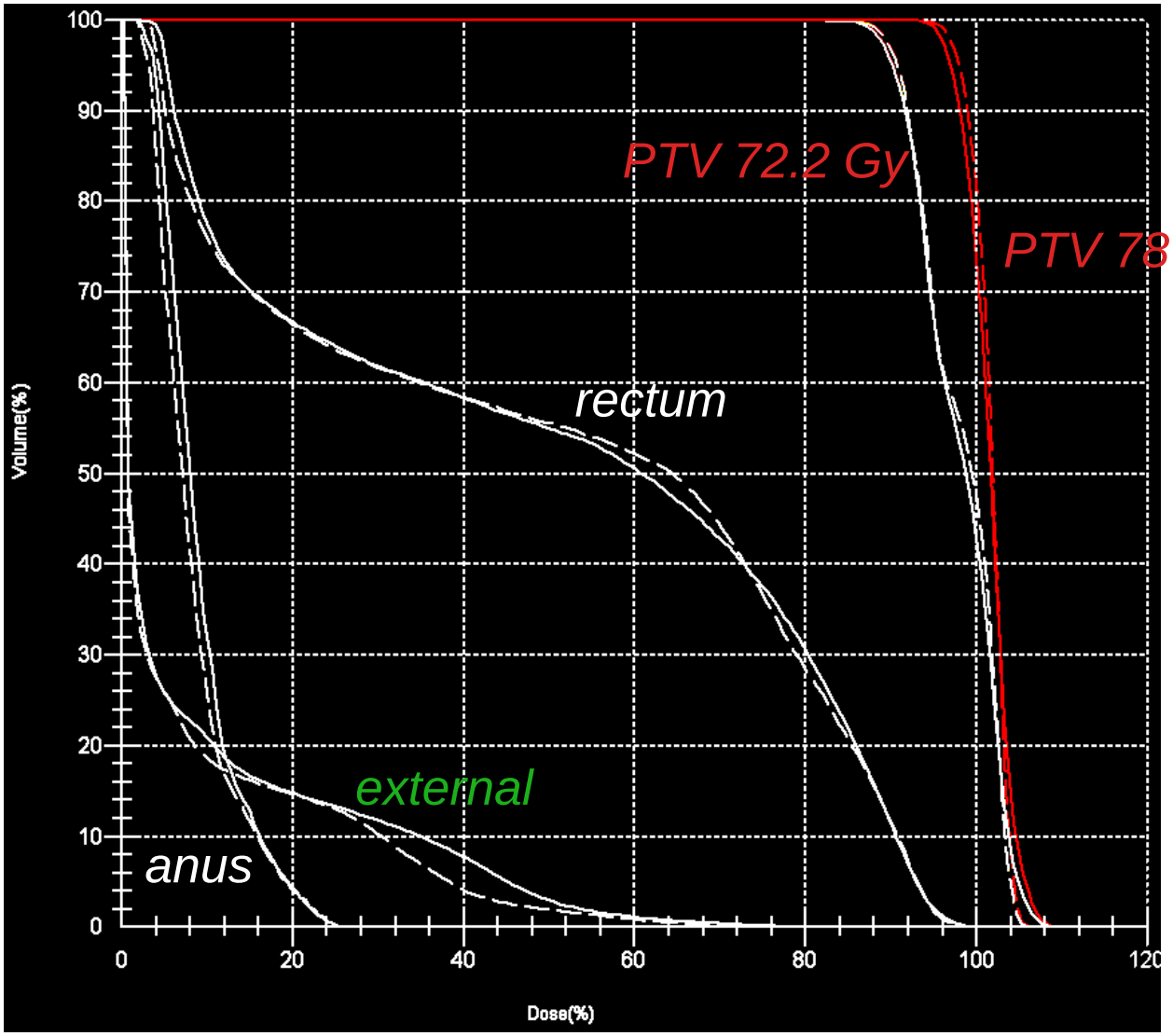
prostate planning: 5 vs 7 beams

5 beams

7 beams



prostate planning: 5 vs 7 beams



5 beams

7 beams

prostate planning: 5 vs 7 beams

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

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

beam angle optimization

Beam angle optimization

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

beam angle optimization (BAO):

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

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

Beam angle optimization

Rotterdam:

- 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.

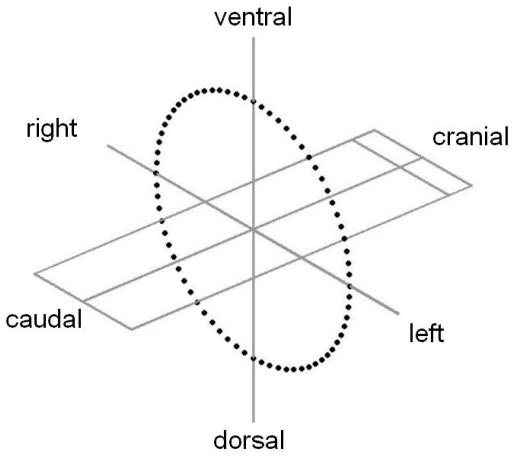
iCycle: Integrated, multicriterial beam angle, and profile optimization for generation of coplanar and noncoplanar IMRT plans.

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

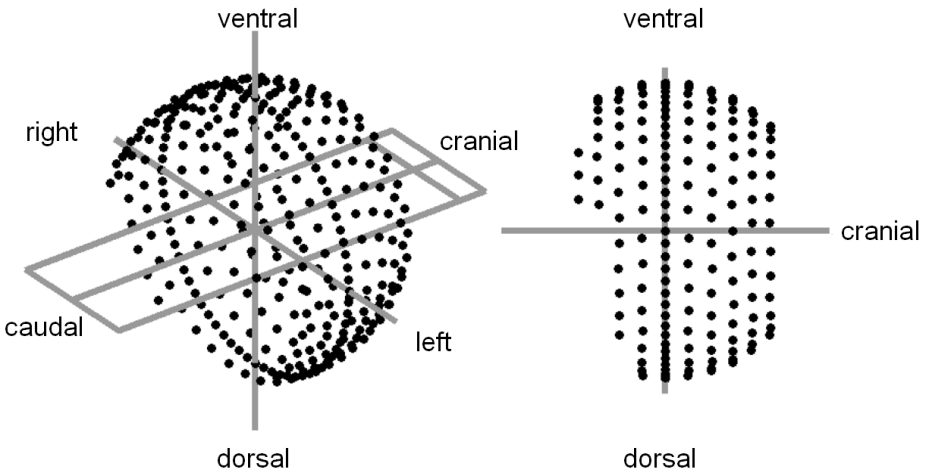
Department of Radiation Oncology, Erasmus MC Rotterdam, Groene Hilledijk 301, 3075 EA Rotterdam, The Netherlands. s.breedveld@erasmusmc.nl

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

Example iCycle output

Non coplanar

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

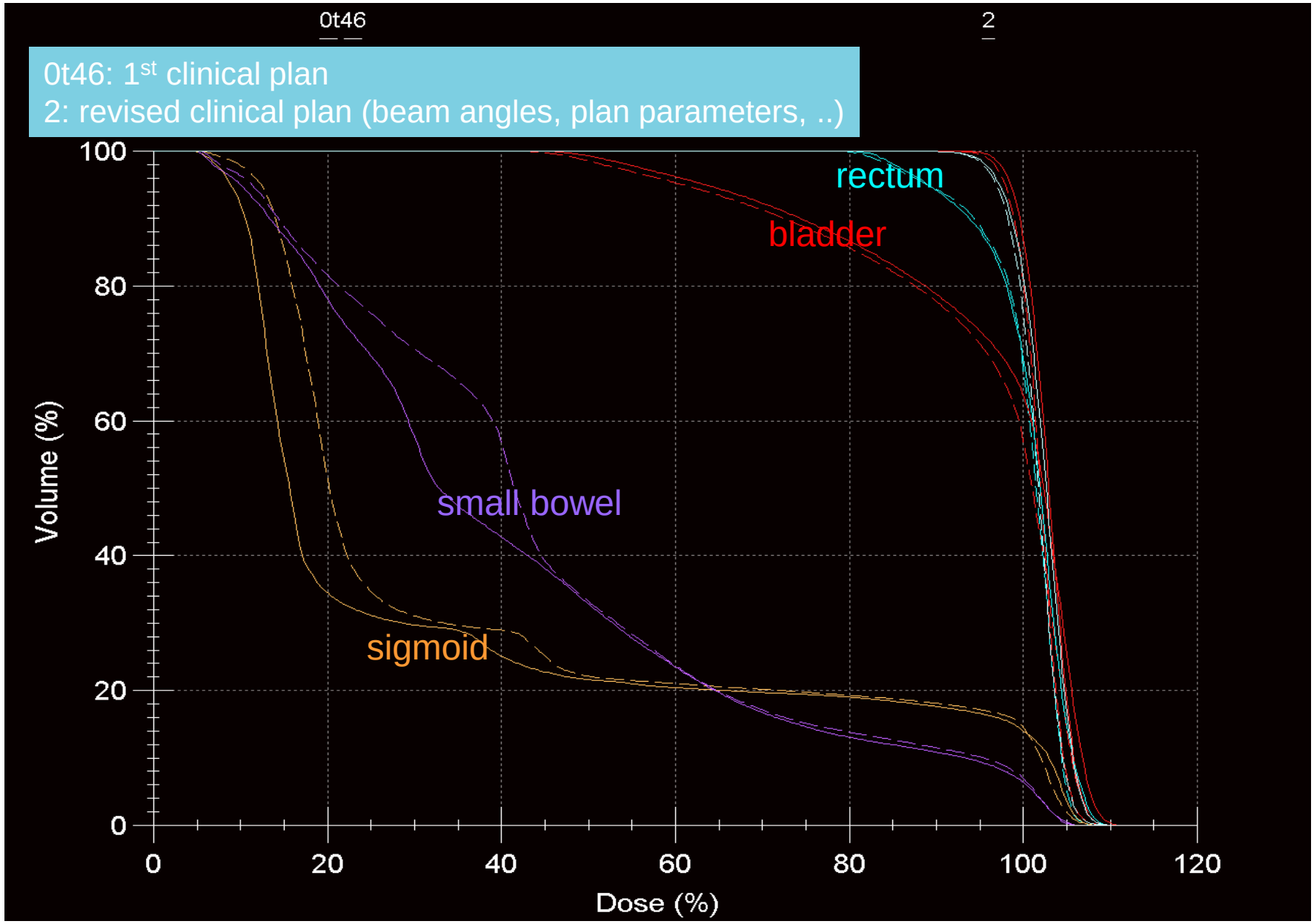
gain per added beam →

Angles:

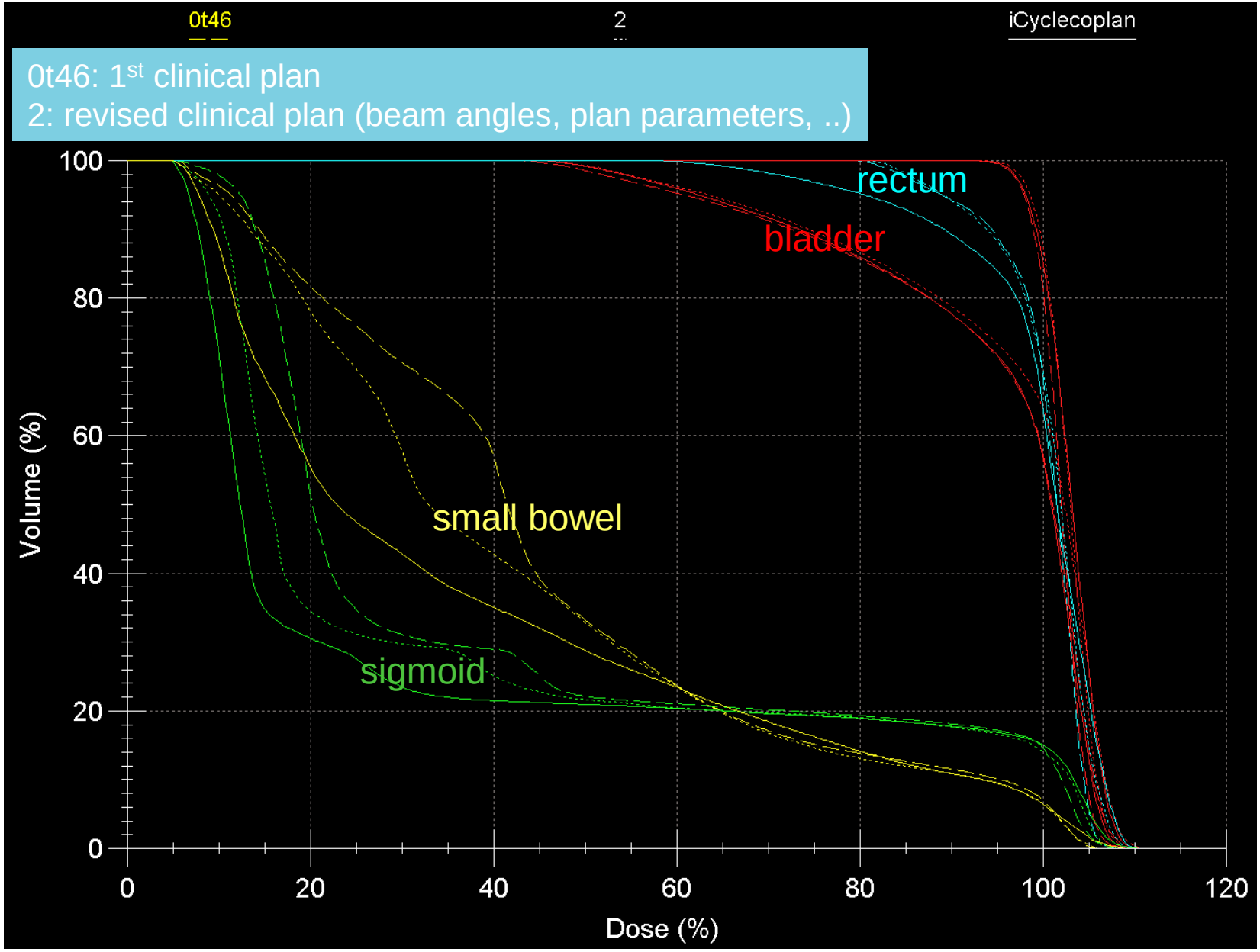
(Gantry, Cou	(59, -56, 6)	(59, -56, 6)	(59, -56, 6)	(59, -56, 6)
	(309, -36, 6)	(309, -36, 6)	(309, -36, 6)	(309, -36, 6)
	(68, 39, 6)	(68, 39, 6)	(68, 39, 6)	(68, 39, 6)
	(292, 50, 6)	(292, 50, 6)	(292, 50, 6)	(292, 50, 6)
	(313, -76, 6)	(313, -76, 6)	(313, -76, 6)	(313, -76, 6)
	(38, -74, 6)	(38, -74,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

Optimality when using small number of beams?

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

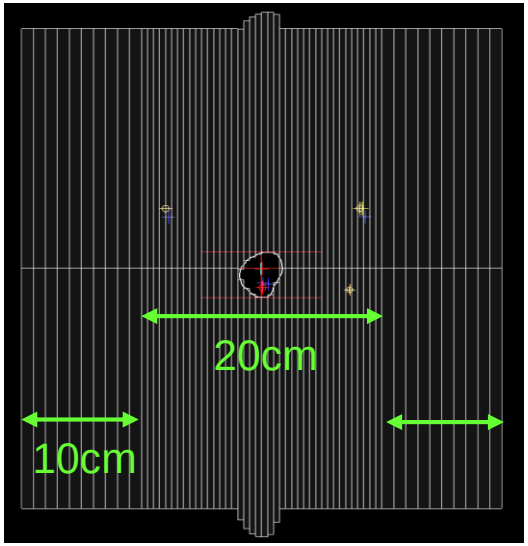
  - 6 MV in pelvic region??

  - combination of different energies is a good option

    (computer based choice?)

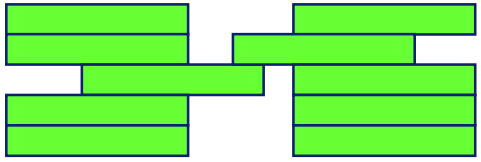
MLC geometry: Varian (millenium MLC)

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



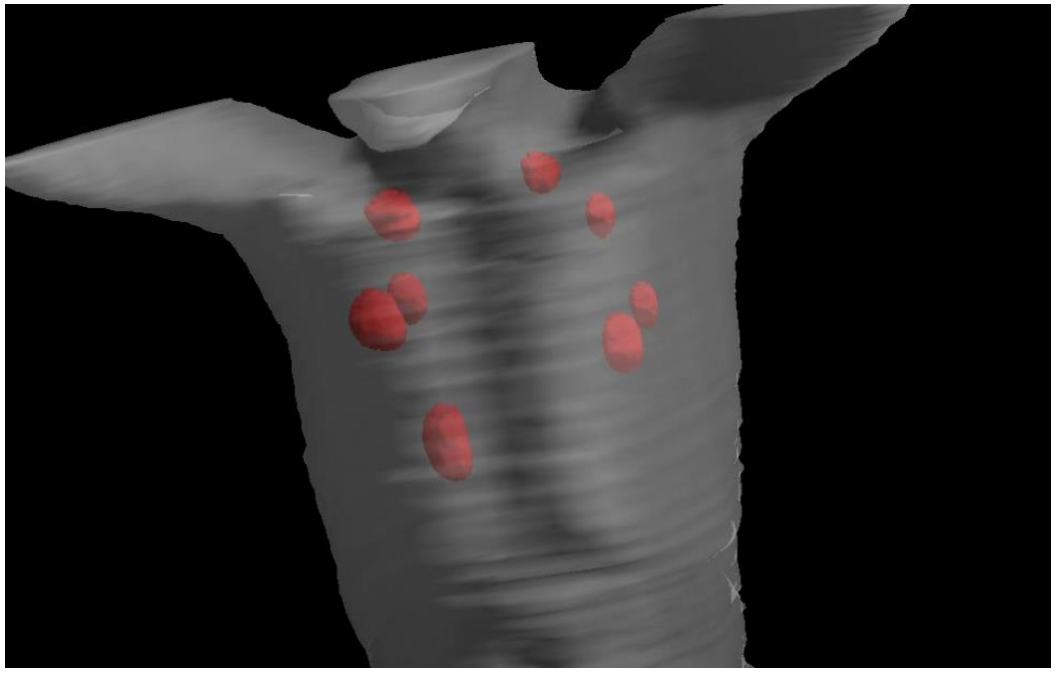
- maximum overtravel in (IMRT) fields is 14.3 cm:
  - so, if an IMRT field width ≥ 14.3 cm ⟶ splitting beam
  - field width ≈ 28 cm ⟶ splitting again (‘*carriage positions*’)

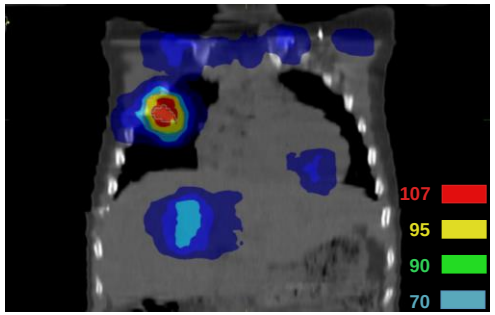
- inter-digitating MLC’s
- closing opposing leaf-pairs

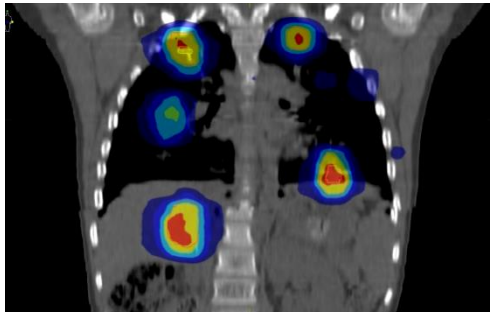


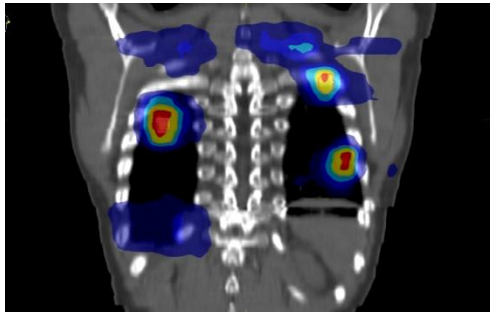
Clinical example multiple PTV case

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

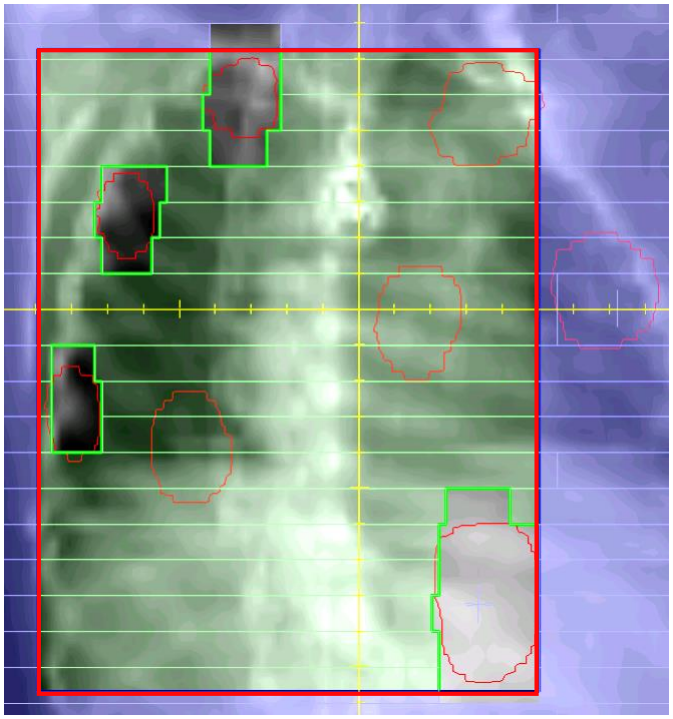








Example multiple PTV (8!) IMRT plan: Varian



segment 1

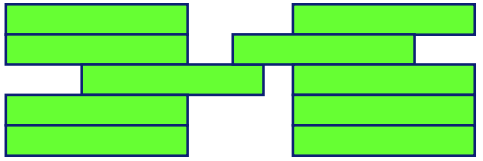
segment x

1.8 Gy / fraction
8 fields
38 segments, 555 MU

MLC geometry: Elekta (MLCi, MLCi2)

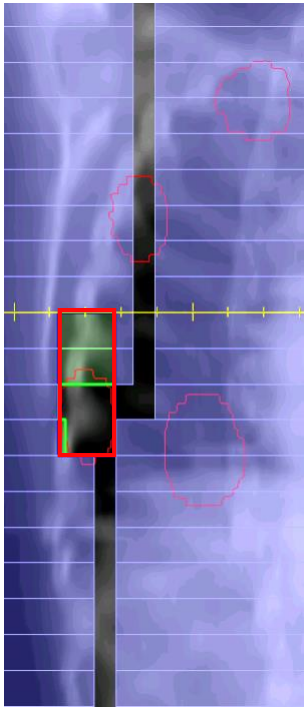
- no splitting of beams

- MLCi : no interdigitating leafs
- MLCi2 : interdigitating leafs

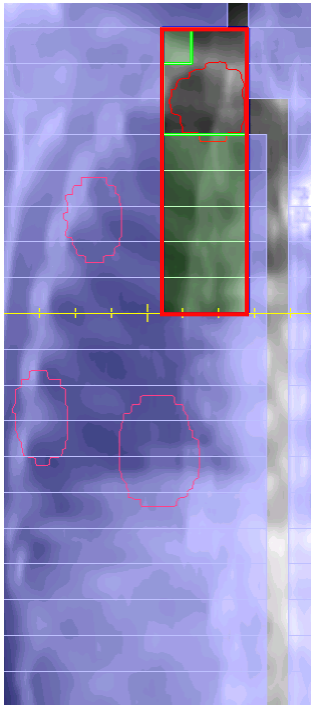


- minimum gap for opposing leaf pairs : 5 mm (MLCi , MLCi2)
- No overtravel on Y-jaws (MLCi , MLCi2)

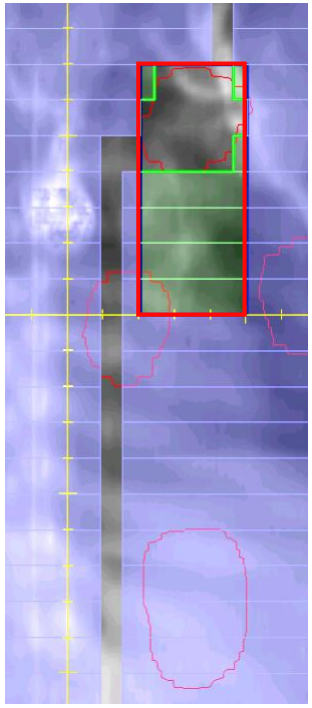
Example multiple PTV IMRT plan: Elekta , MLCi



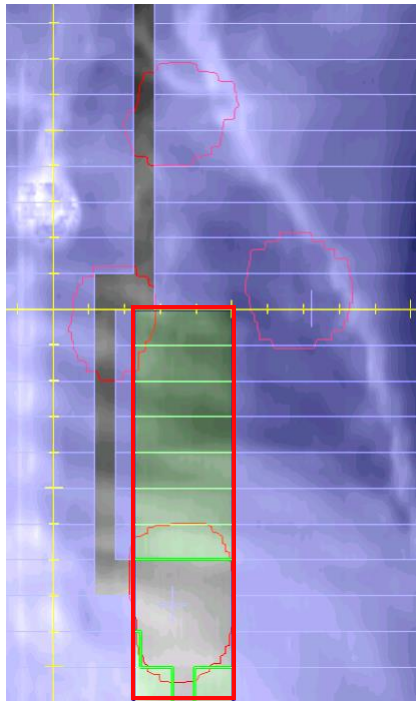
segment 1



segment 2



segment 3



segment x

1.8 Gy / fraction
8 fields
131 segments, 2239 MU

similar DVH's Varian - Elekta

Example multiple PTV IMRT plan: Elekta versus Varian

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

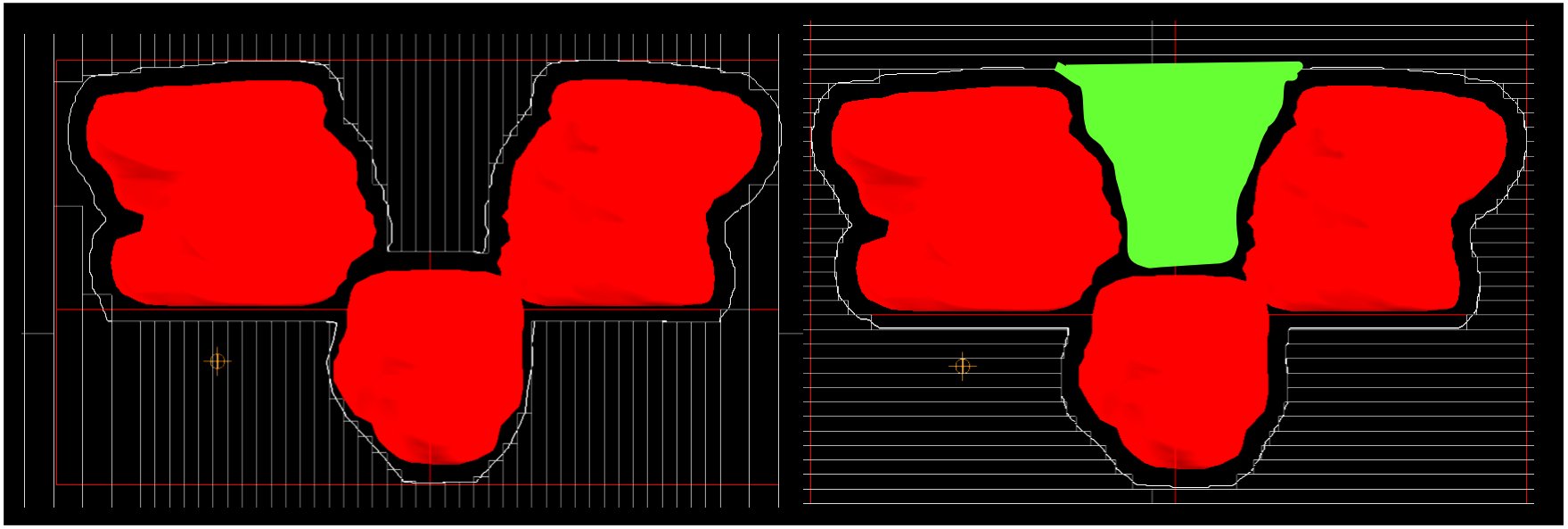
- in this example the MLC limitations resulted in large differences.

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

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

Collimator angle

- effect of collimator angle depends on the IMRT restrictions

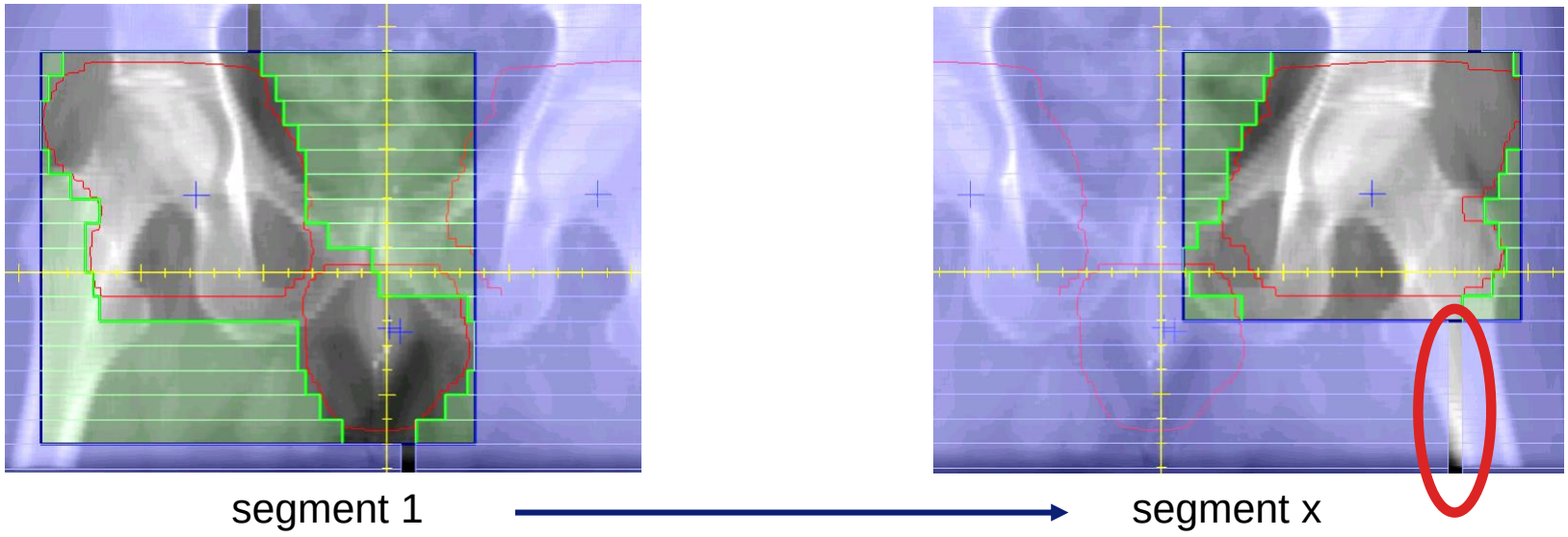


Collimator 90º

Collimator 0º

Effect of collimator angle depends on the IMRT delivery

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



- in d-MLC delivery:

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

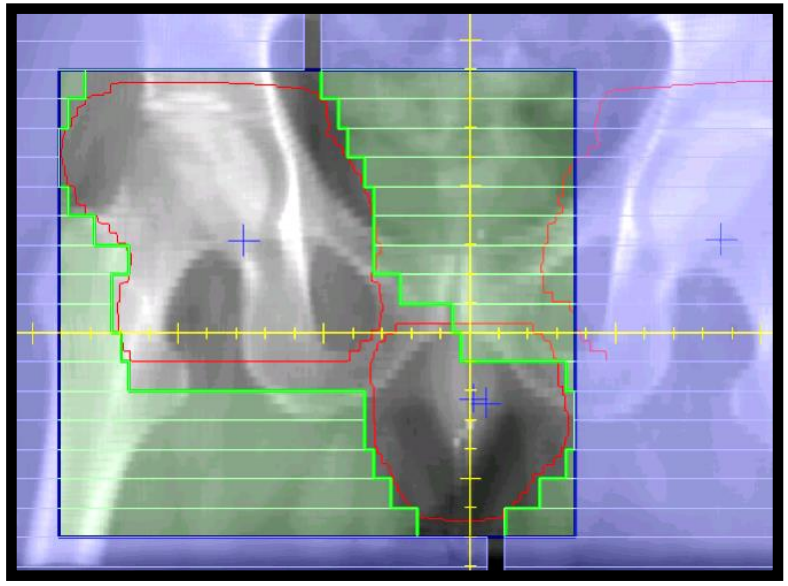
  Elekta MLCi 90º versus Varian / Elekta MLCi2: 0º / 90º

  or allow for ‘*move only segments*’

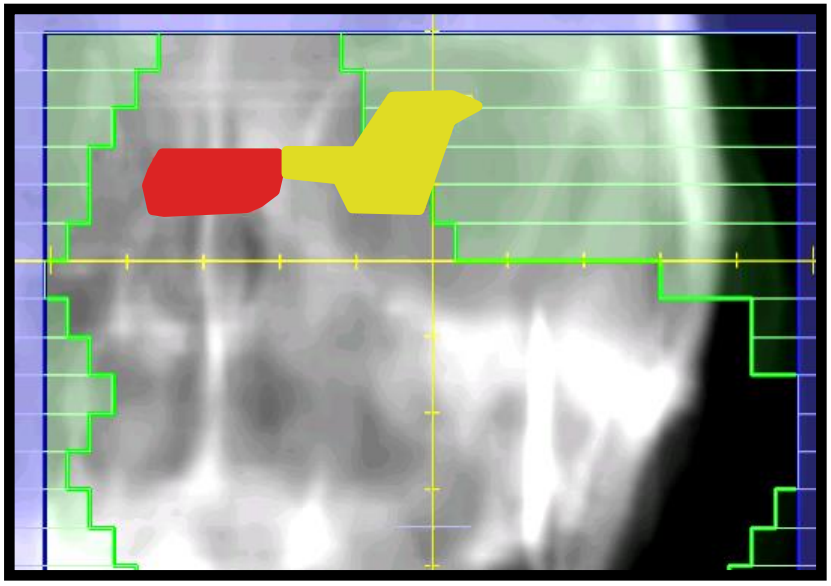
Leaf width

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

  however …. the effect of leaf width is relative!



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



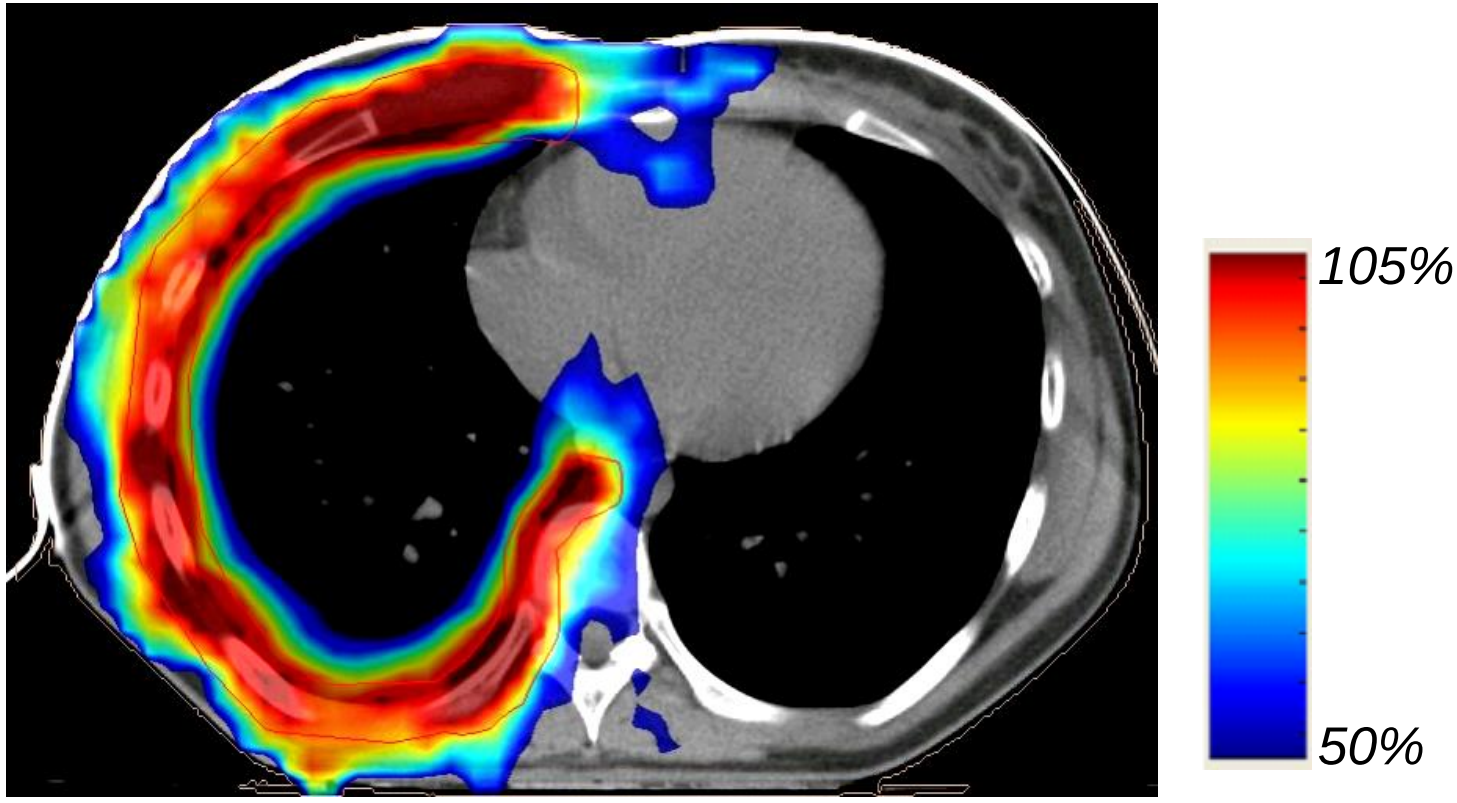
0.5 cm width might be too coarse for small OARs

optimize collimator rotation and isocenter position

Number of MU in IMRT planning

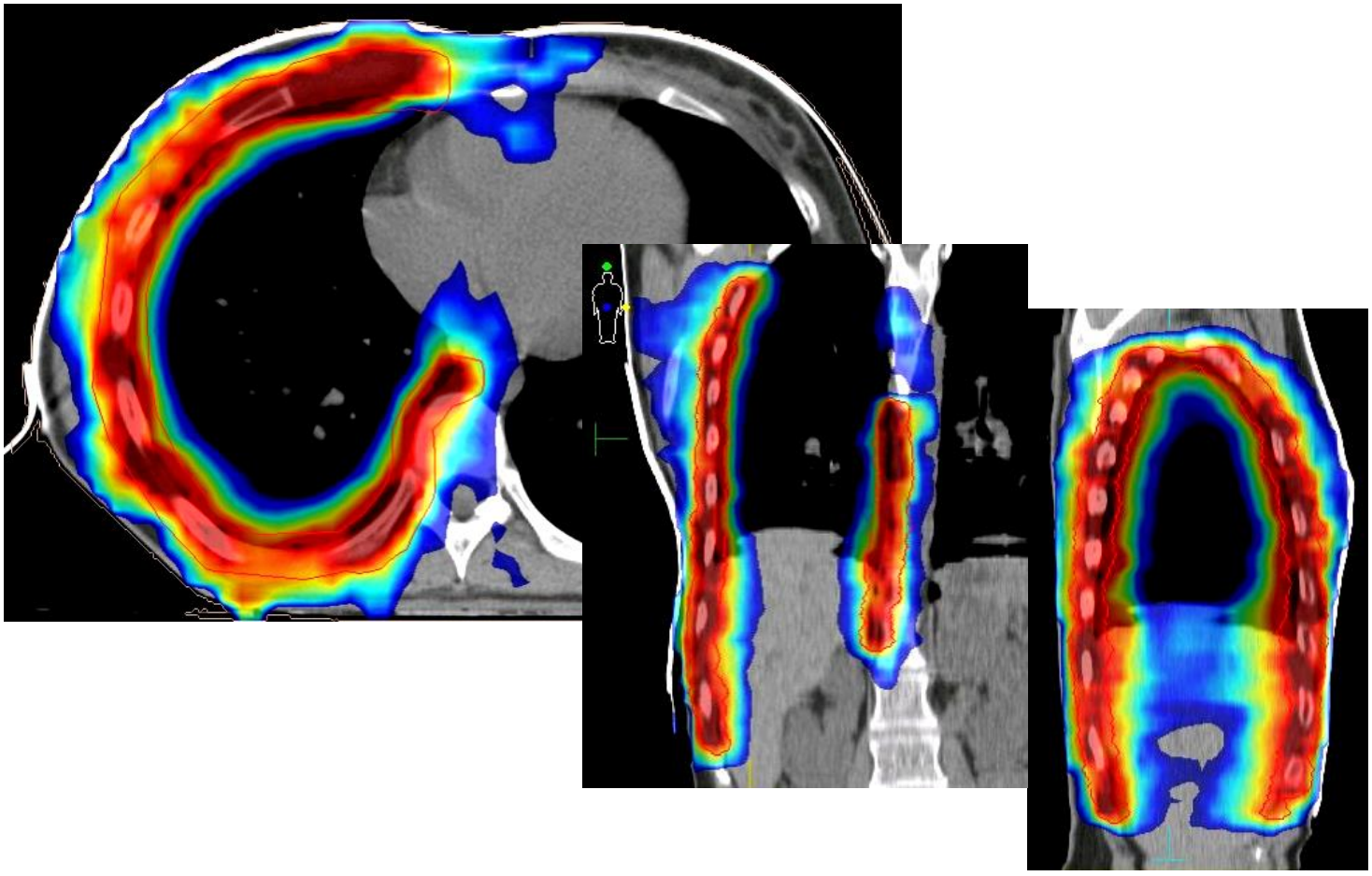
- is there a maximum in the number of MU to be delivered?

  how many MU/Gy do we accept?



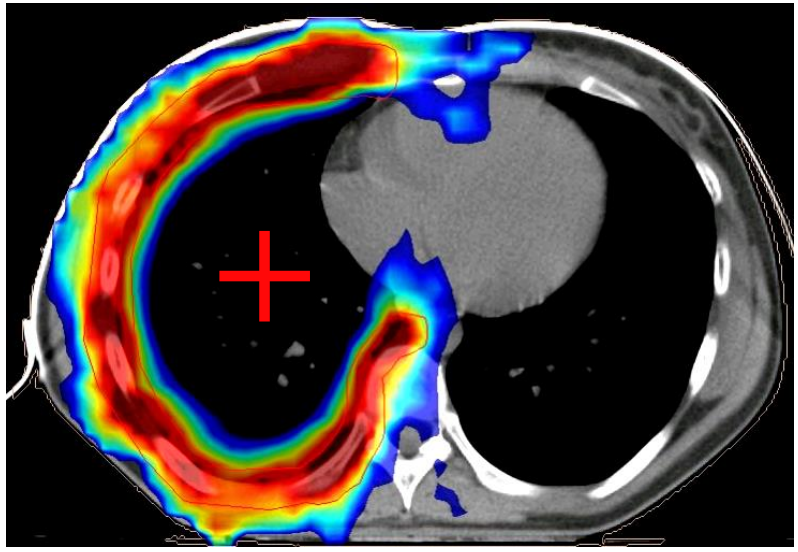
Number of MU in IMRT planning

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



Isocenter position

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



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

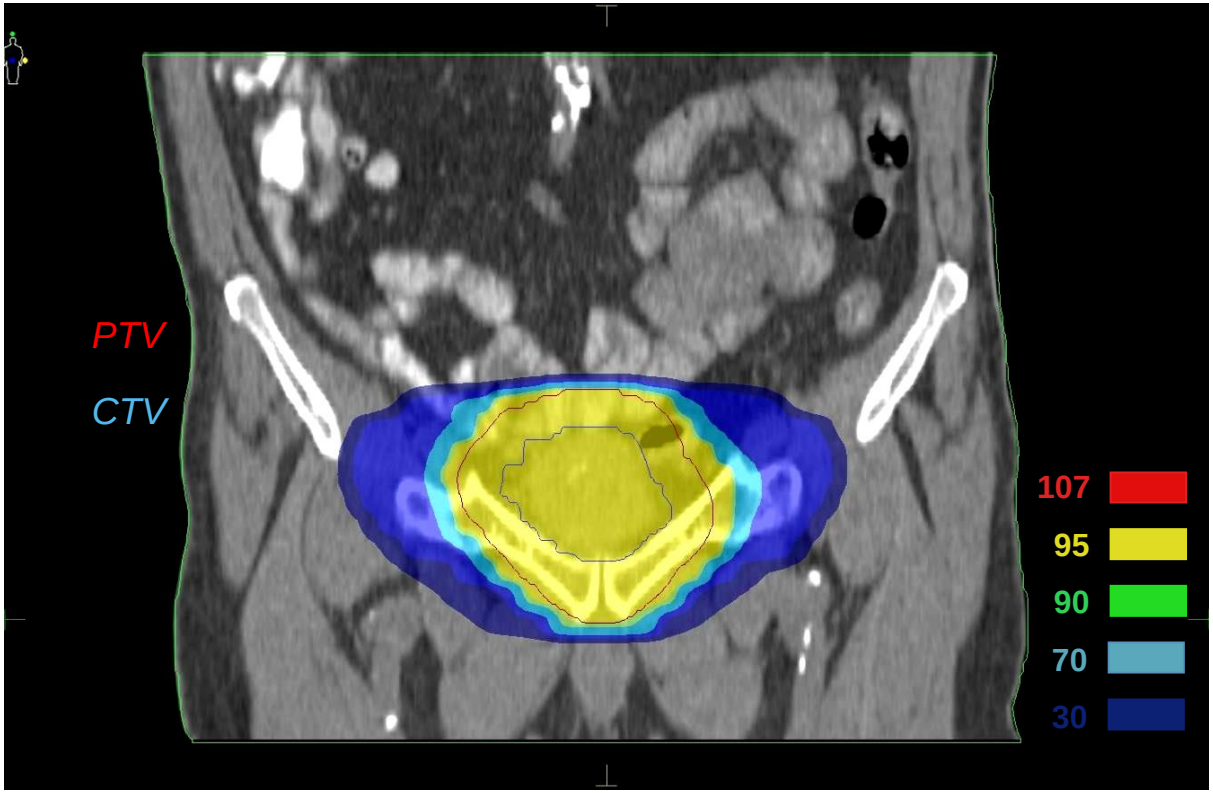
IMRT as efficiency tool for ‘simple 3D-CRT’

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

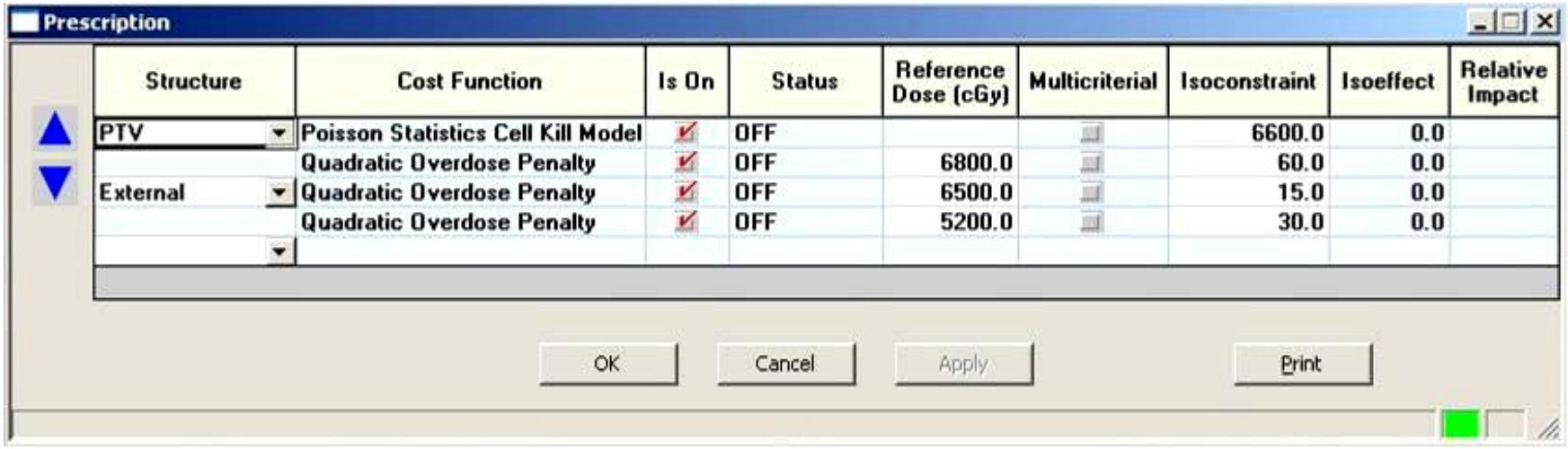
  - what about using it for ‘simple’ 3D conformal plans?

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

- bladder : 33 x 2.0 Gy



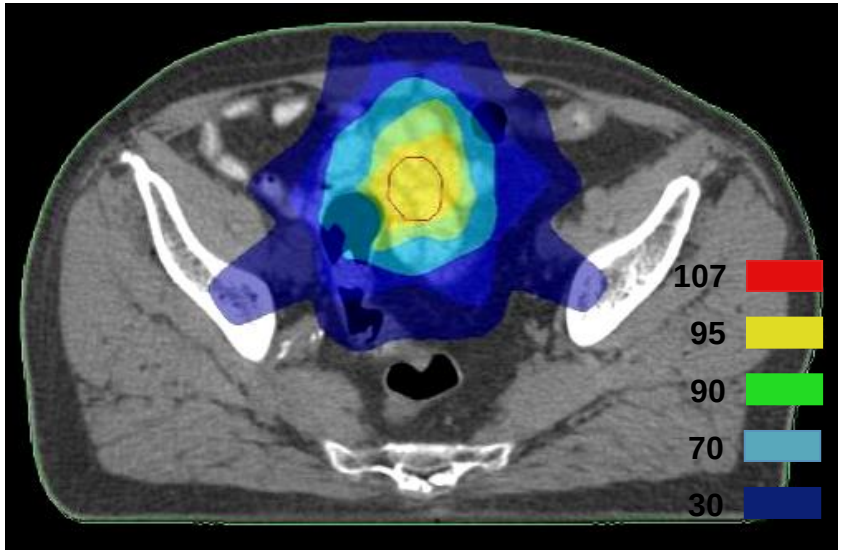
IMRT as efficiency tool for ‘simple 3D-CRT’ : Bladder

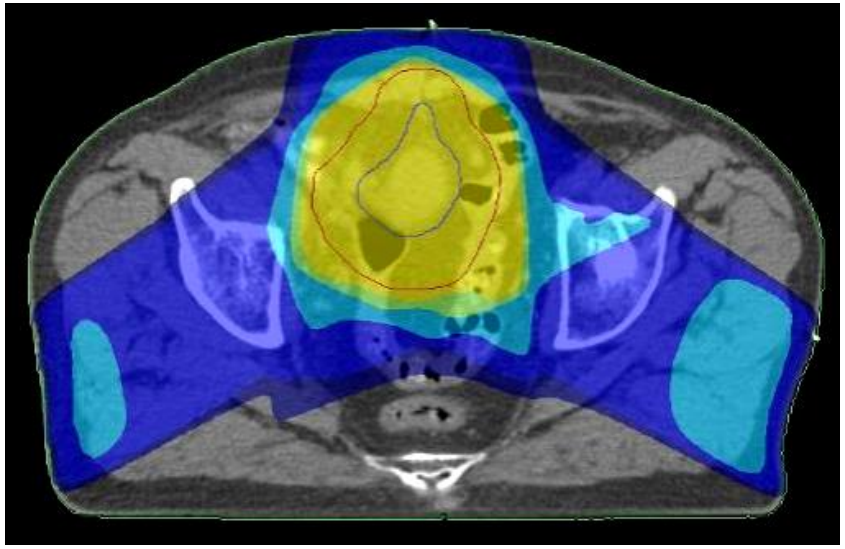


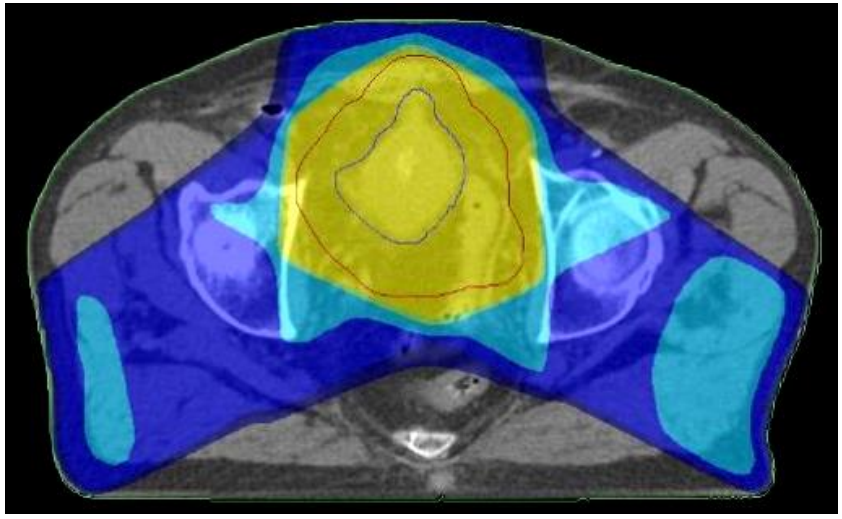
challenges:

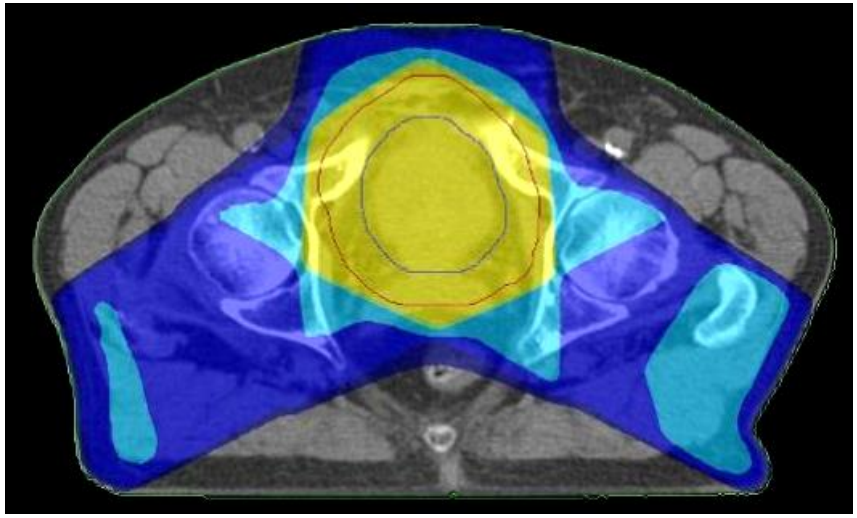
- coverage at least similar to 3DCRT
- reduction of planning time
- no increase in treatment time

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

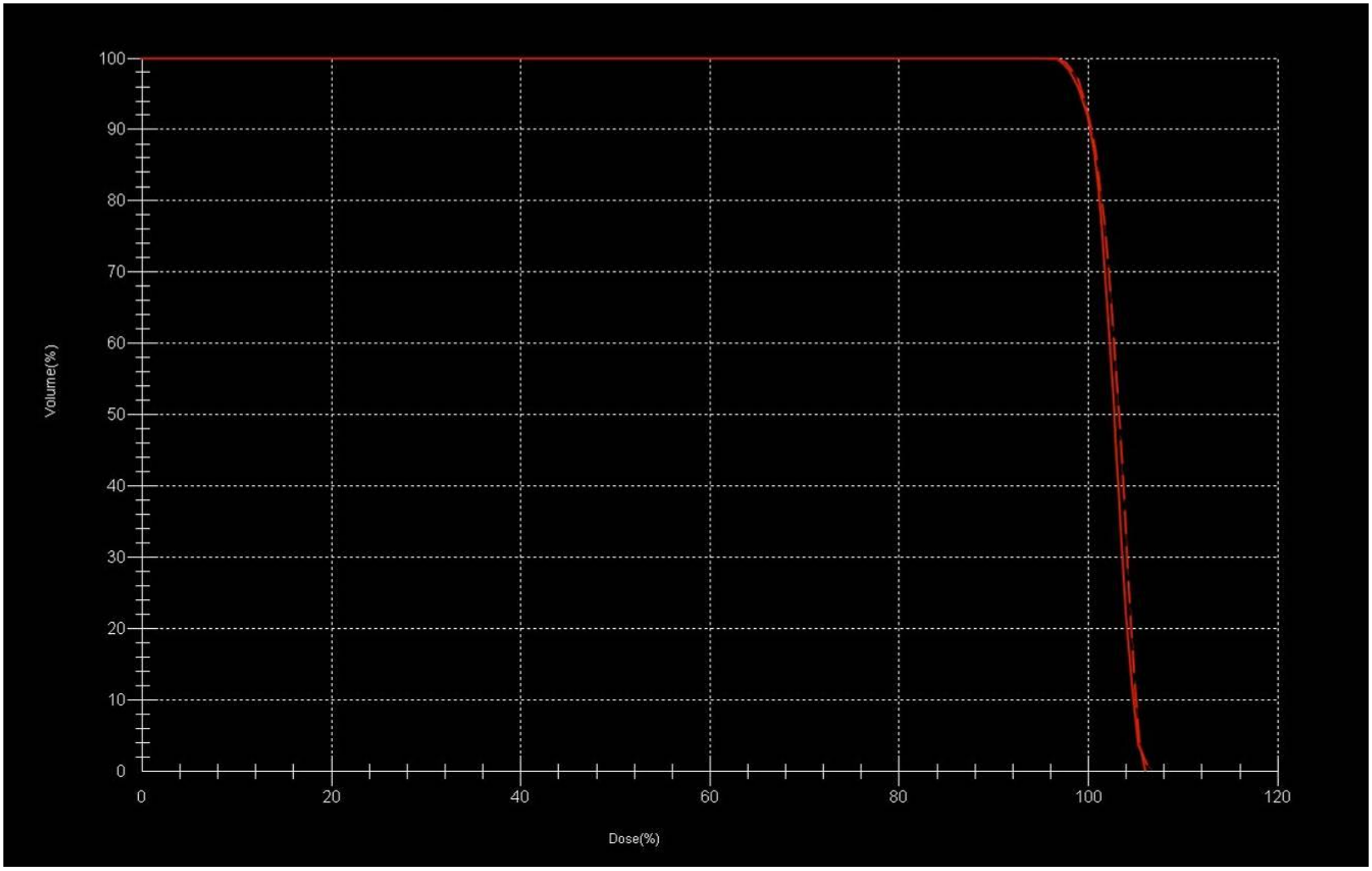








IMRT as efficiency tool for ‘simple 3D-CRT’ : Bladder



IMRT

3DCRT

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

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

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

ESTRO School

Geometric uncertainties and how to deal with them

Marcel van Herk

Institute of Cancer Sciences
Manchester University
The Christie NHS Trust

(Formerly at the Netherlands Cancer Institute)

MANCHESTER 1824
The University of Manchester
Manchester Cancer Research Centre

The Christie NHS
NHS Foundation Trust

Problems in radiotherapy:

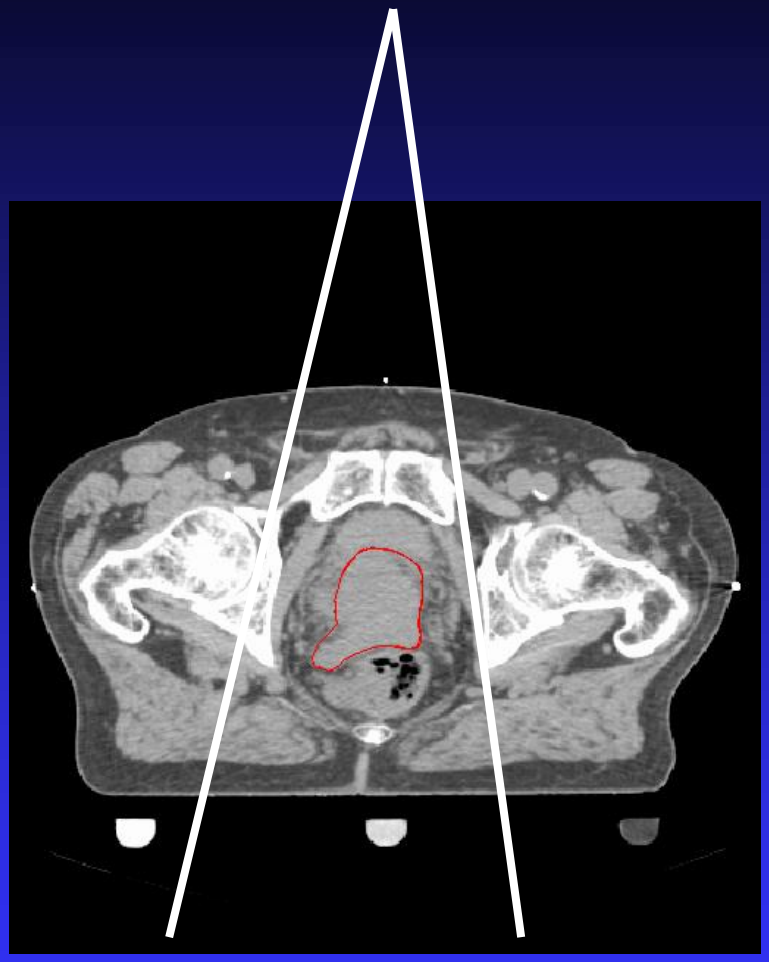
The patient is nervous, did not sleep the night before and lay wriggling on the CT scanner

The physician was in a rush when drawing the target volume

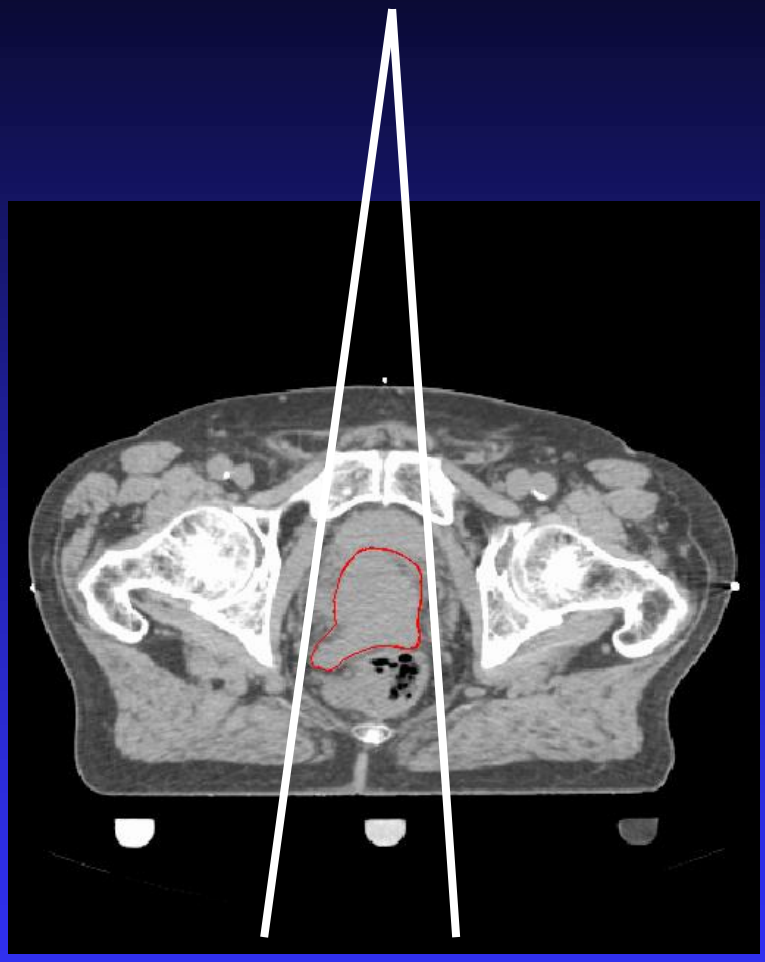
The patients belly flopped from day to day, letting the skin marks move all over the place

The patient was breathing

How can we solve this problem ?



1. Use large margins, irradiating too much healthy tissues



2. Use small margins, and risk missing the target

3. Or: use image guided radiotherapy

Image Guided Radiotherapy

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

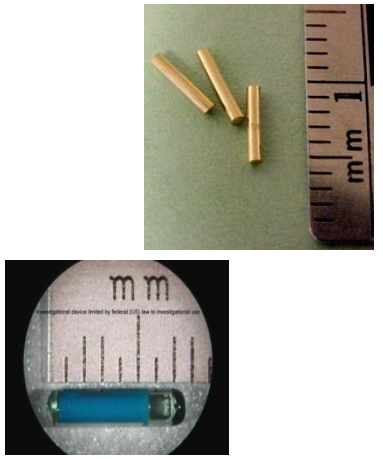
Image guidance does not solve all geometrical uncertainties and variations *and introduces new ones*

IGRT Technologies

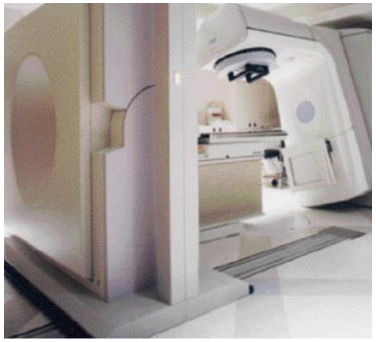
Ultrasound

kV Radiographic

Portal Imaging

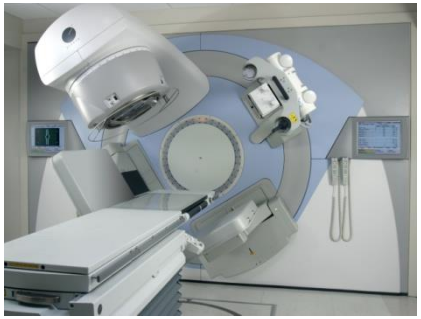


Markers
(Active and Passive)



Siemens
PRIMATOM™

TomoTherapy
Hi-Art™



Elekta Synergy

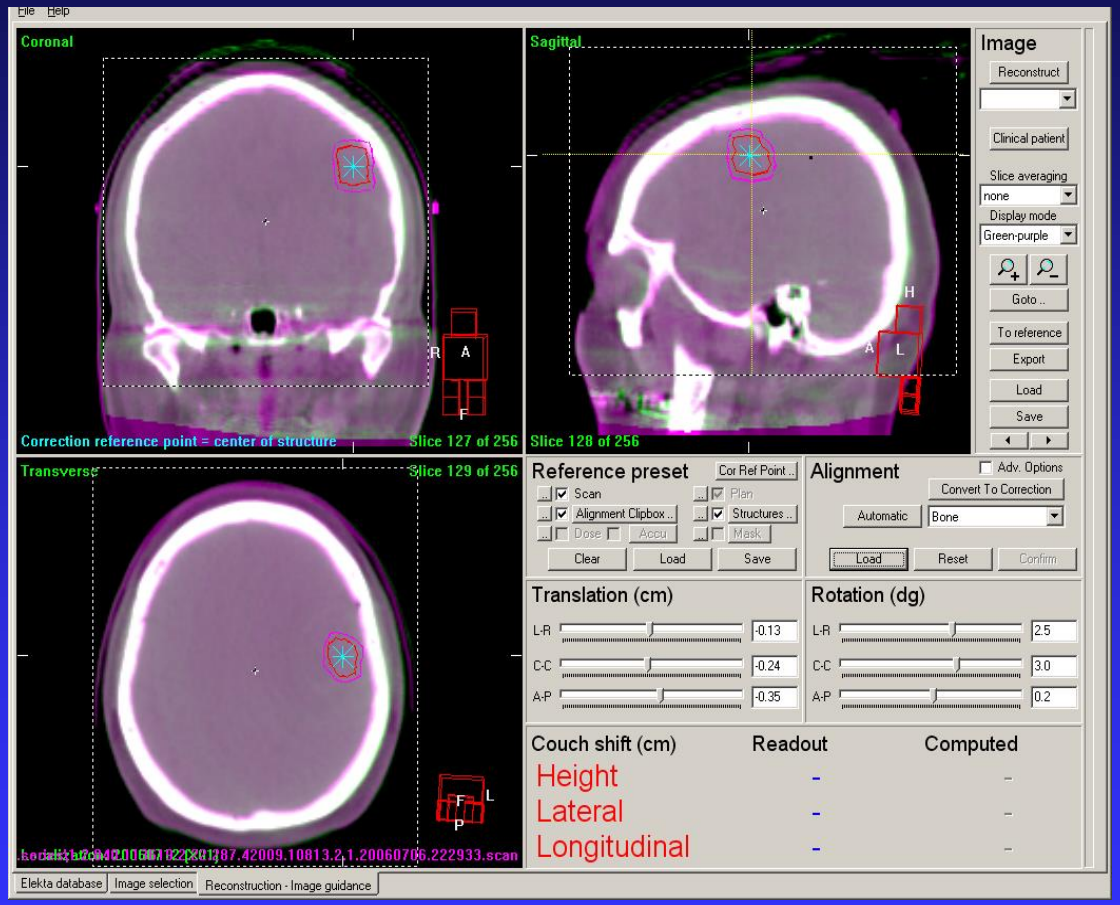
Varian OBI™

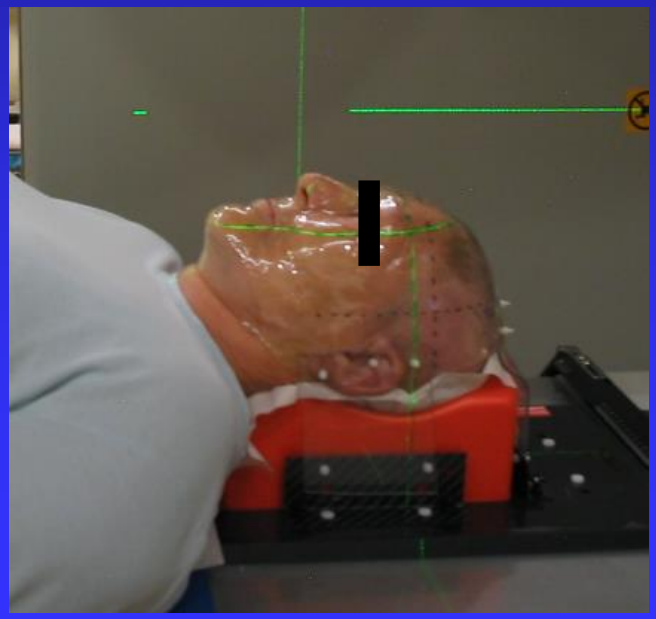
kV CT

MV CT

kV and MV Cone-beam CT

IGRT is brilliant !





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

Nomenclature

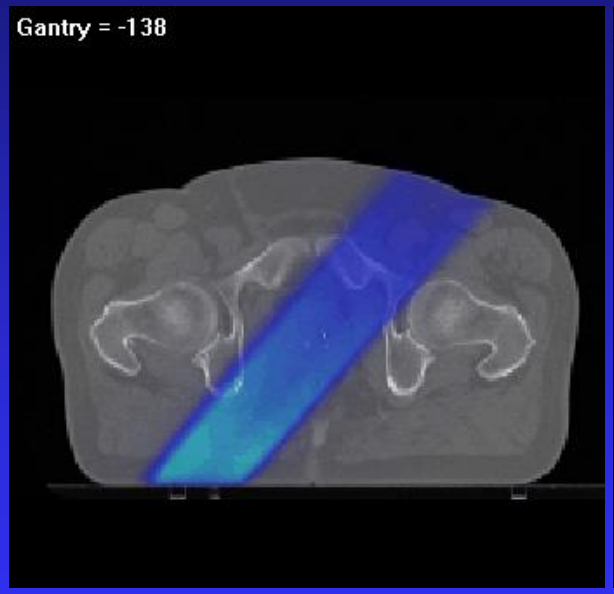
- Gross error: mistakes, transcription errors, software faults:
  - must be caught by QA
- Error: difference between planned value and its true value during treatment, however small
- Uncertainty: the fact that unpredictable errors occur – quantified by standard deviations
- Variation: the fact that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

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

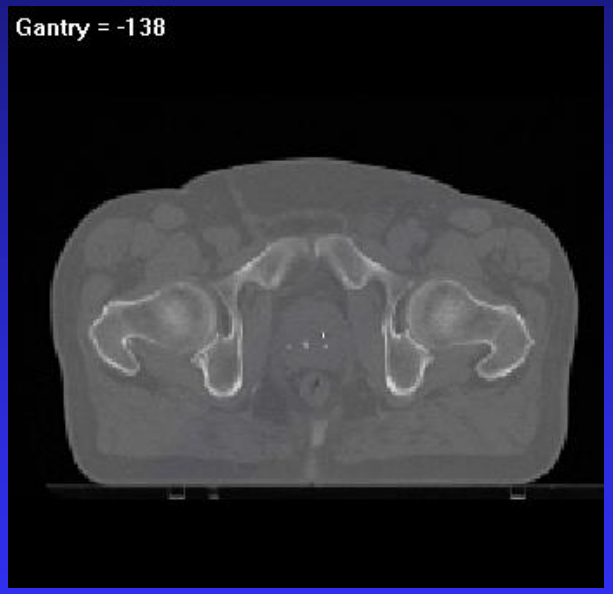
EPID movie

-140° 140°

Reconstructed EPID dose (VMAT case)



per frame



cumulative

Precision: within few %, enough to catch gross errors

Mans et al, 2010

Gross errors detected in NKI

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

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

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

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

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

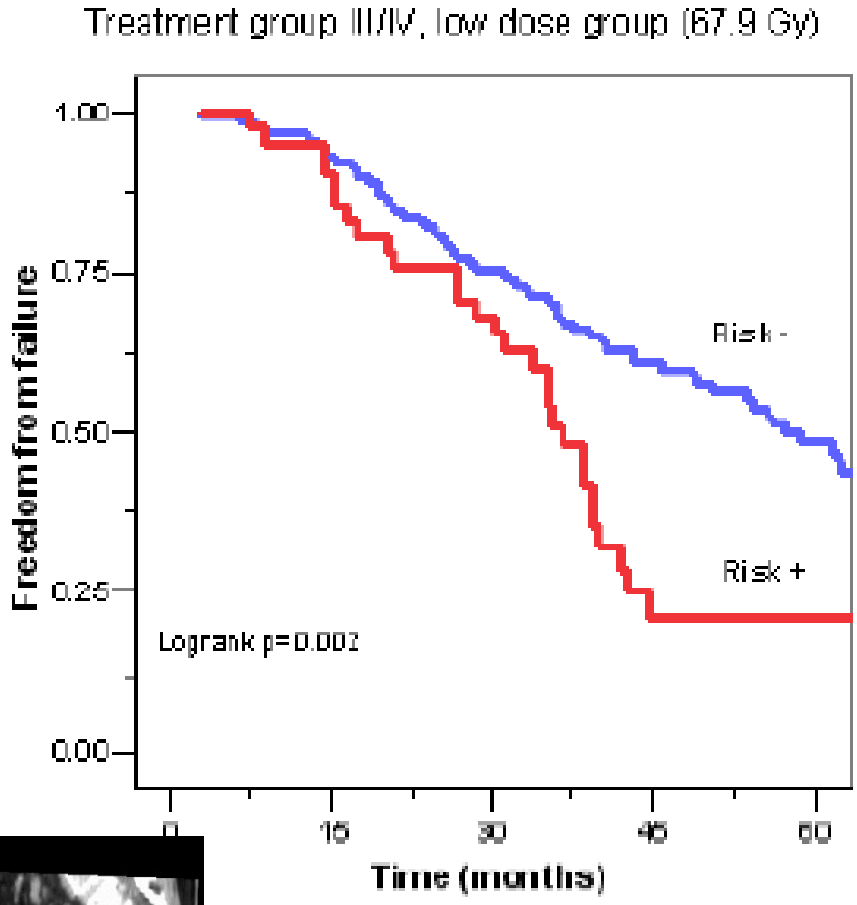
Mans et al, 2010

What happens in the other 99.6% ?

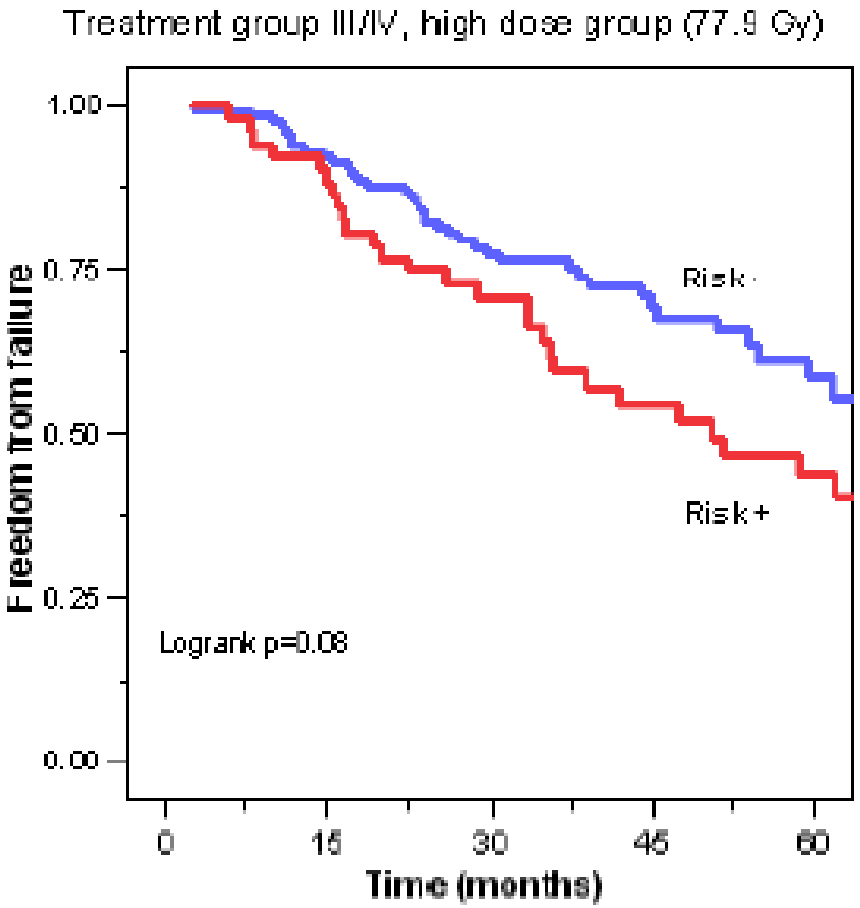
- There are many small unavoidable errors (mm size) in all steps of radiotherapy
  - In some cases many of these small errors point in the same direction
  - I.e., in some patients large (cm) errors occur(ed)
- This is not a fault, this is purely statistics
- What effect does this have on treatment?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

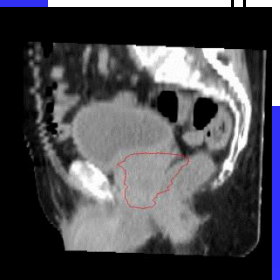
Motion counts? Prostate trial data (1996)

N=185 (42 risk+)



N=168 (52 risk+)





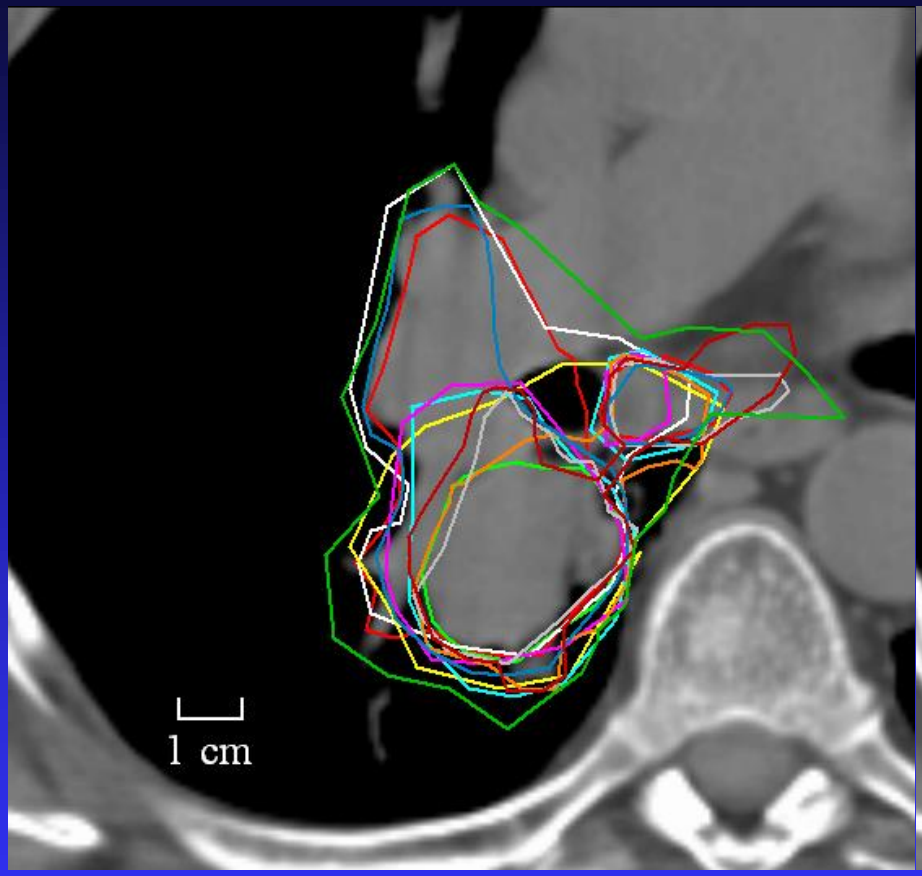
Risk+: initial full rectum, later diarrhea

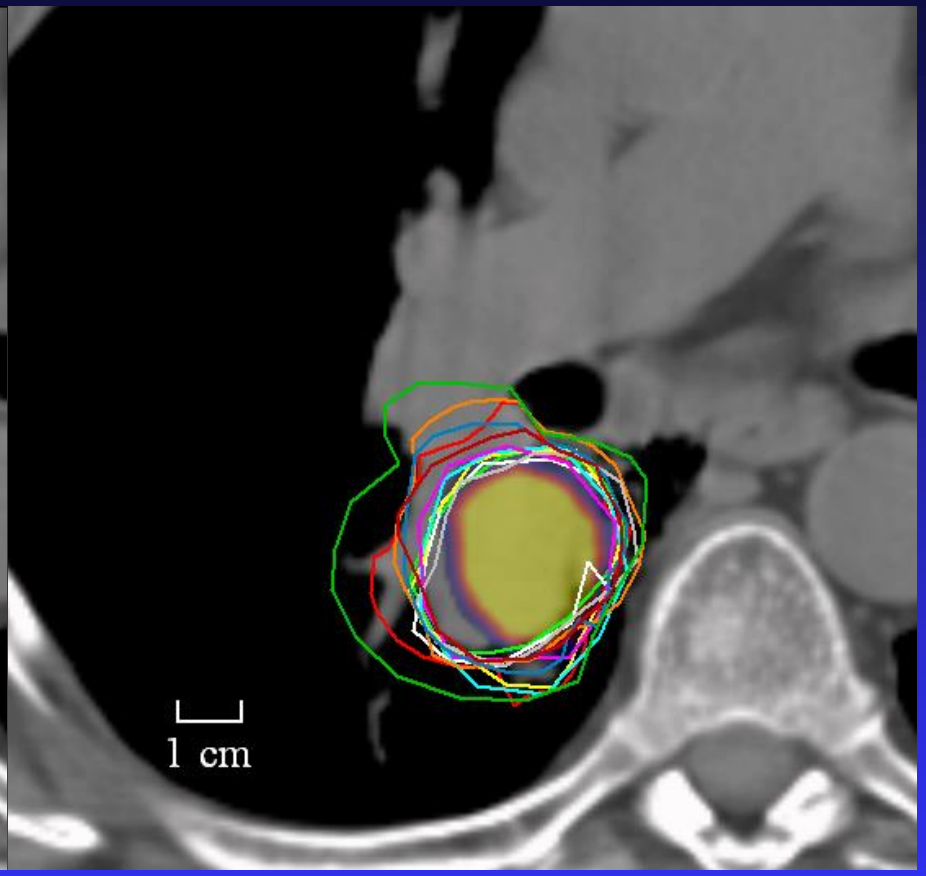
Heemsbergen et al, IJROBP 2007

The major uncertainties not solved by IGRT

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

Delineation variation: CT versus CT + PET





CT (T_2N_2)

SD 7.5 mm

CT + PET (T_2N_1)

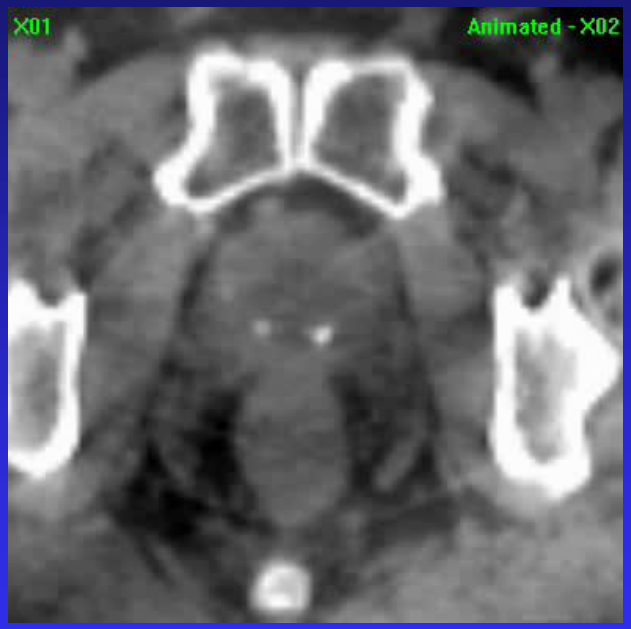
SD 3.5 mm

Consistency is imperative to gather clinical evidence!

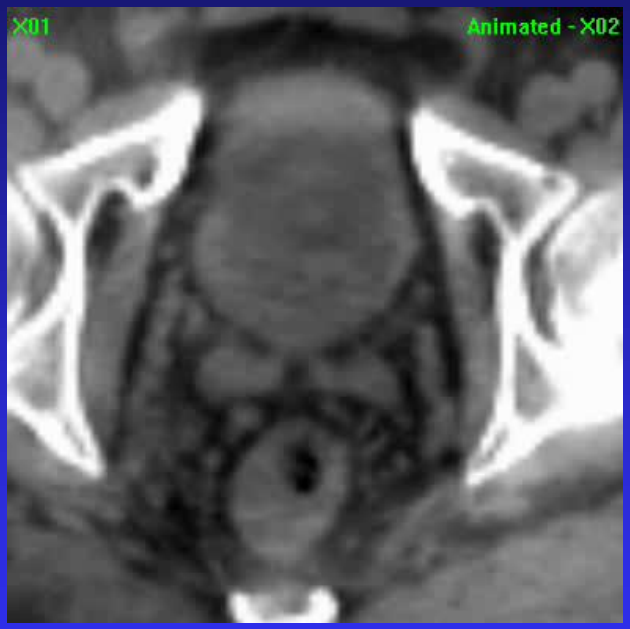
Steenbakkers et al, IJROBP 2005

Are prostate markers perfect ?

Apex



Base



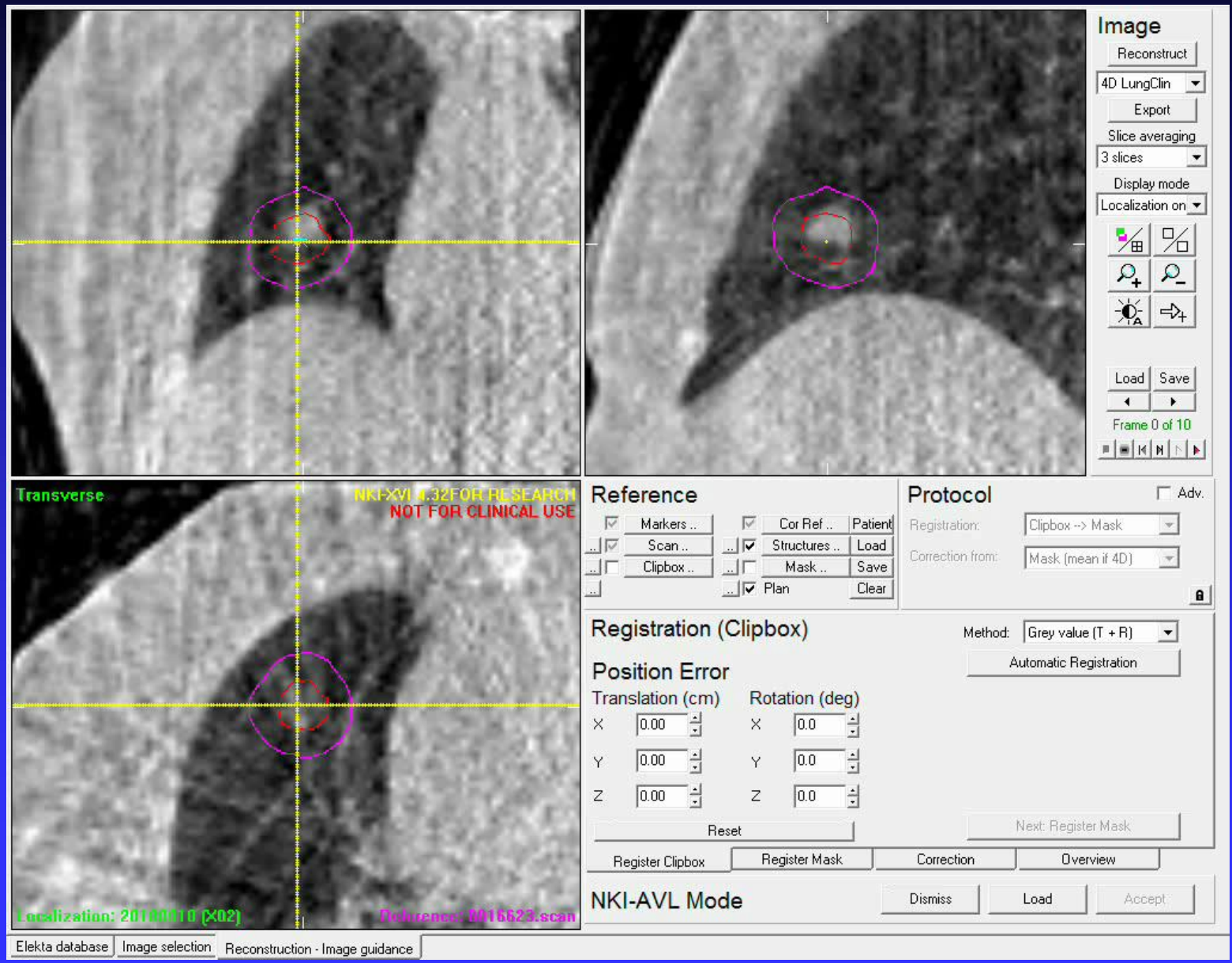
Sem. Vesicles

→ +/-1 cm margin required

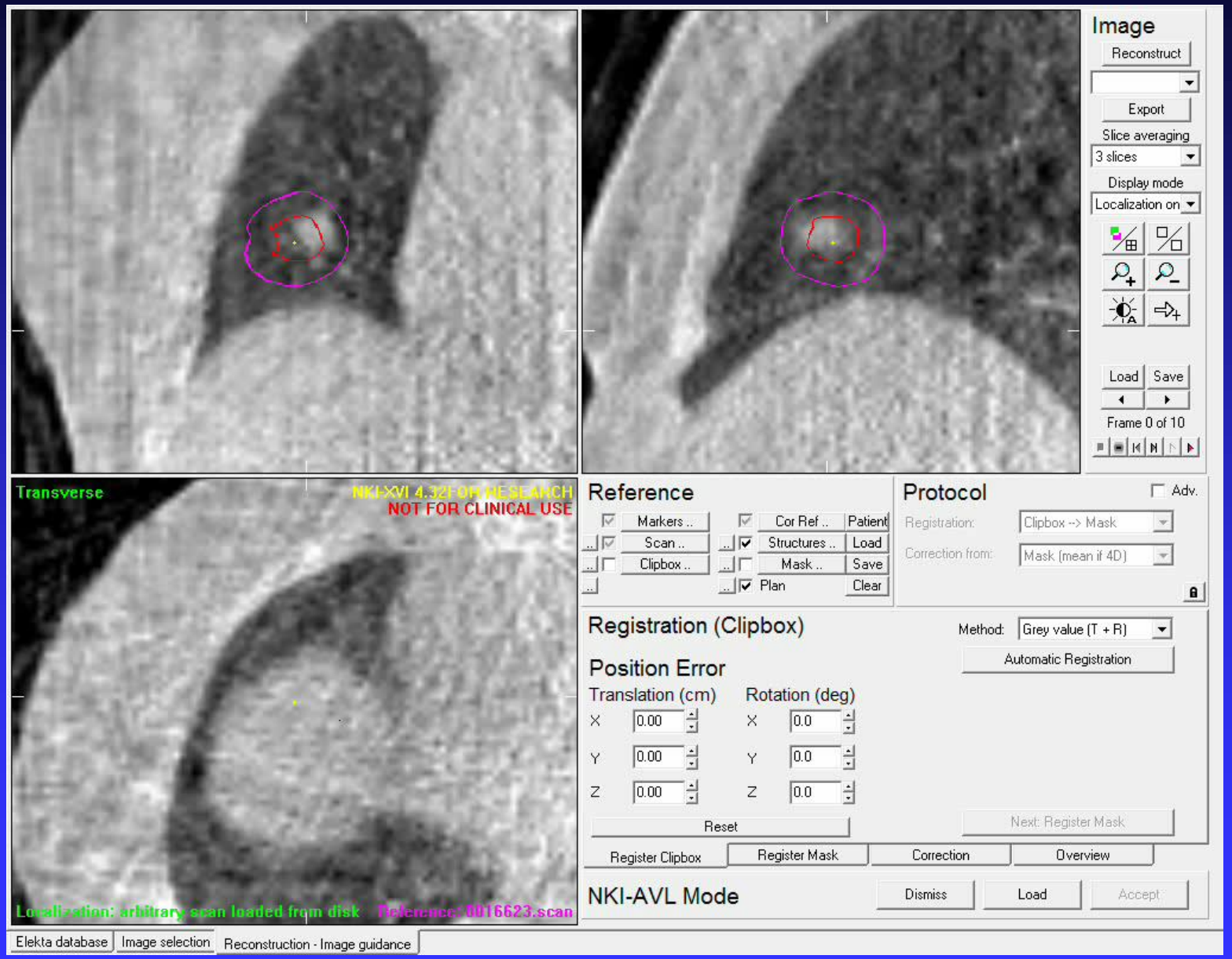
Best: combine markers with low dose CBCT

van der Wielen, IJROBP 2008
Smitsmans, IJROBP 2010

Intra-fraction motion: CBCT during VMAT



Intra-fraction motion: CBCT during VMAT



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

Definitions (sloppy)

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

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

- PTV margin: distance between CTV and PTV

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

Analysis of uncertainties
Keep the measurement sign!

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

mean =M
SD = Σ
RMS = σ

Intra-fraction

0.0

0.3

0.4

0.1

0.3

Mean = 0.2

RMS of SD = σ_f

M = mean group error (equipment)

Σ = standard deviation of the inter-patient error

σ = standard deviation of the inter-fraction error

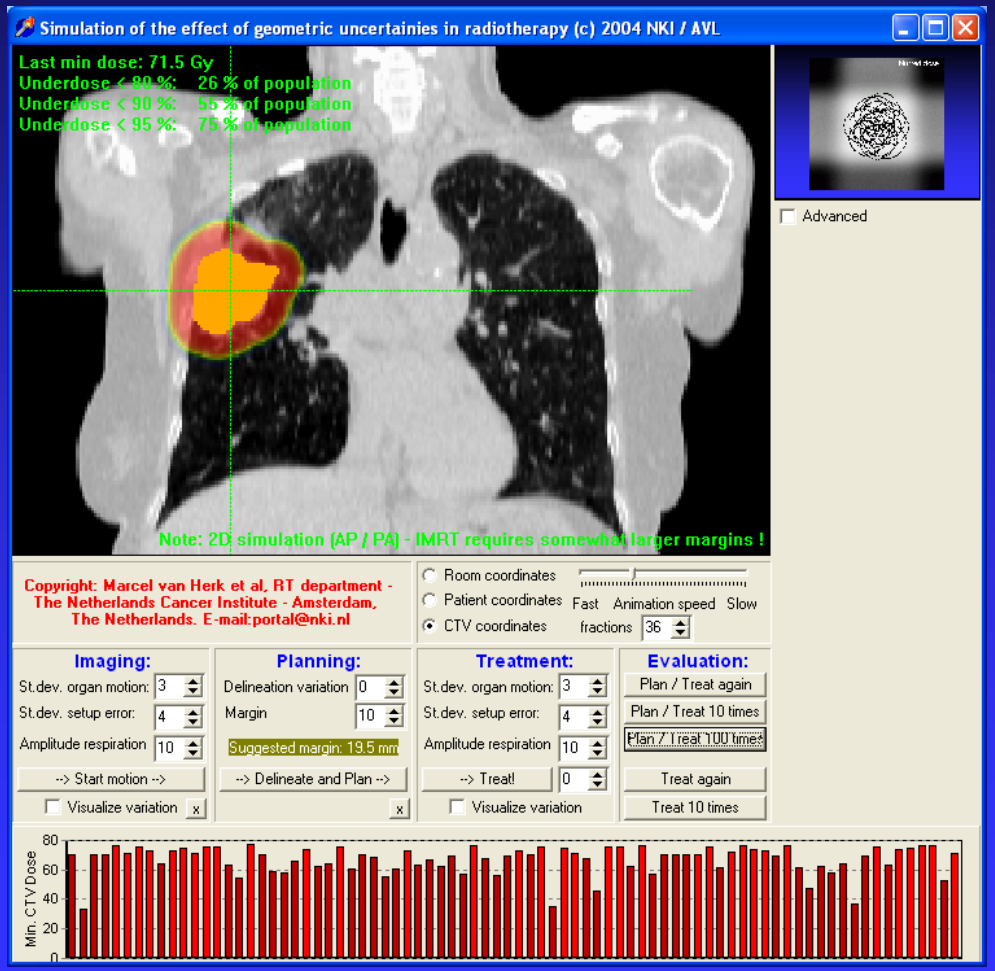
σf = standard deviation of the intra-fraction motion

van Herk et al, Sem Rad Onc 2004

Demonstration – errors in RT

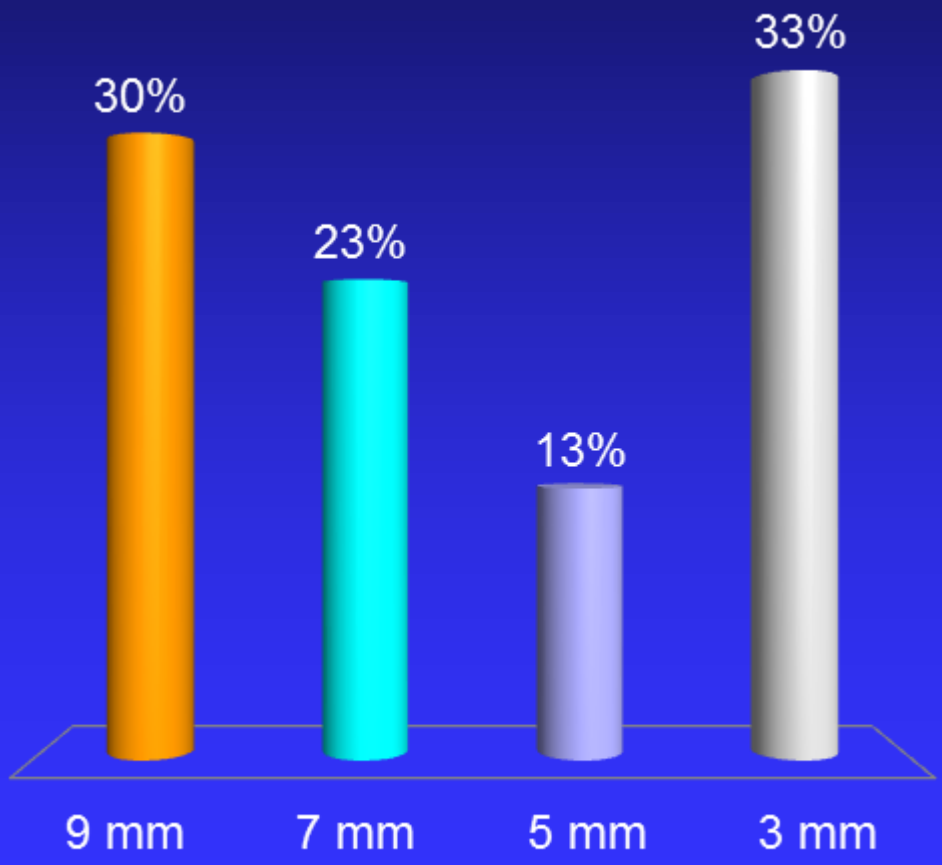
- Margin between CTV and PTV: 10 mm

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



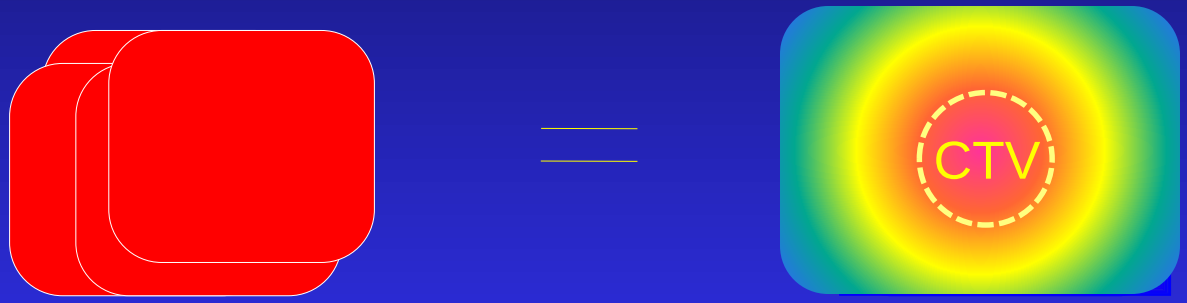
If we would gate the beam during treatment (eliminating respiratory movement) how much can the margin be reduced to keep 90% of patients treated correctly ?

A. By 1 cm
B. By 5 mm
C. By 2 mm
D. By 1 mm

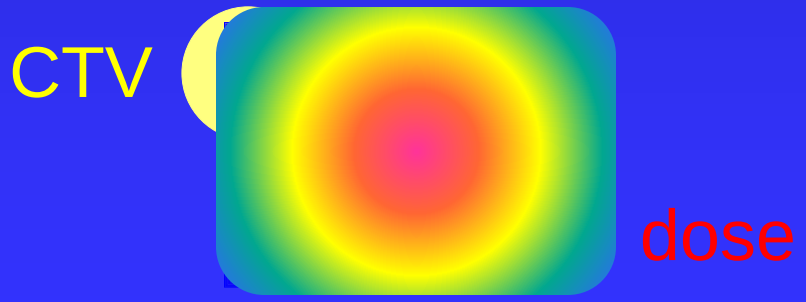


What is the effect of geometrical errors on the CTV dose ?

Random: Breathing, intrafraction motion, IGRT inaccuracy



Systematic: delineation, intrafraction motion, IGRT inaccuracy

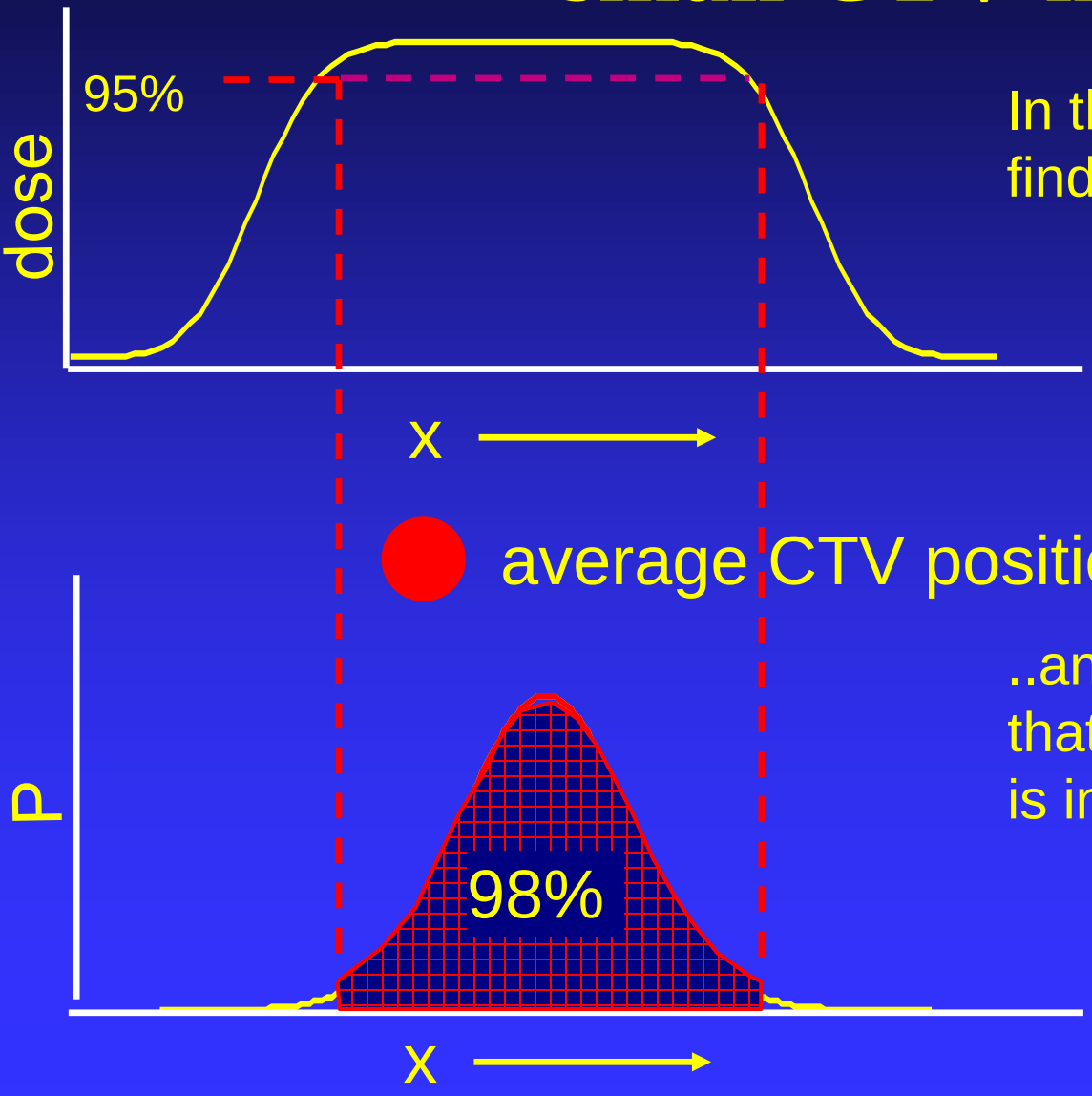


Analysis of CTV dose probability

- 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

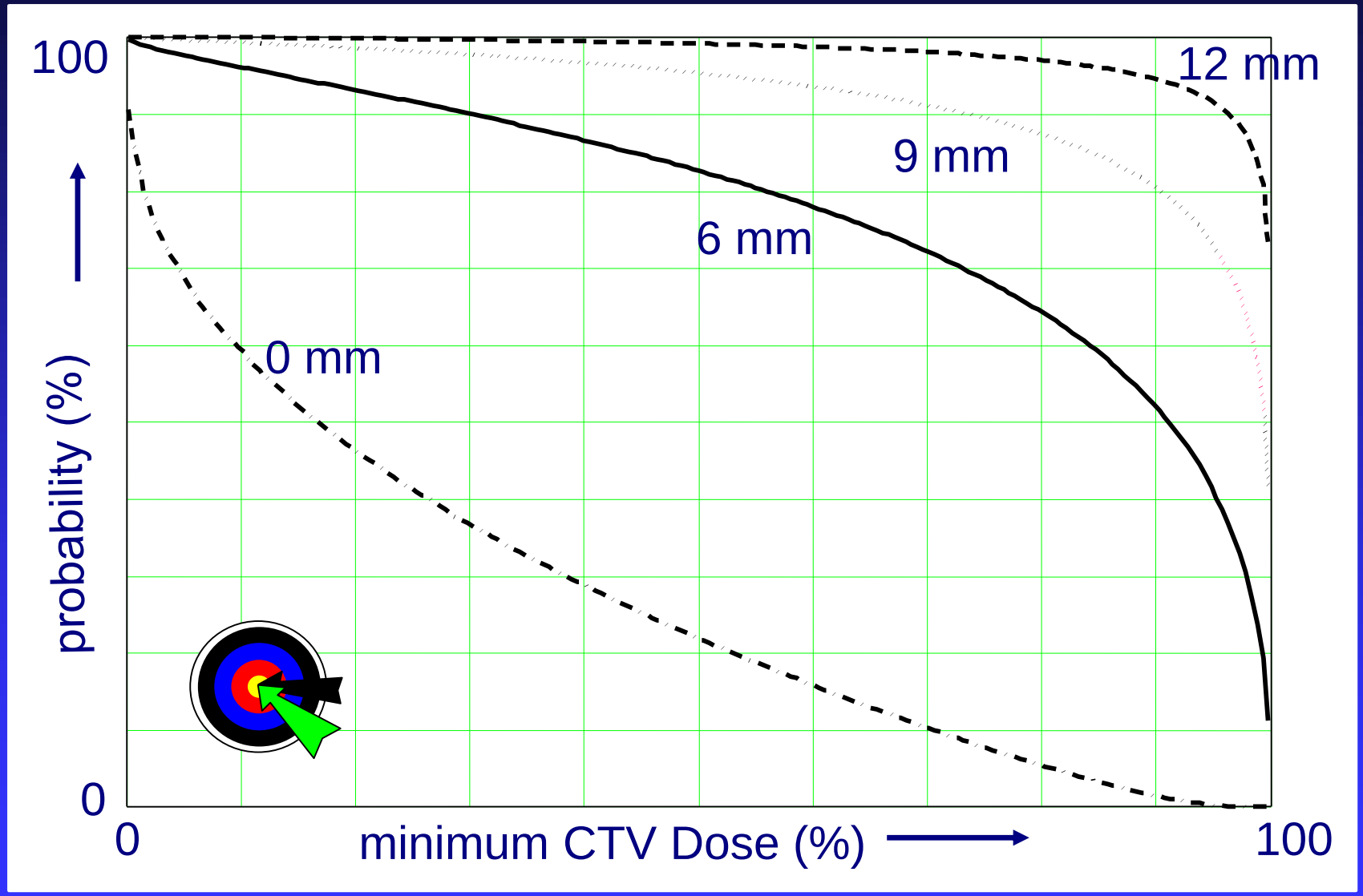
Computation of the dose probability for a small CTV in 1D



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

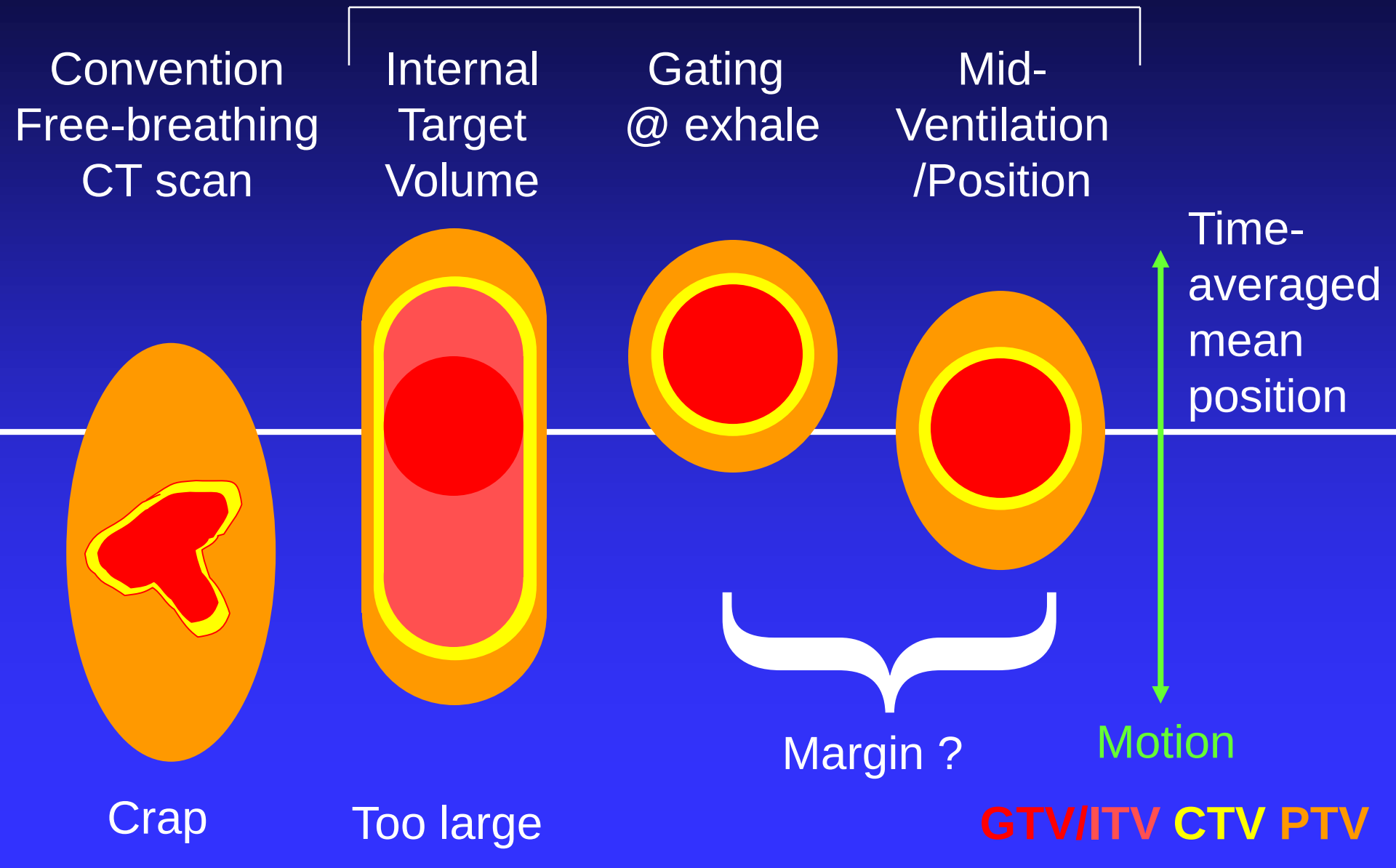
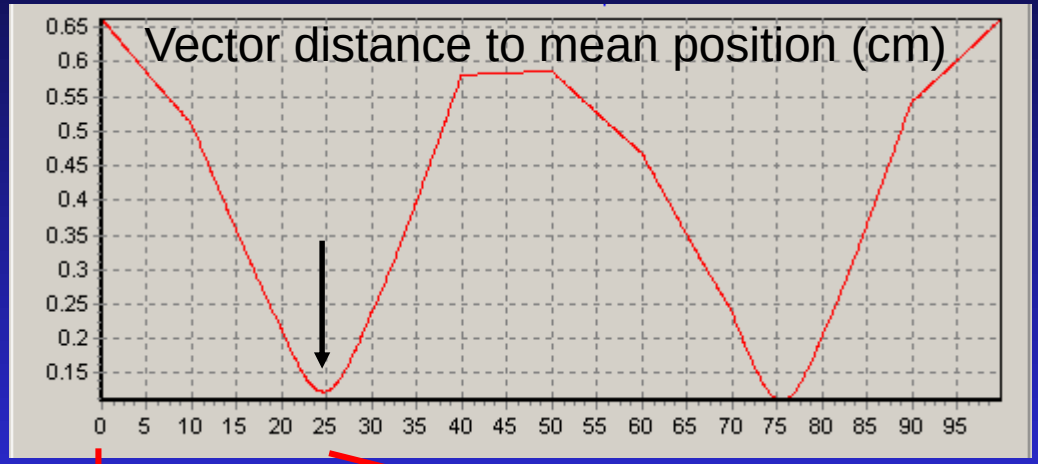
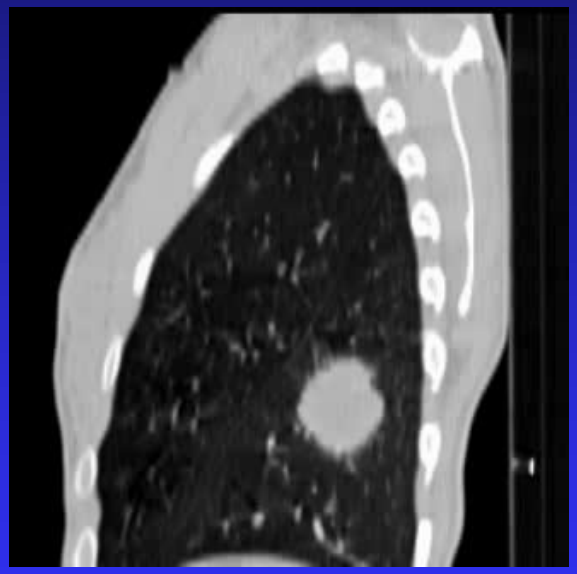
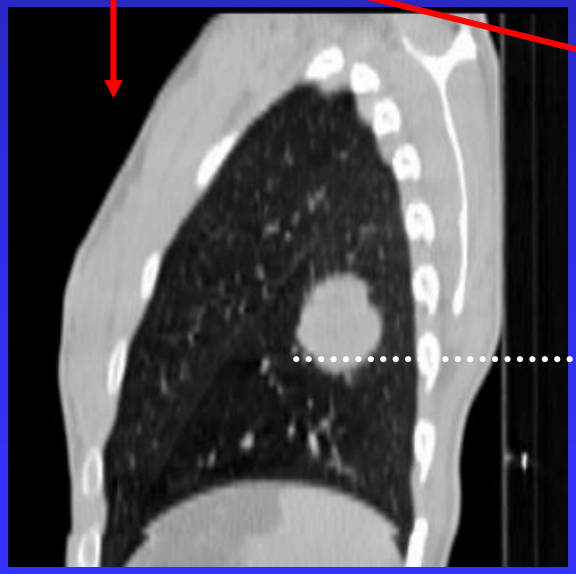


Image *selection* approaches to derive representative 3D data

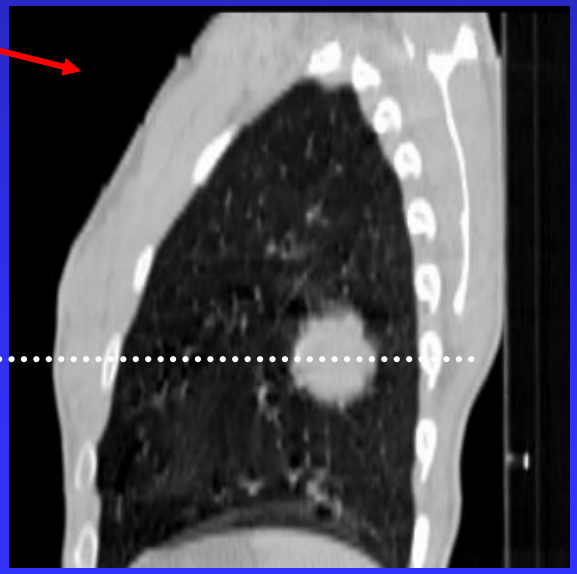




4D CT



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**			

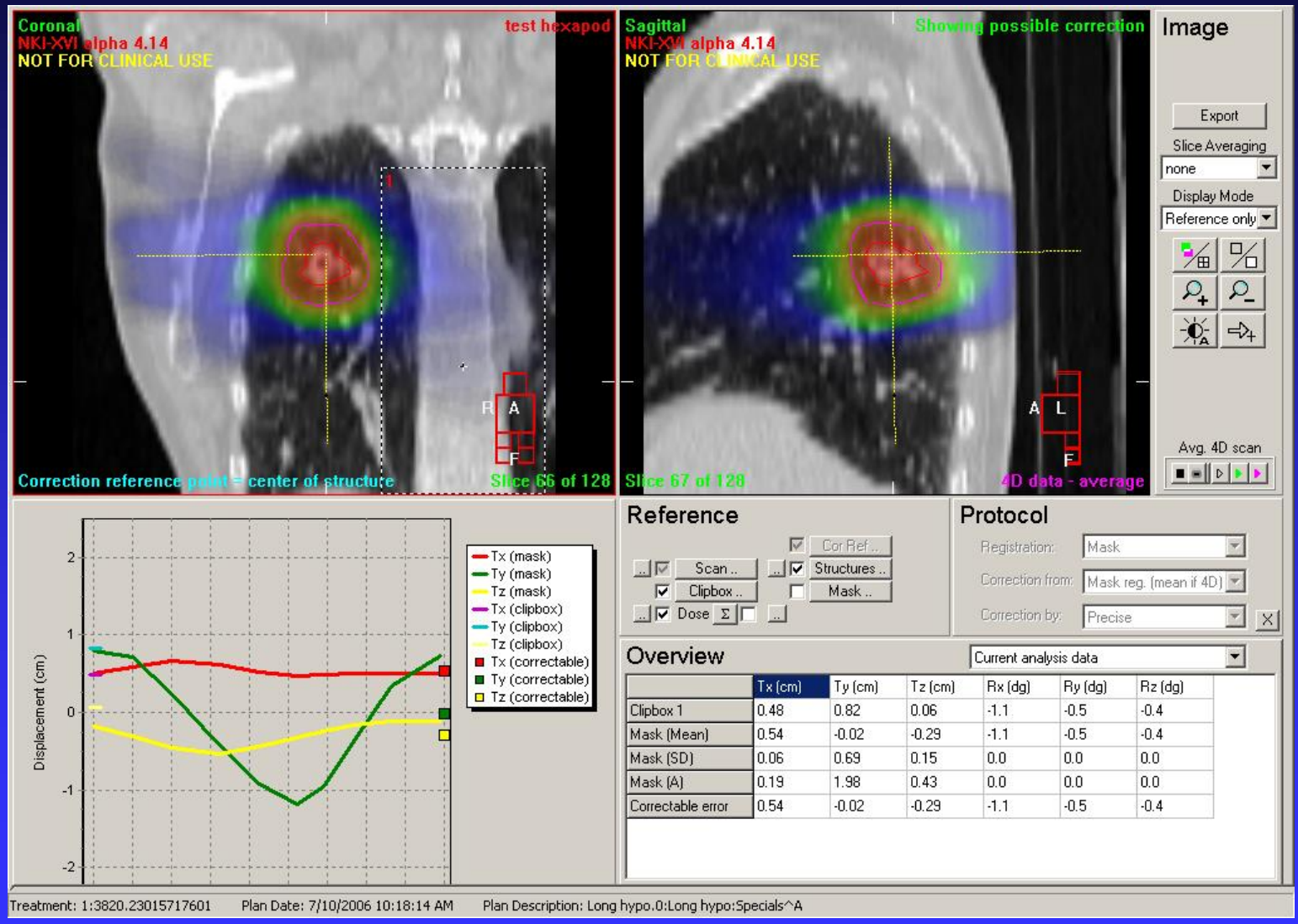
Using conventional fractionation, prescription at 95% isodose line in lung

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**			

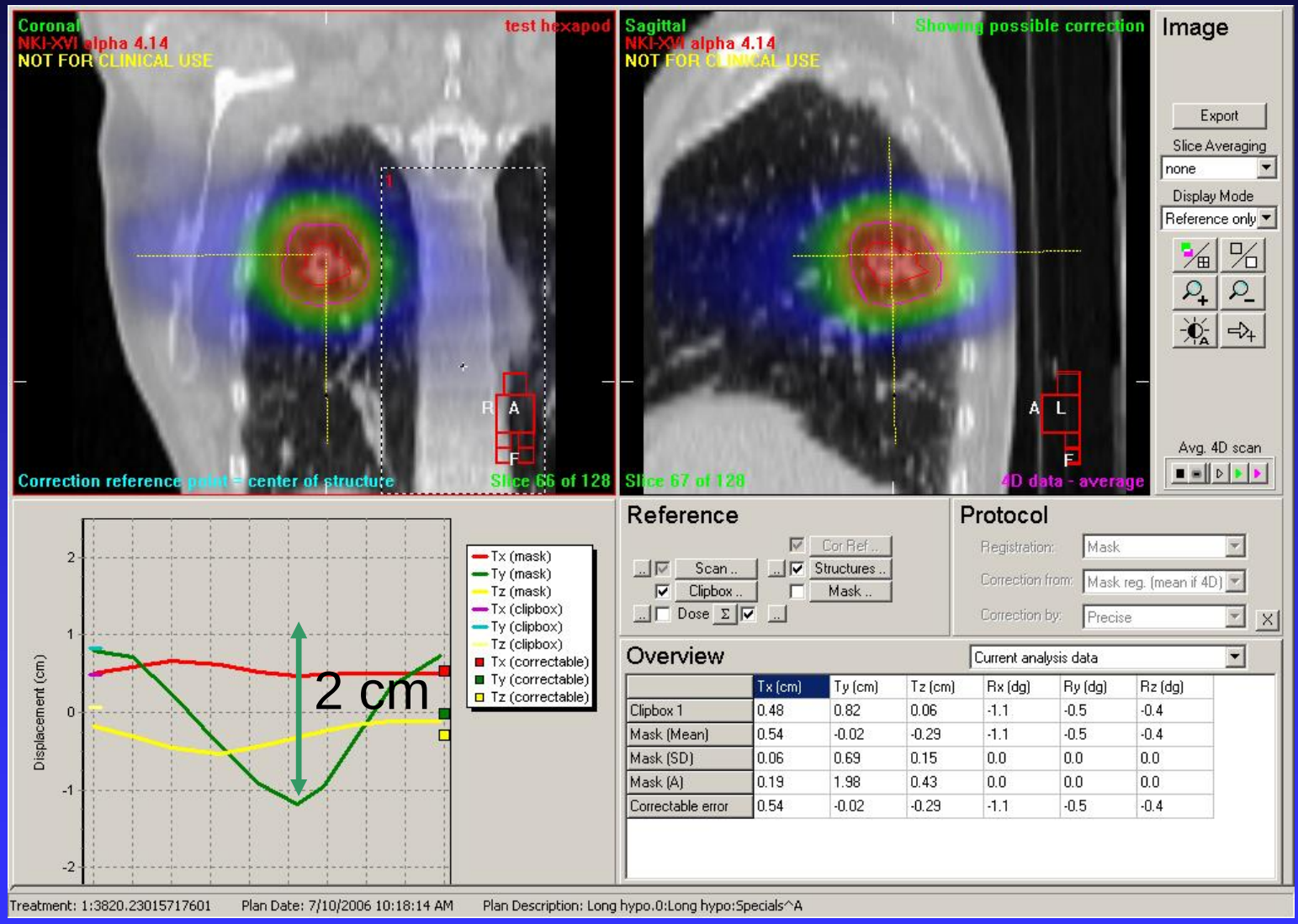
Using hypo-fractionation, prescription at 80% isodose line in lung

Planned dose distribution: hypofractionated lung treatment 3x18 Gy



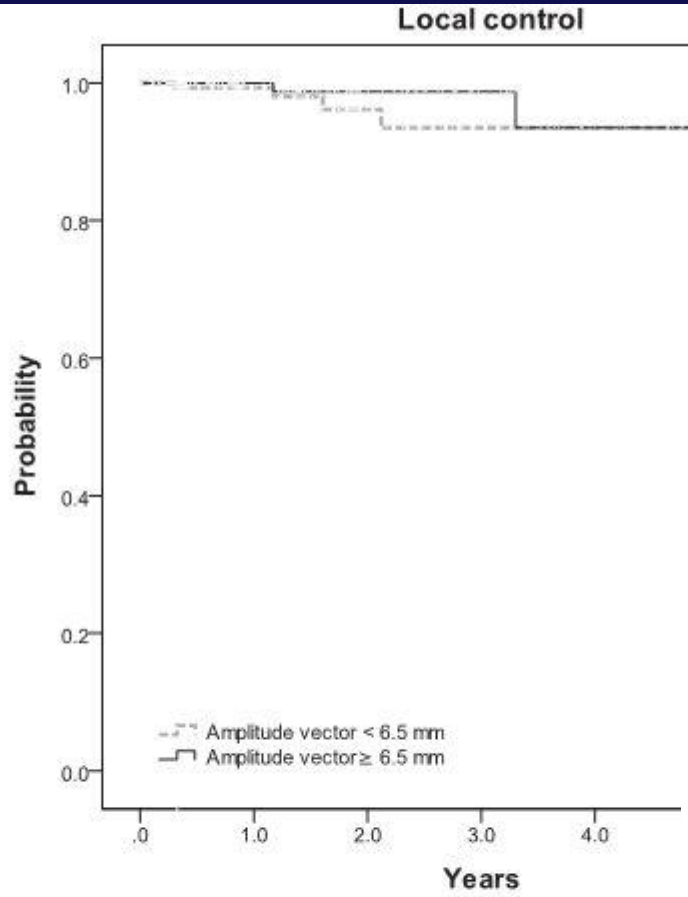
	Tx (cm)	Ty (cm)	Tz (cm)	Rx (dg)	Ry (dg)	Rz (dg)
Clipbox 1	0.48	0.82	0.06	-1.1	-0.5	-0.4
Mask (Mean)	0.54	-0.02	-0.29	-1.1	-0.5	-0.4
Mask (SD)	0.06	0.69	0.15	0.0	0.0	0.0
Mask (A)	0.19	1.98	0.43	0.0	0.0	0.0
Correctable error	0.54	-0.02	-0.29	-1.1	-0.5	-0.4

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



9 mm margin is adequate even with 2 cm intrafraction motion

Clinical results with mid-V



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

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

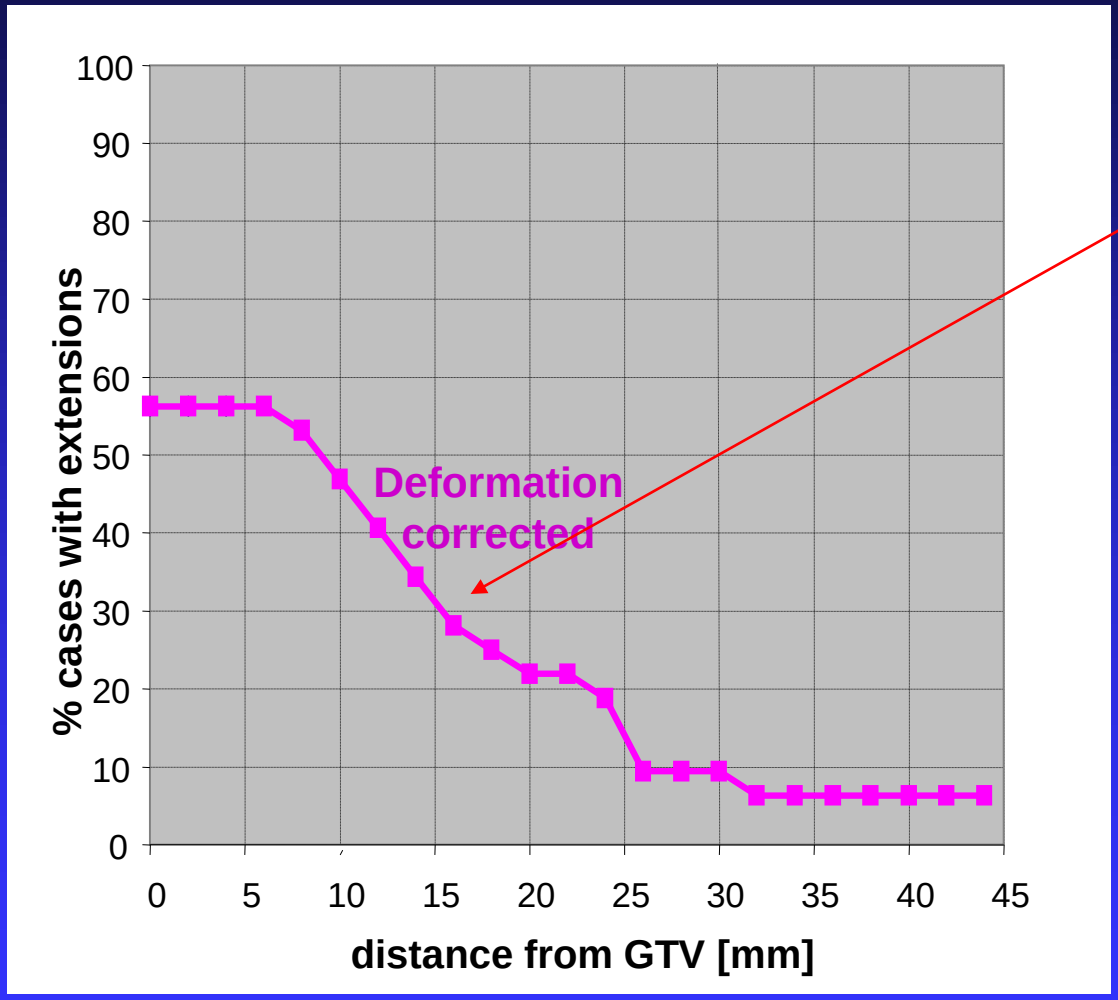
and 3 mm (range 0–18 mm), respectively. The median amplitude vector was 6.5 mm (range 0–39 mm) for all tumors as well as for the locally controlled tumors. In case of local recurrence, the median amplitude vector was significantly *smaller*: 3.0 mm (range 1–8.1 mm) ($p = 0.04$). In patients with a local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

Peulen et al, R&O 2014

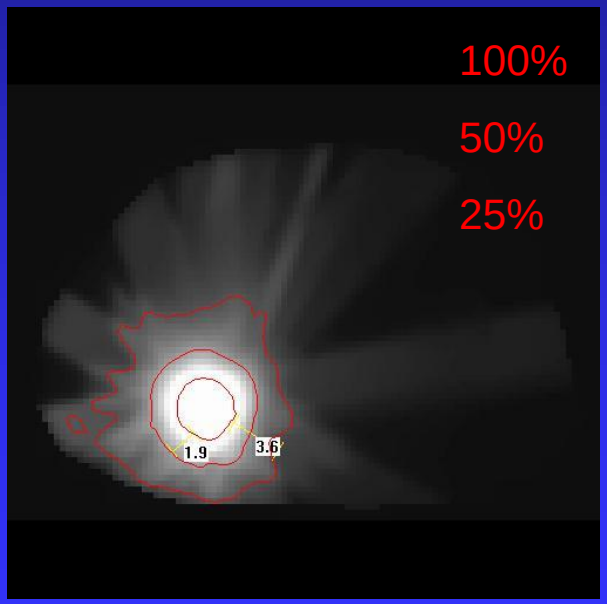
But what about the CTV ?

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

Hard data: microscopic extensions in lung cancer



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

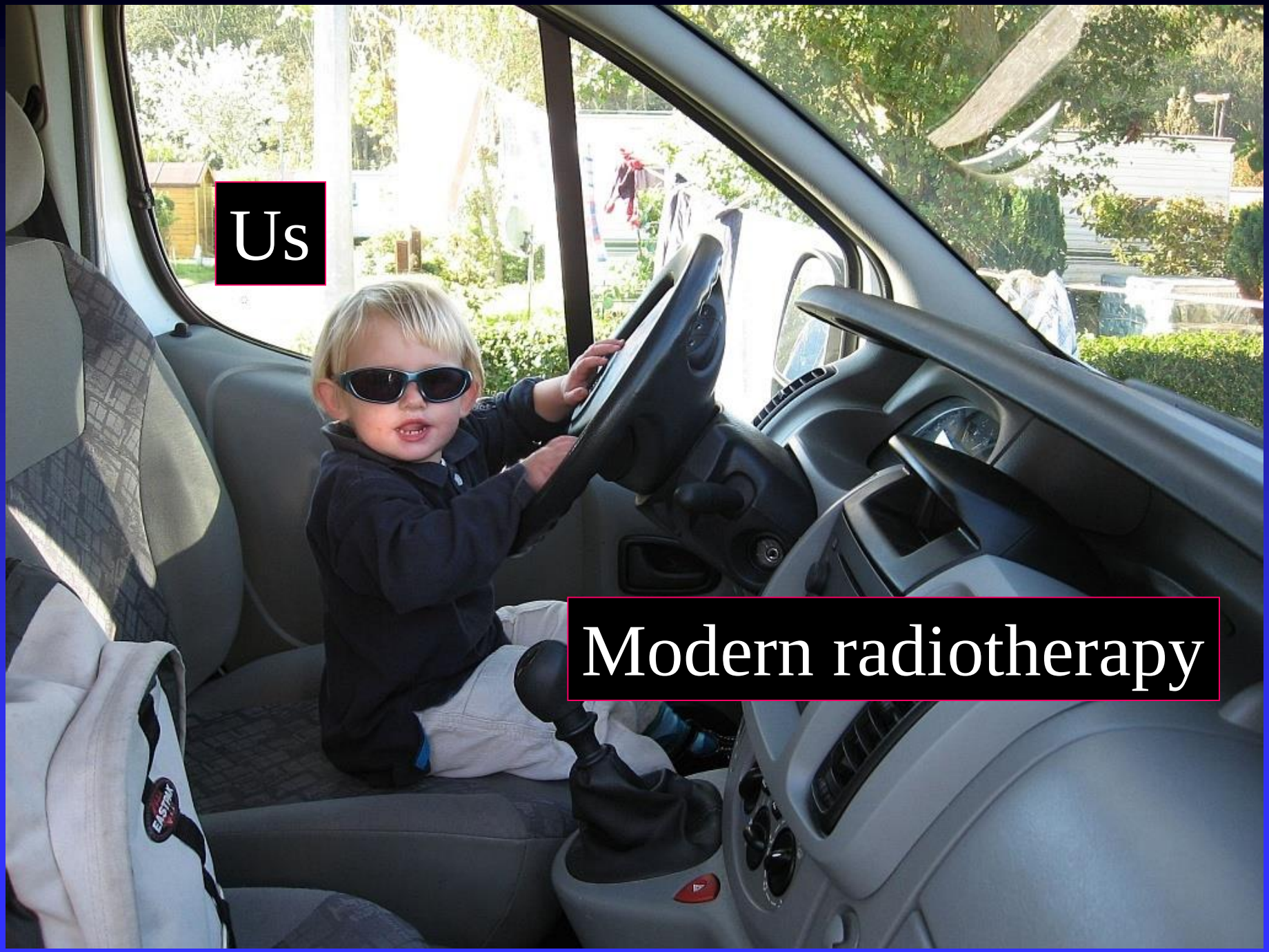


Having dose there may be essential!

Slide courtesy of Gilhuijs and Stroom, NKI

Conclusions

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

Advanced Treatment Planning Course
23-27 September 2018 – Athens, Greece

Markus Stock

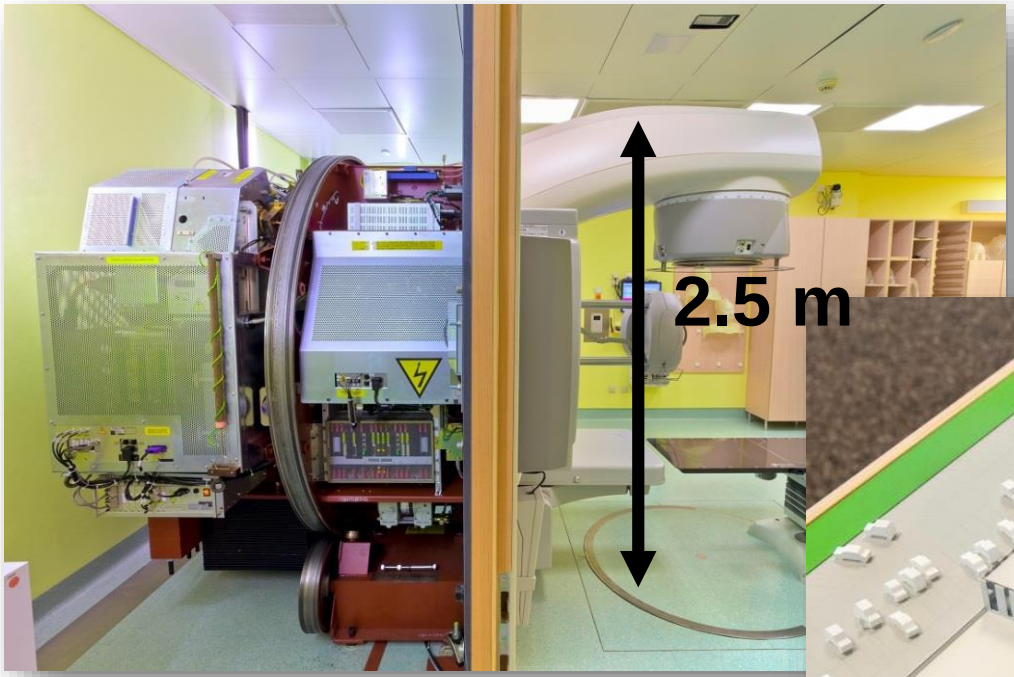
MedAustron

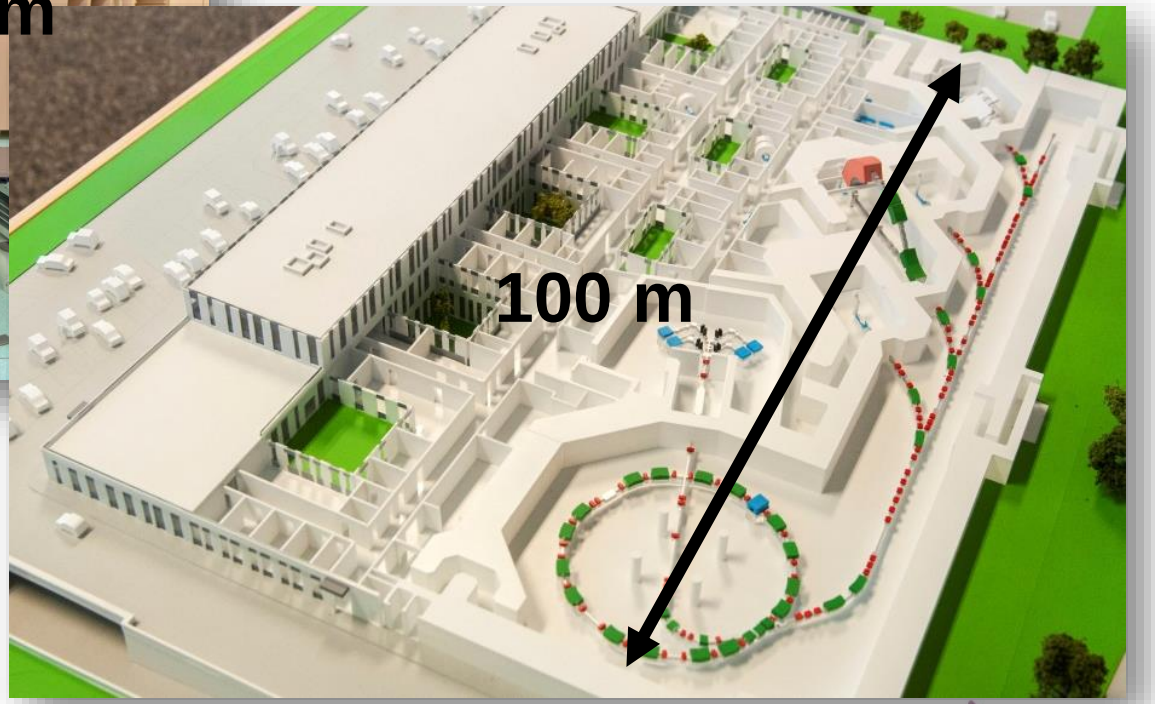
Content

- 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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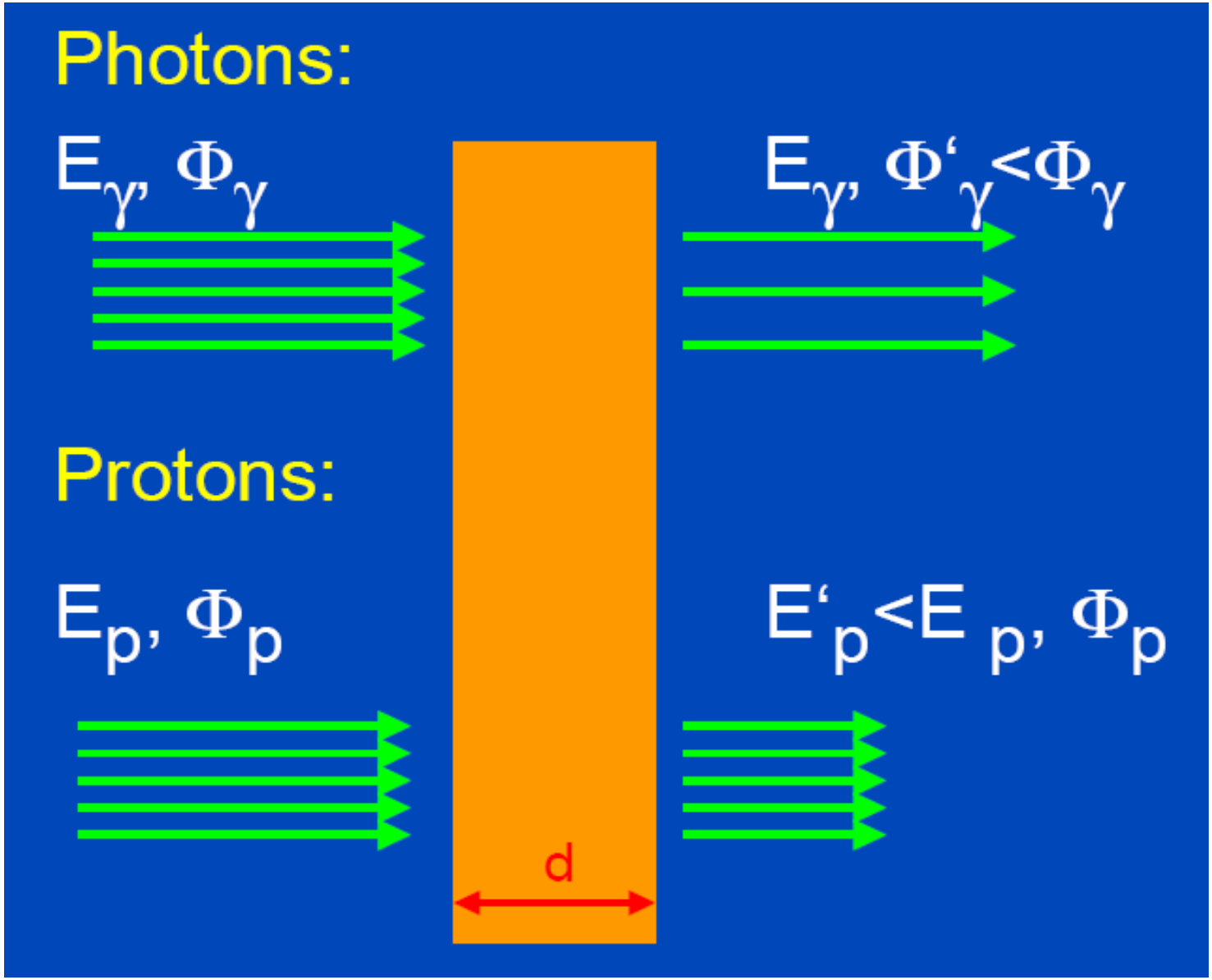
Fundamental Difference in Penetration



Energy lost = Dose deposition

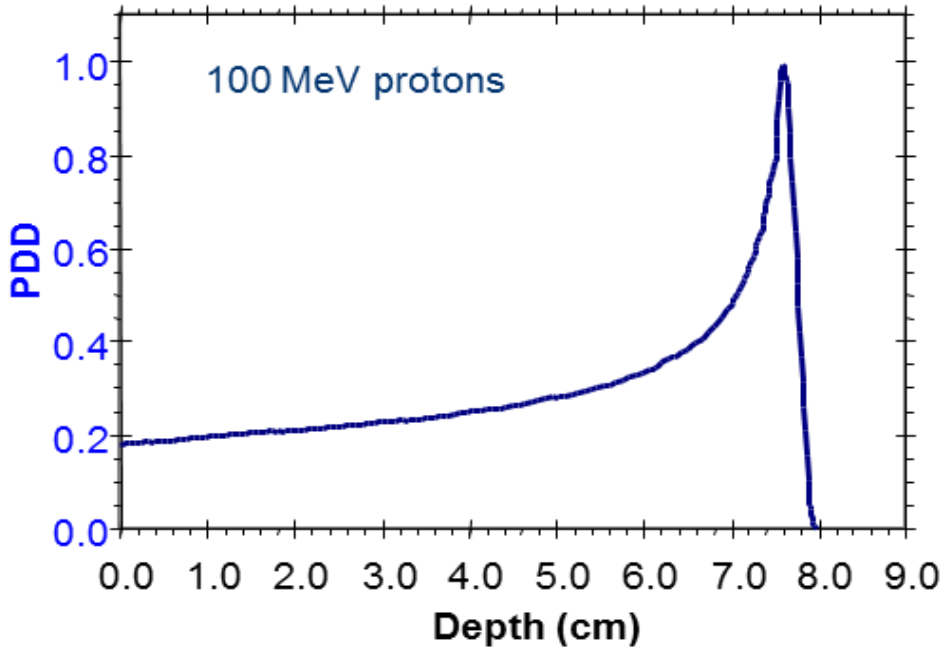
H. Bethe: Annalen der Physik. 397, Nr. 3, 1930

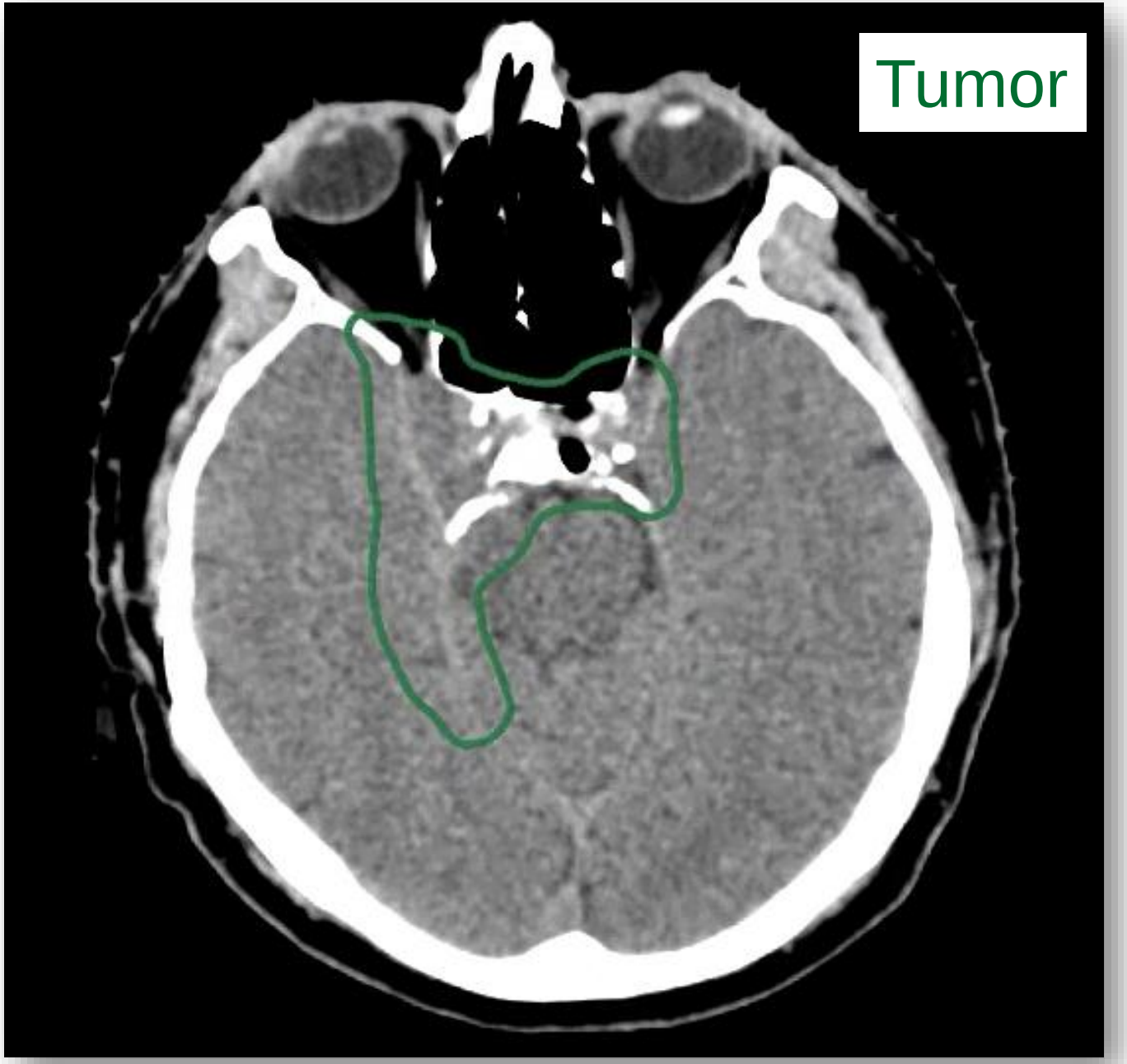
- Heavy charged particle follow the Bethe-Bloch formula:

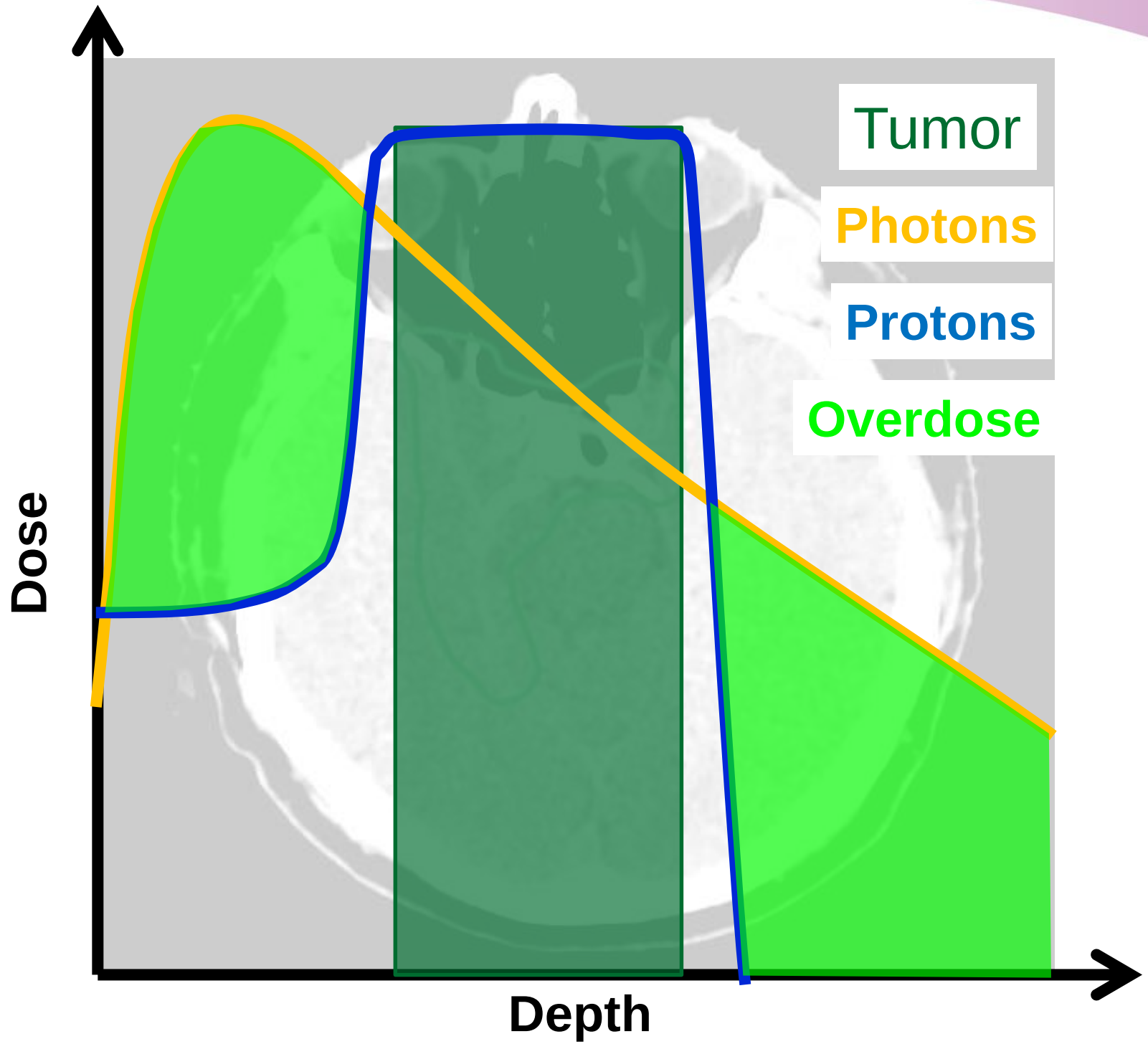
$$-\frac{1}{\rho}\frac{dE}{ds} = \frac{K}{\beta^2}\cdot z^2 \cdot \frac{Z}{A}\left[\frac{1}{2}\ln\left(\frac{2m_e c^2\cdot\beta^2\cdot W_{\max}}{\left(1-\beta^2\right)\cdot I^2}\right) - \beta^2 + SDBB\right]$$

- First approximation:

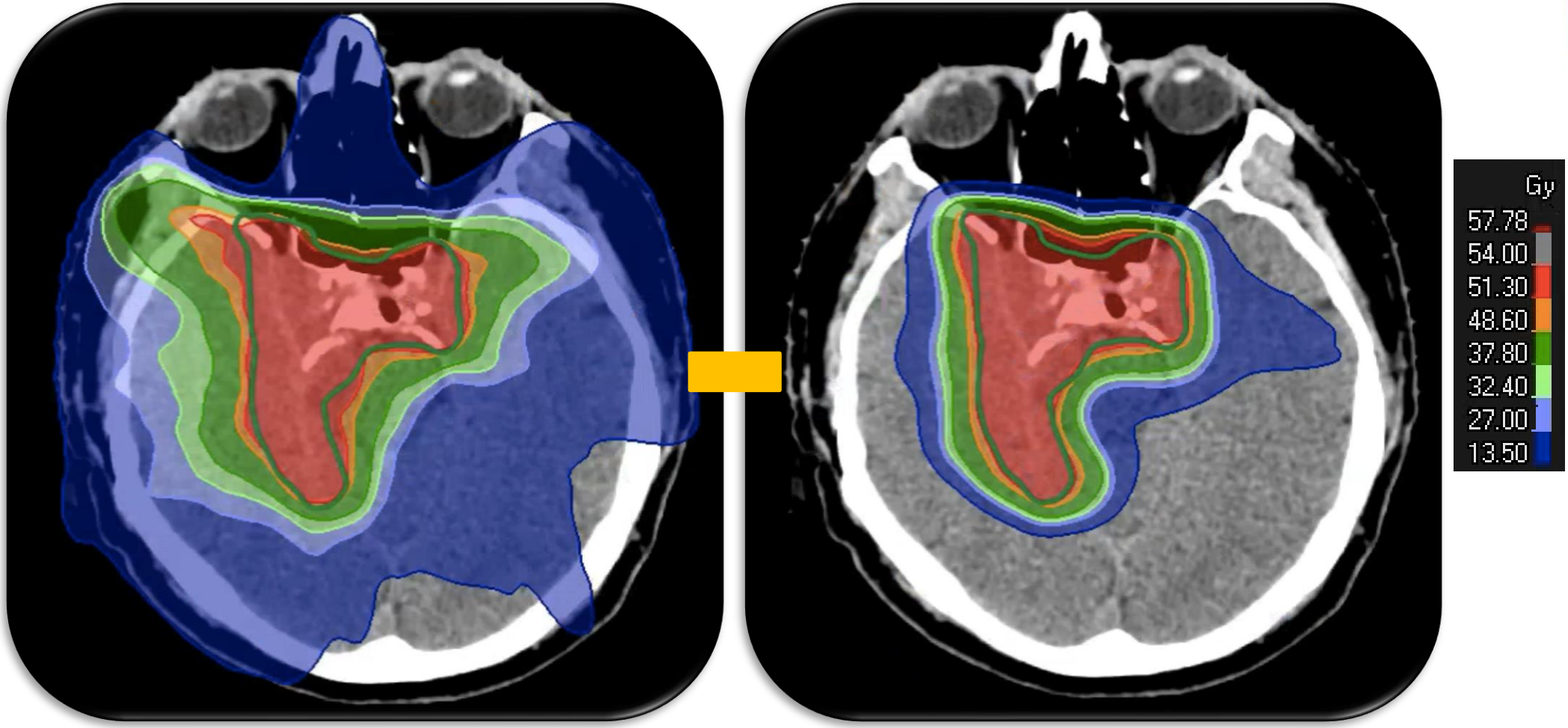
  $1/v^2$ → Bragg peak



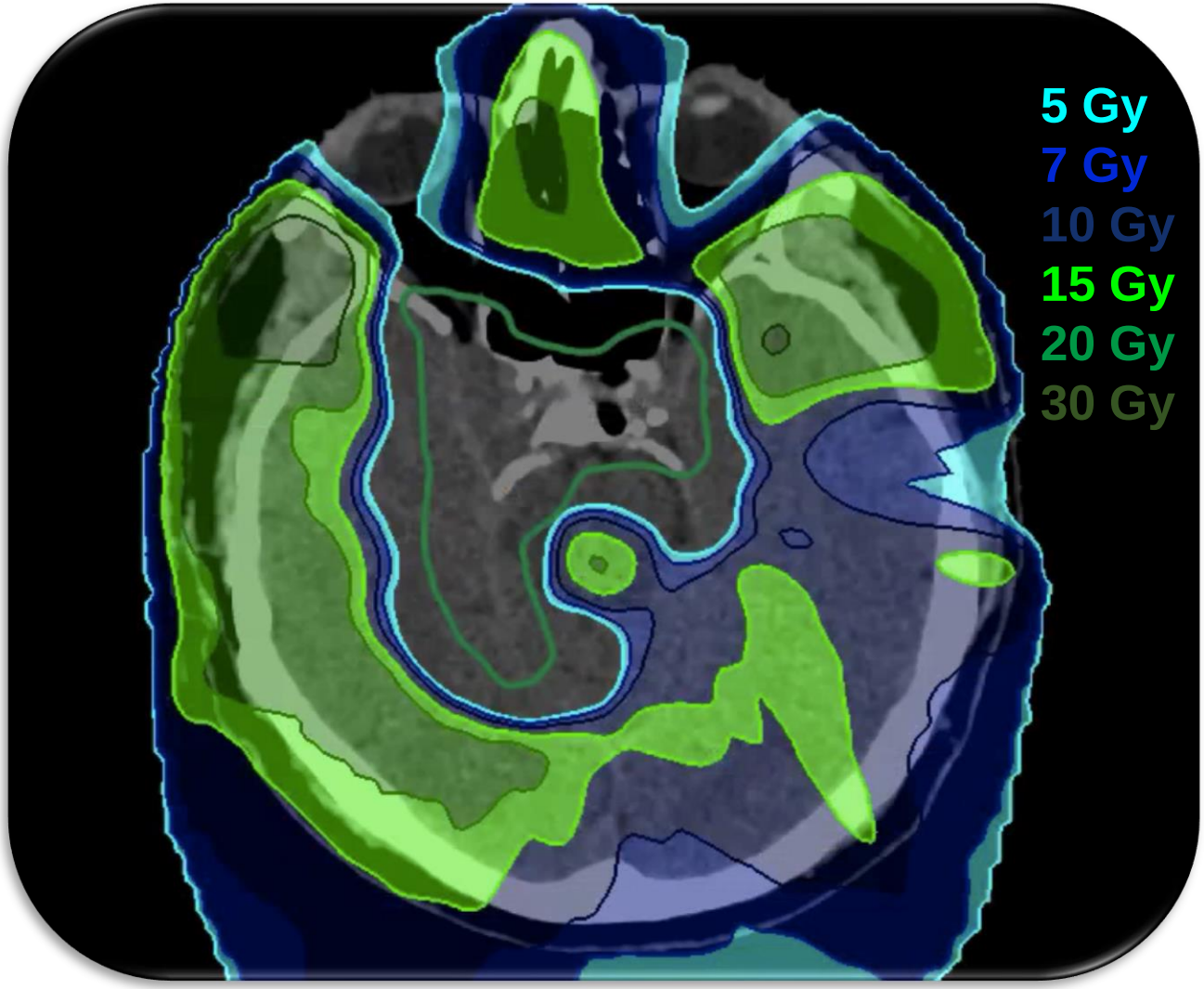

Tumor


Tumor
Photons
Protons
Overdose
Dose
Depth

Photons vs protons



Difference (unwanted dose)



Photons - Protons

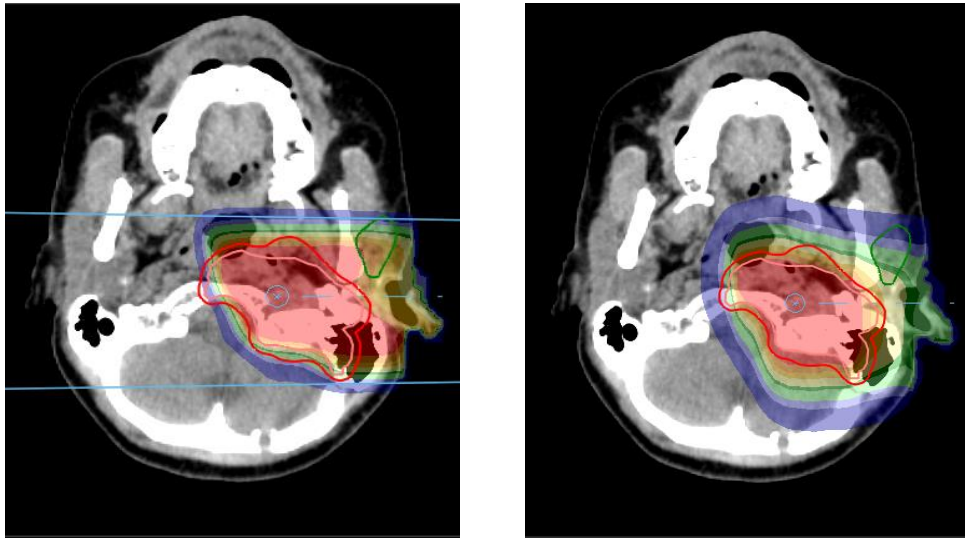
Passive vs. active particle beam delivery

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

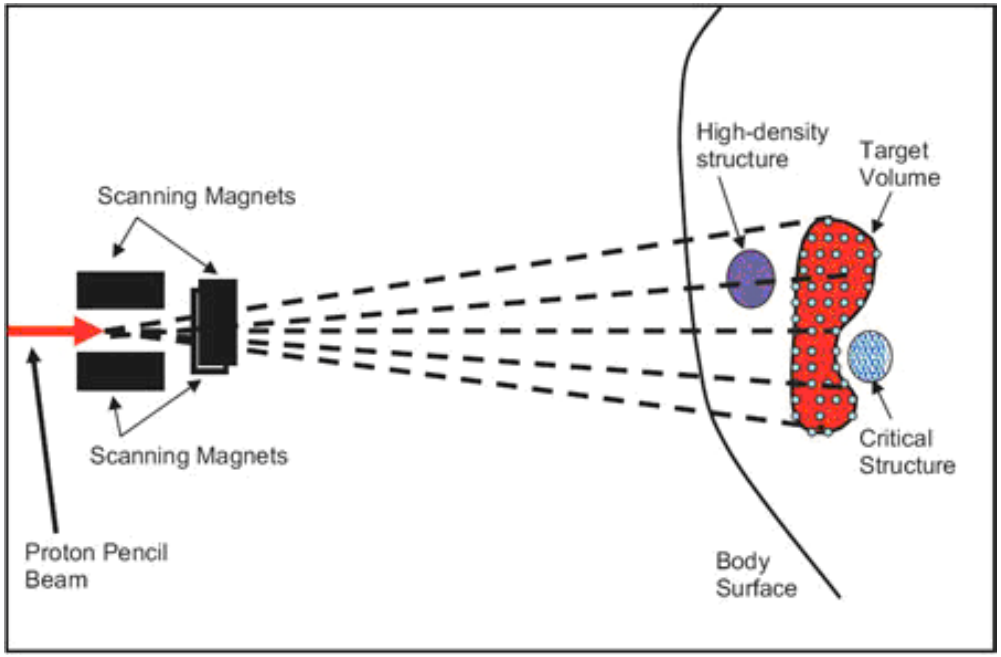
PBS - PROs	PBS - CONs
• less passive elements in the beam line	• penumbra
• no patient customized passive elements	• (without mitigation strategies) less robust to organ motion
• reduced neutron dose	
• superior dose distribution	
• less fields required	

Planning exercise (single field):

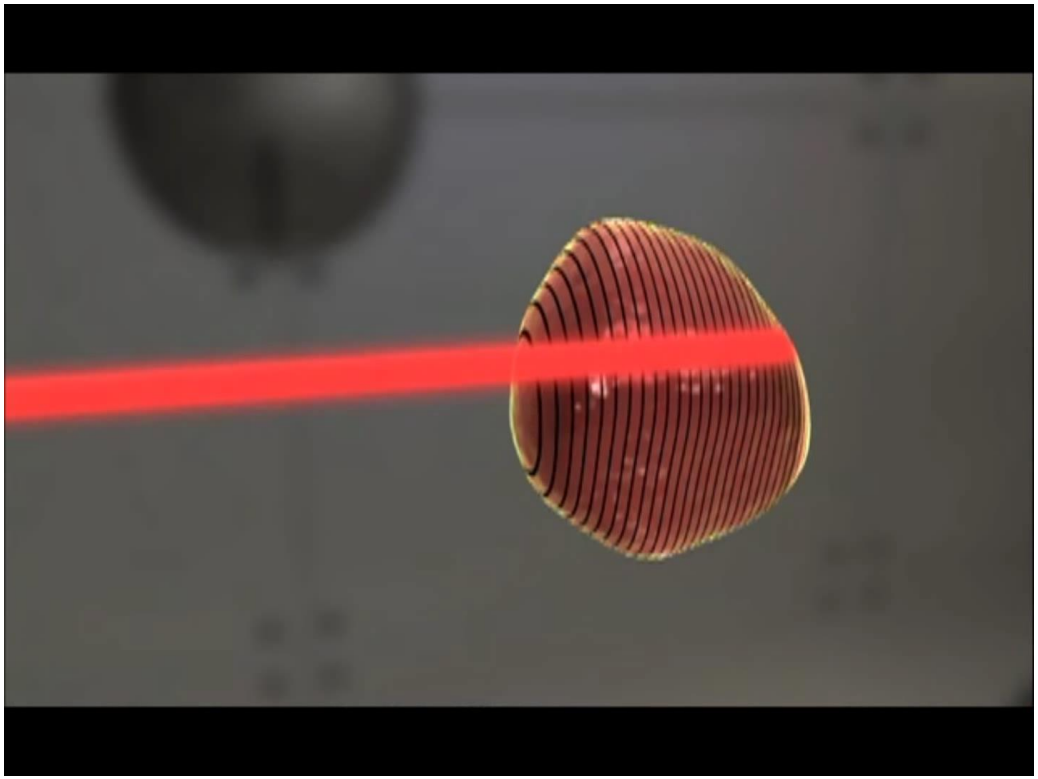
double scattering vs. IMPT



Pencil beam scanning



Courtesy MD Anderson



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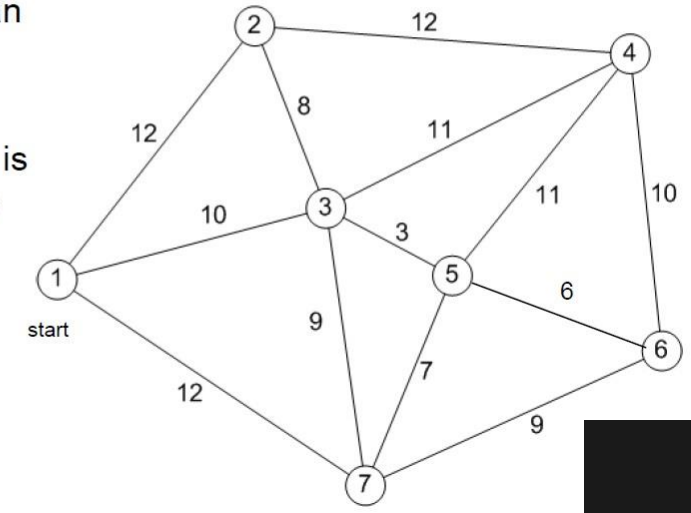
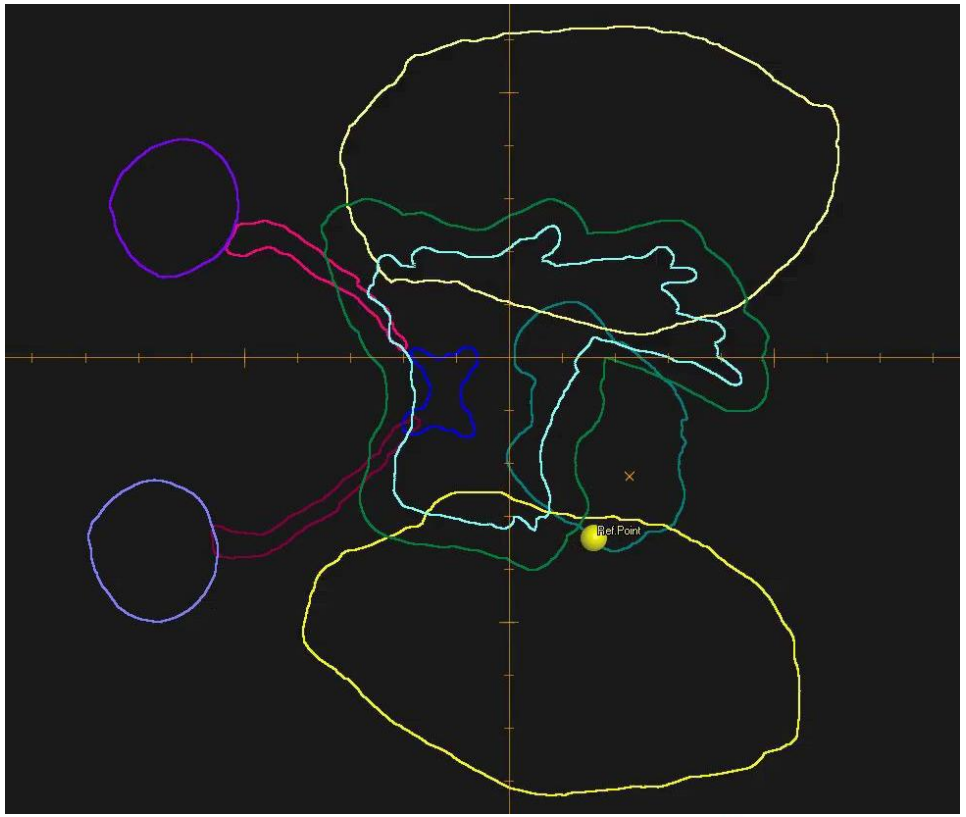
The Traveling Salesman Problem

- 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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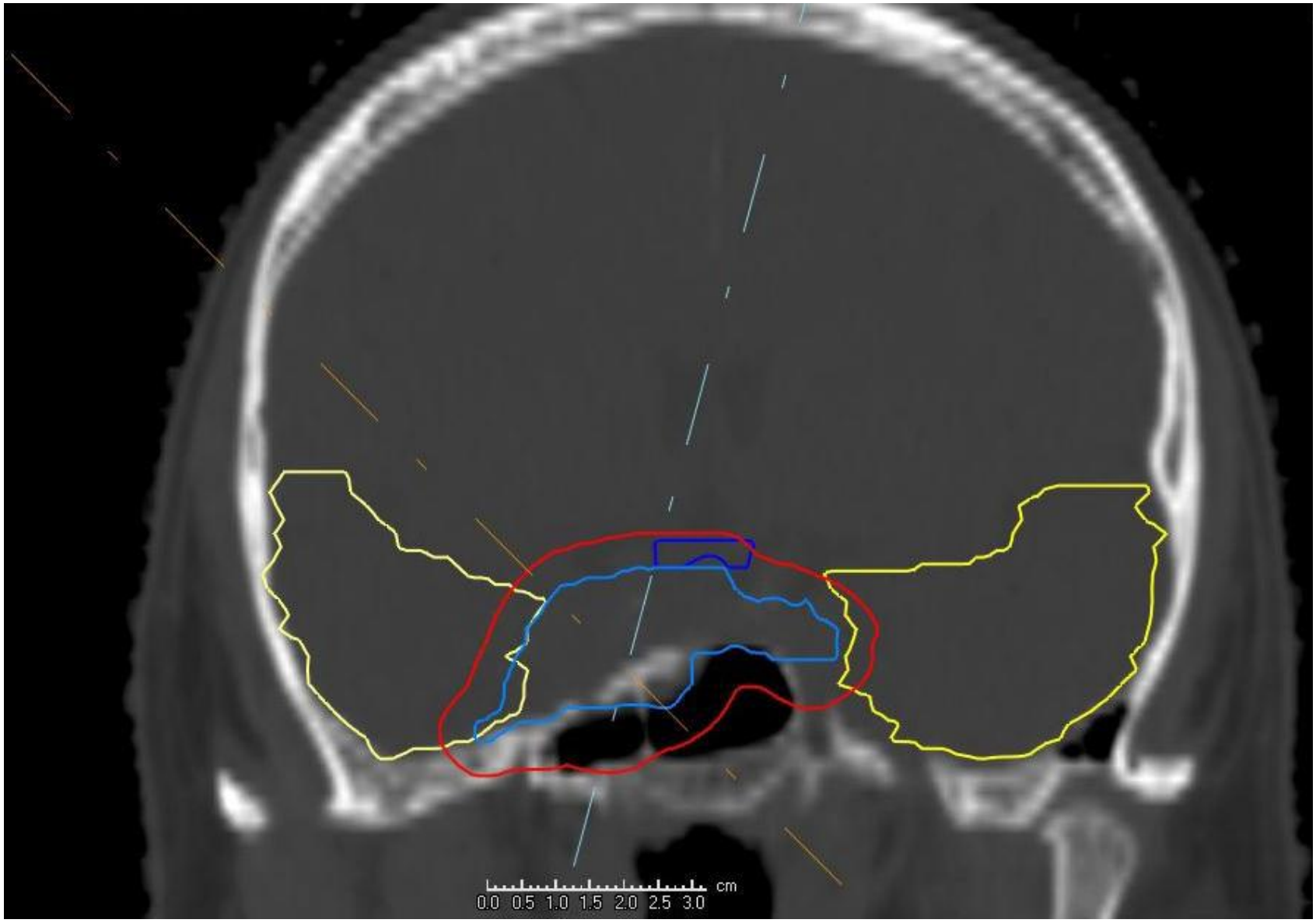
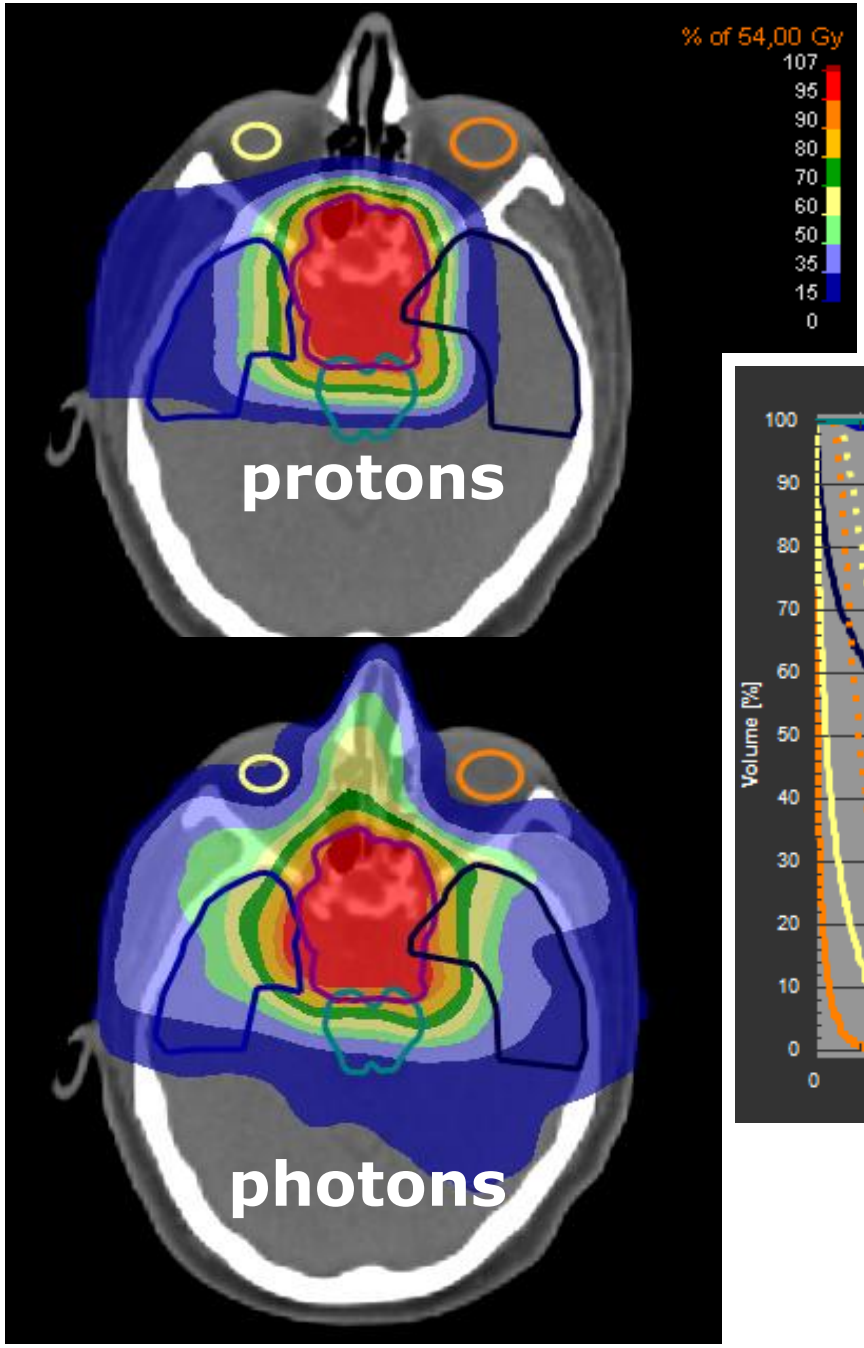
Pencil beam scanning

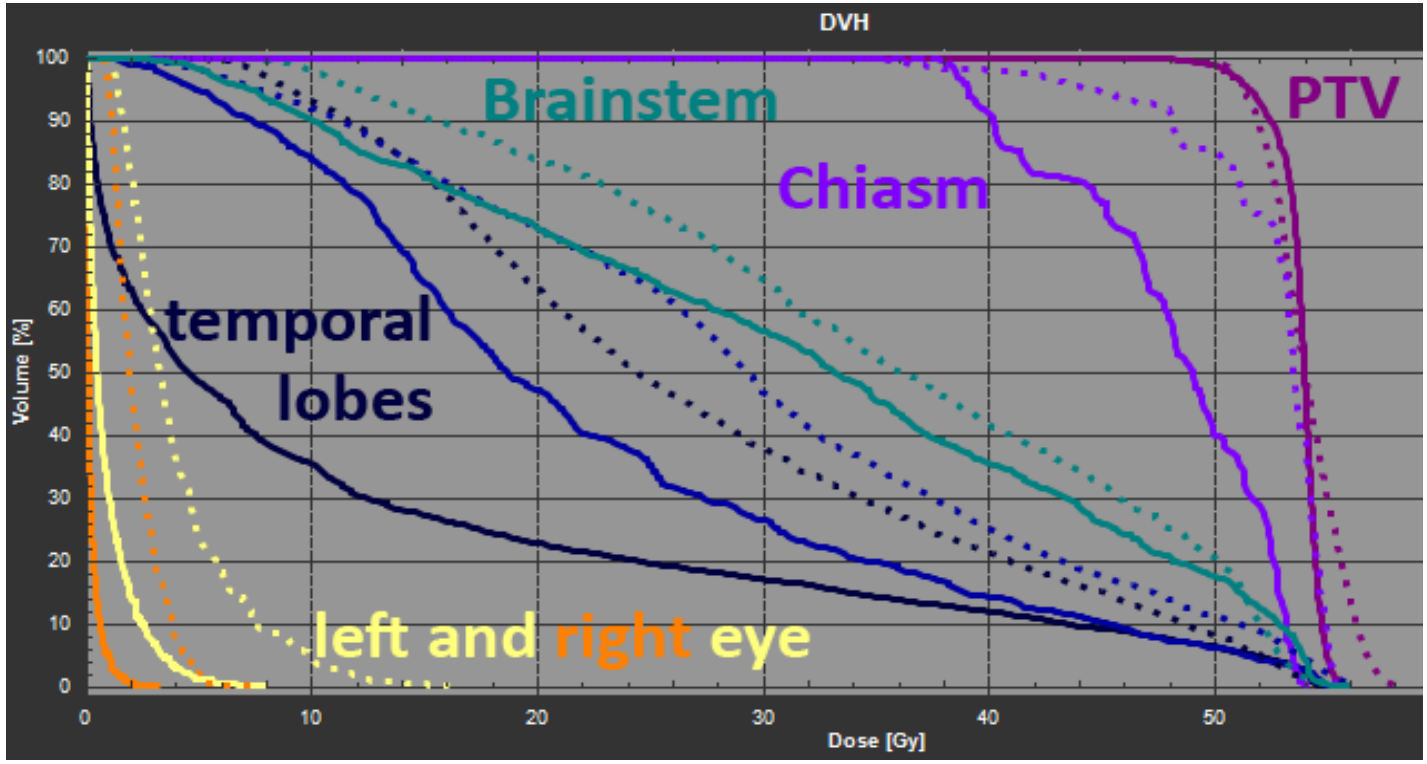


Skull base chordoma

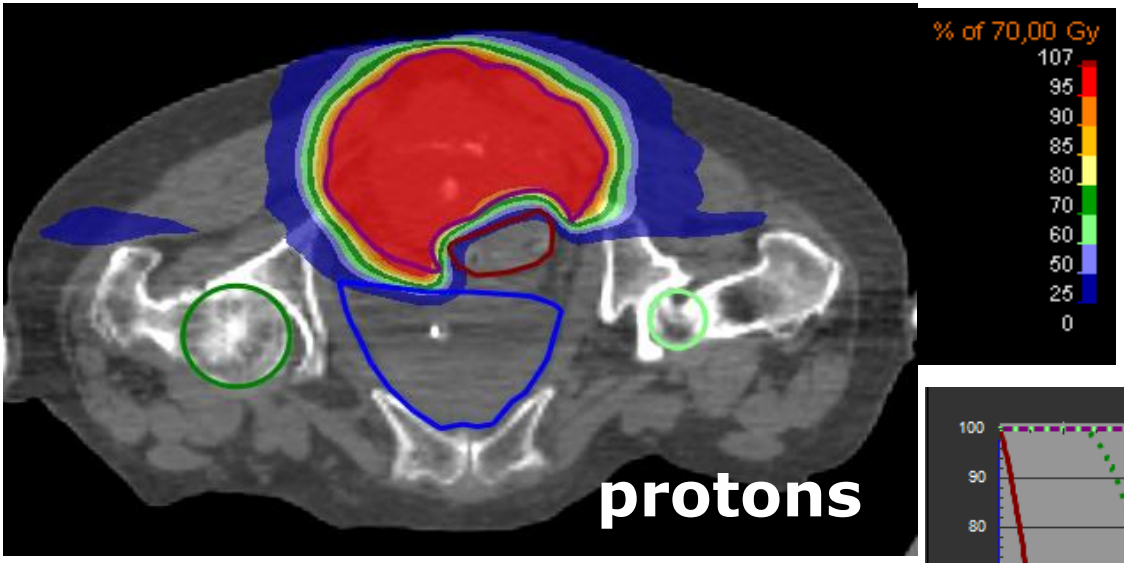


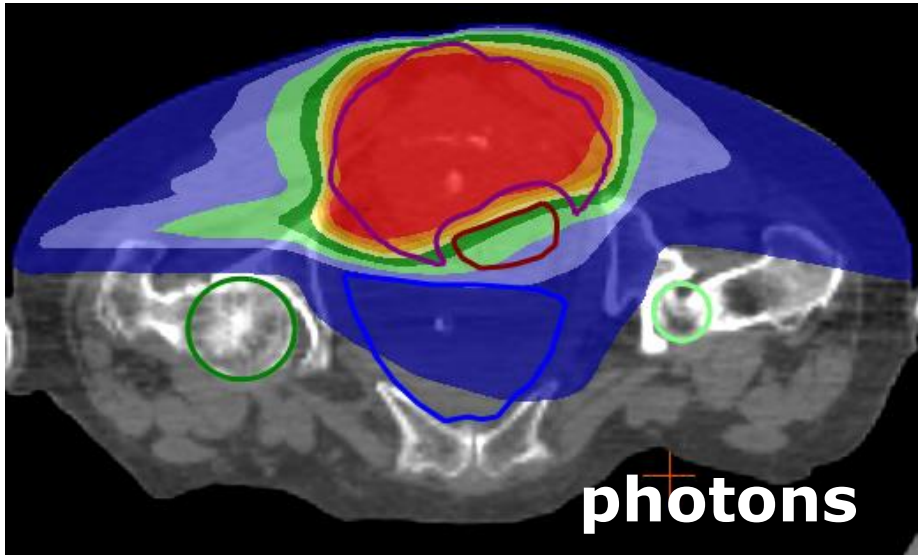
Solid: protons (IMPT)

Dotted: photons (VMAT)



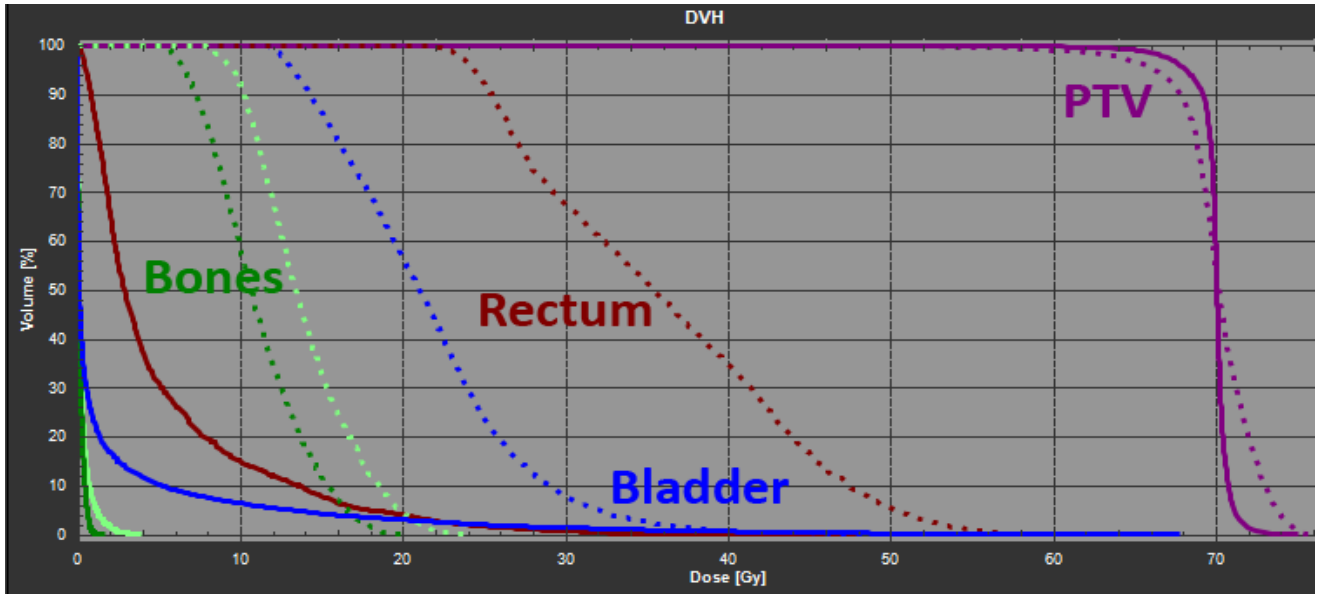
Sacrum chordoma



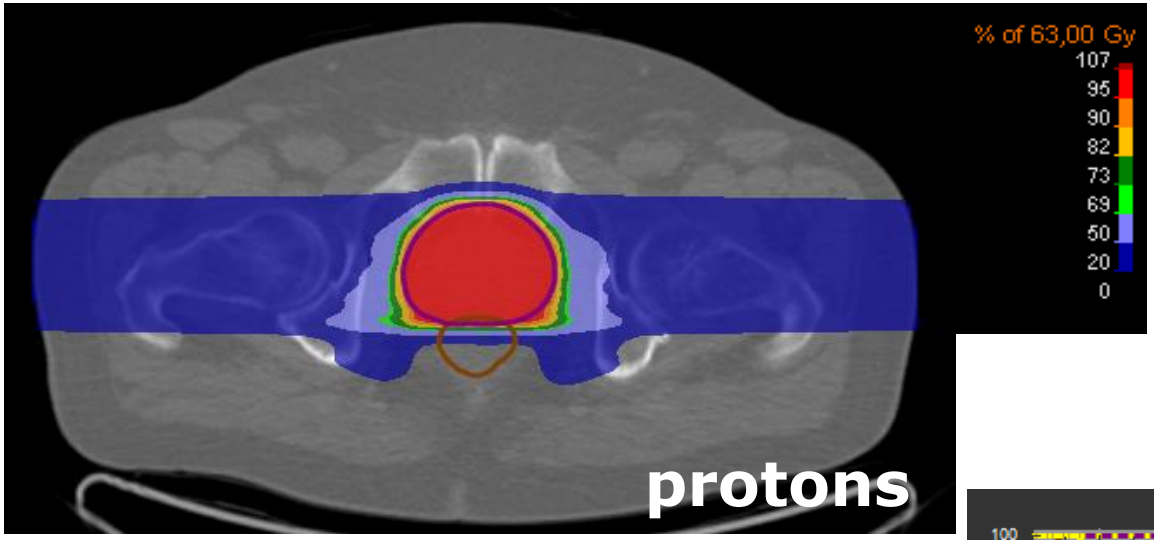


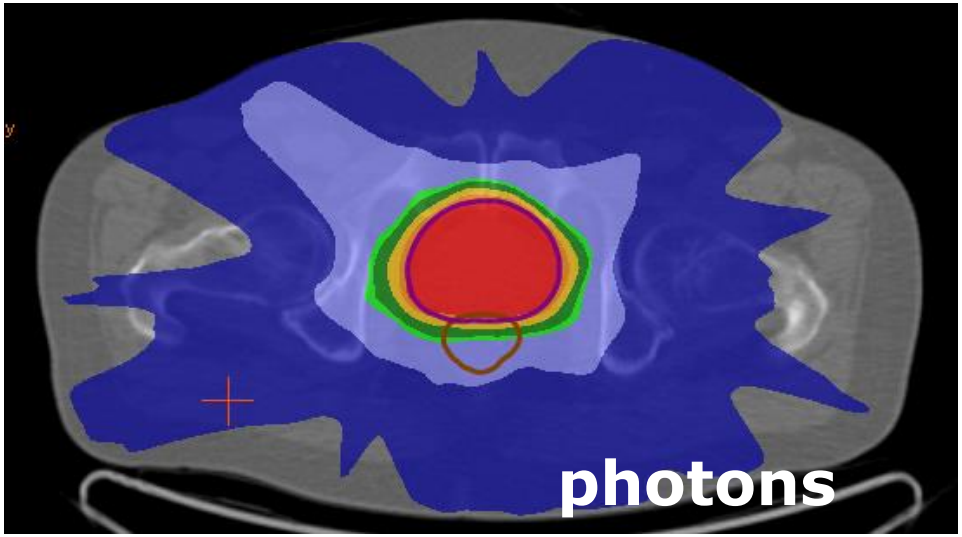
Solid: protons (IMPT)

Dotted: photons (VMAT)



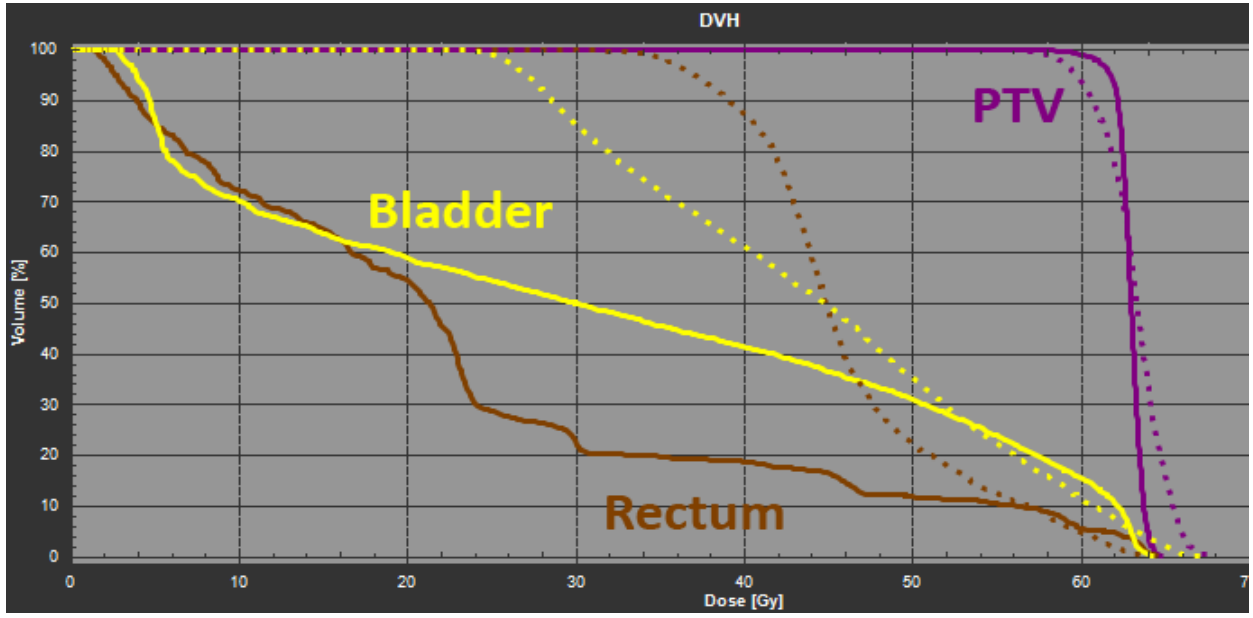
Prostate





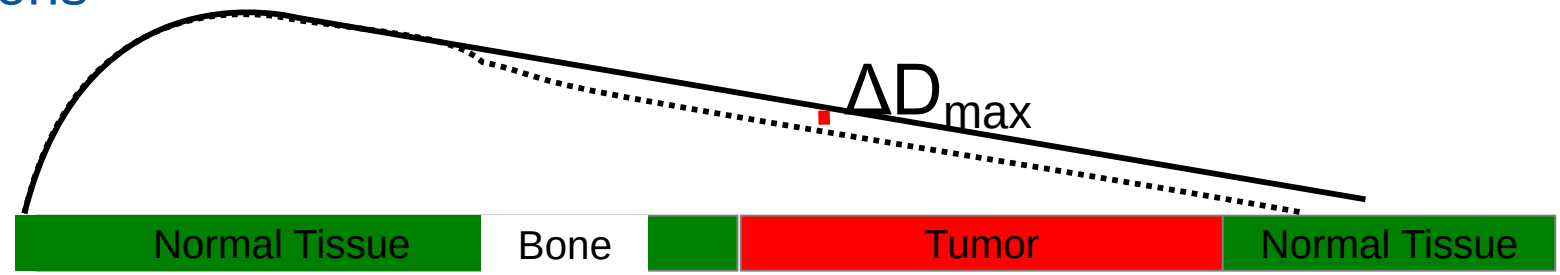
Solid: protons (IMPT)

Dotted: photons (VMAT)

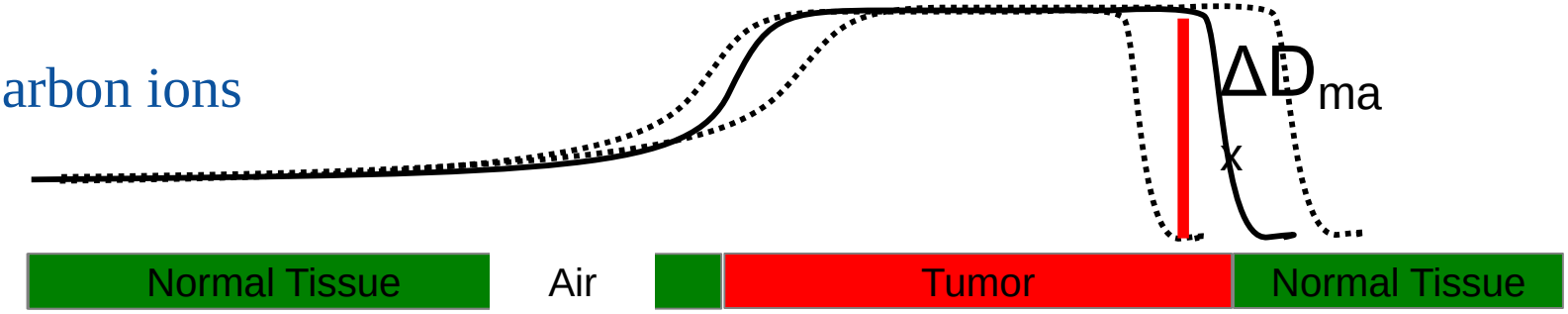


Effect of range uncertainties

MV photons

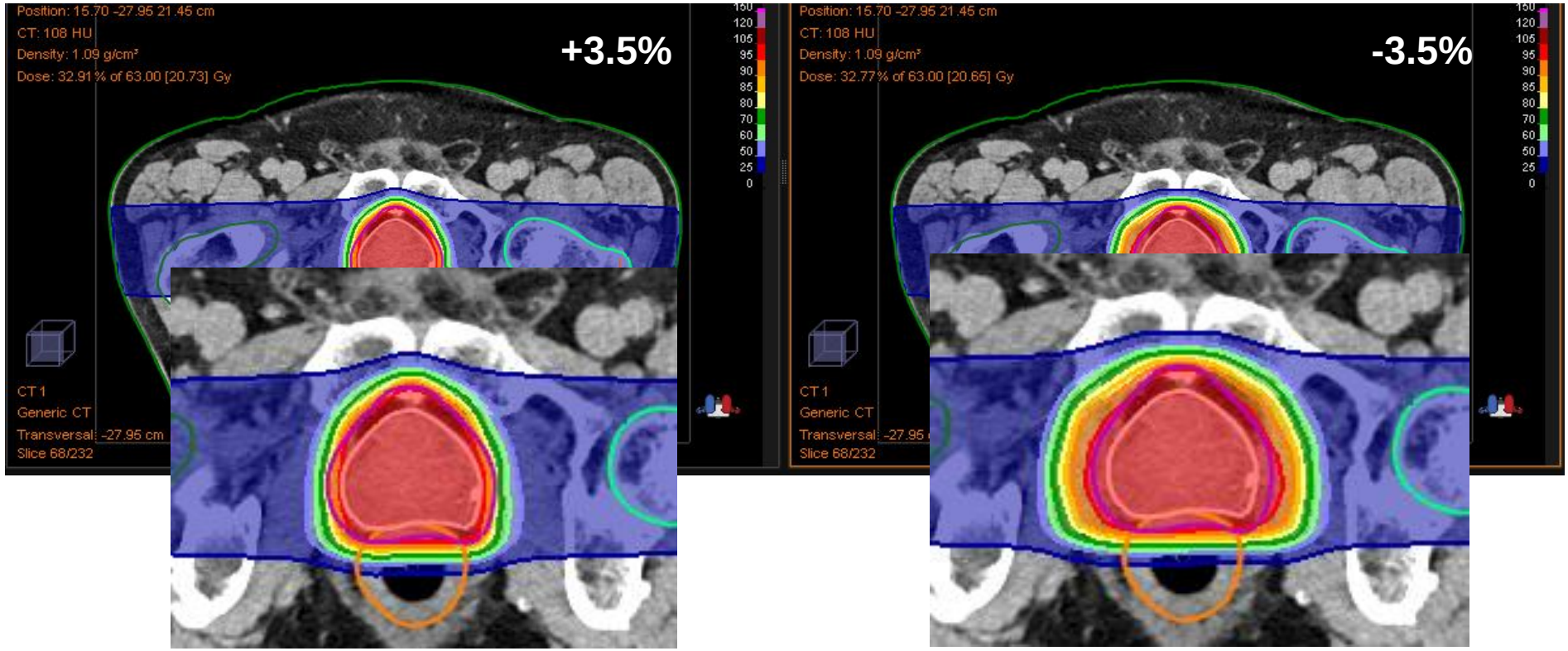


Protons/carbon ions

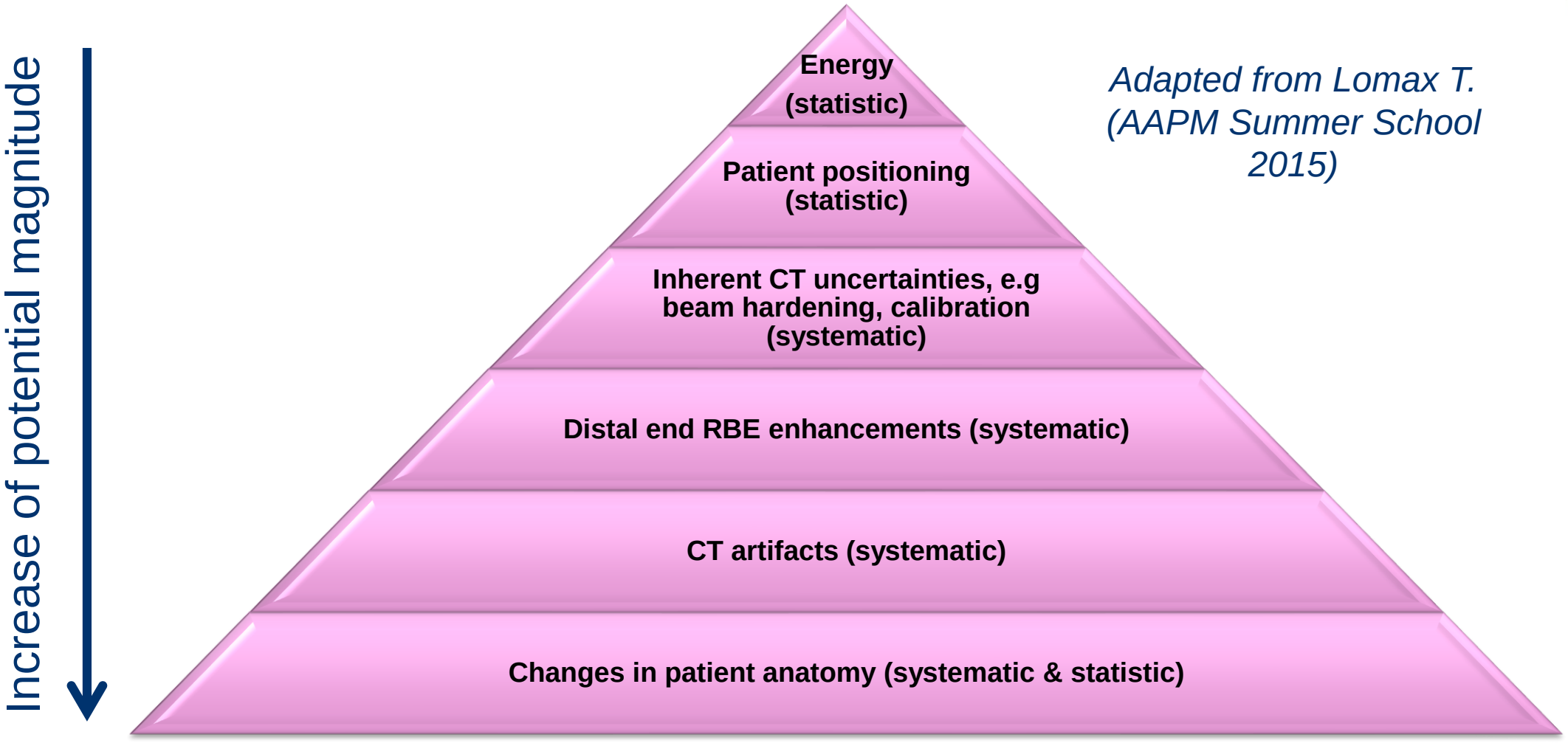


Effect of range uncertainties

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.

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

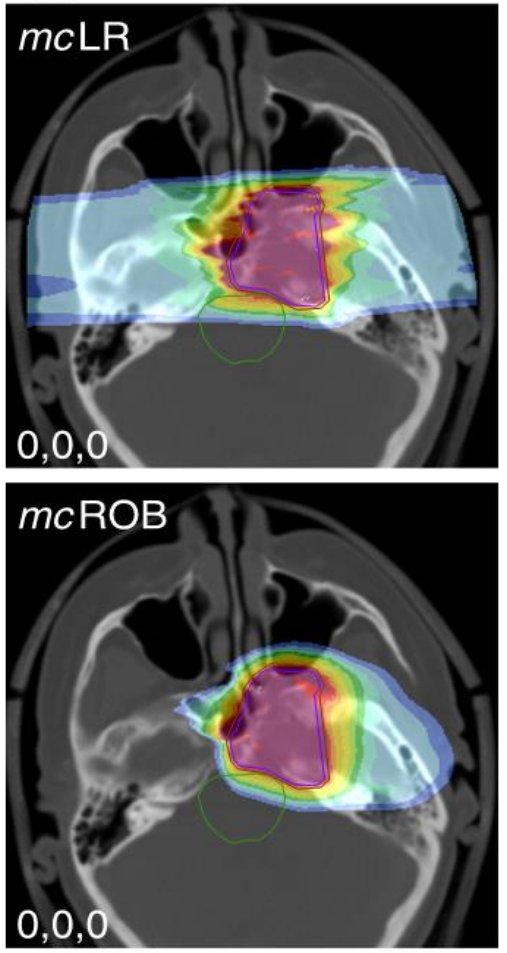
Assessing robustness against set-up errors and patient or organ motion by simulating these variation and their influence on dose distribution

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

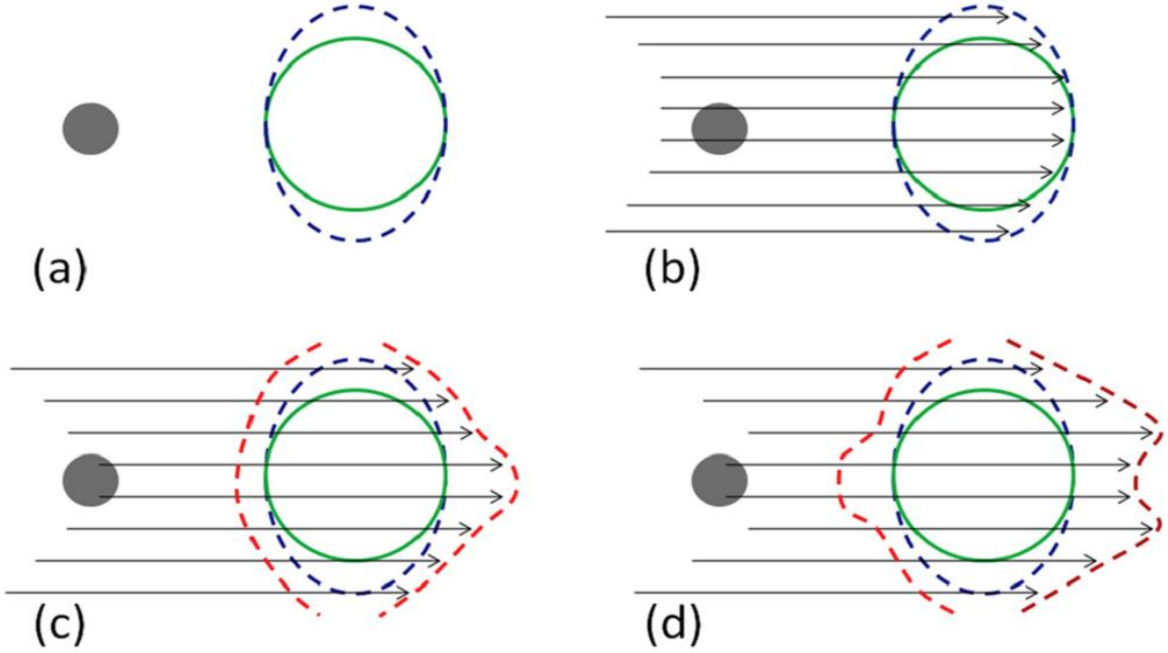
- dose homogeneity: ***choose beam angles avoiding*** large ***density interfaces*** along the beam axis
- range uncertainty: ***avoid*** placing ***Bragg peaks proximal to*** critical ***OARs***
  - beam incidence parallel to OARs
  - spot positioning margins/restrictions around OARs



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.

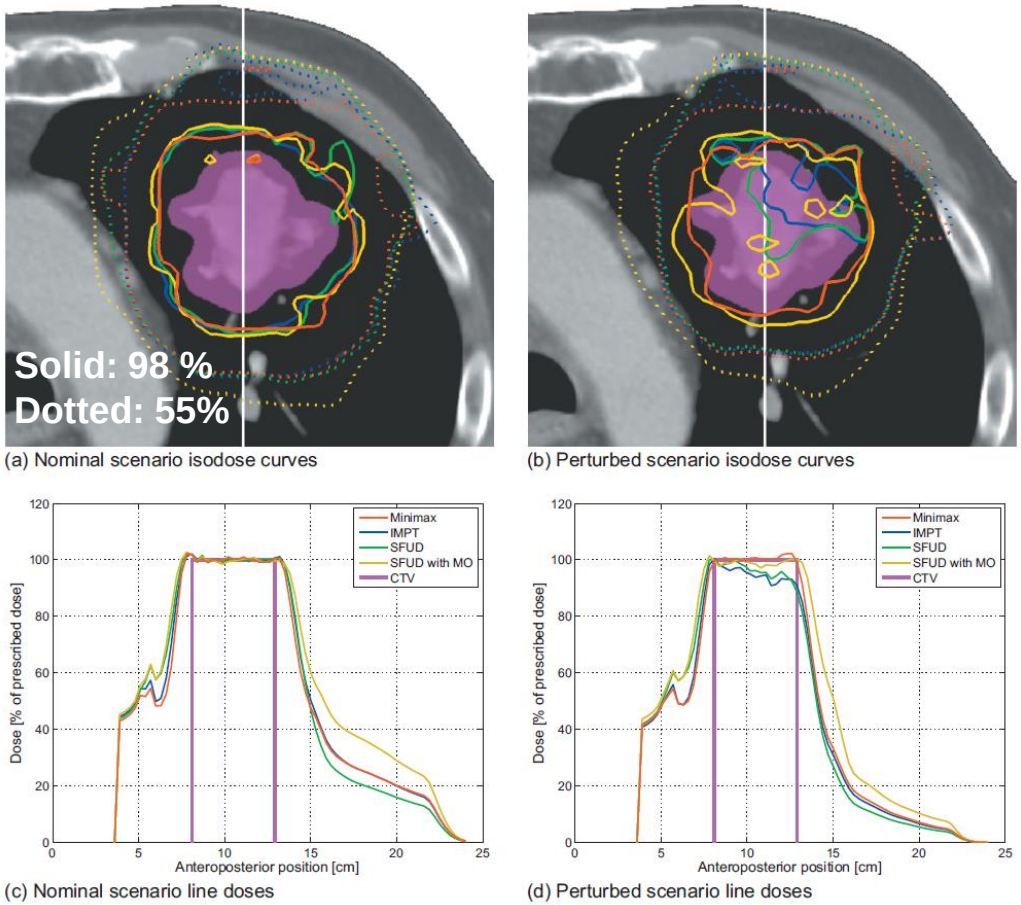


Park et al (2012) IJROBP 82(2):e329-36

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



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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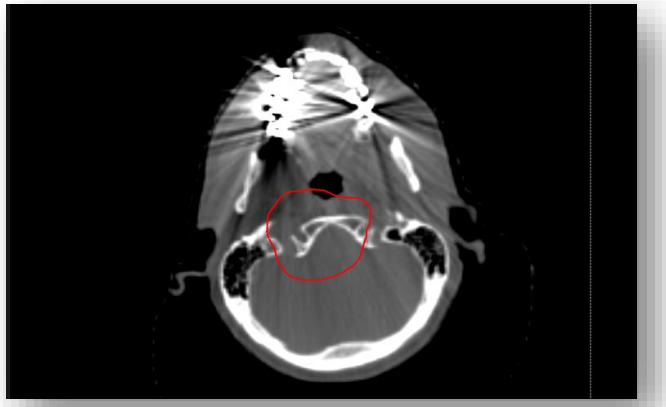
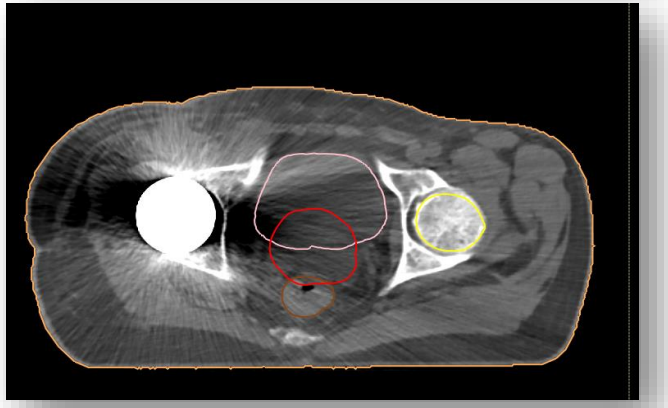
CT artefacts due to metallic implants

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

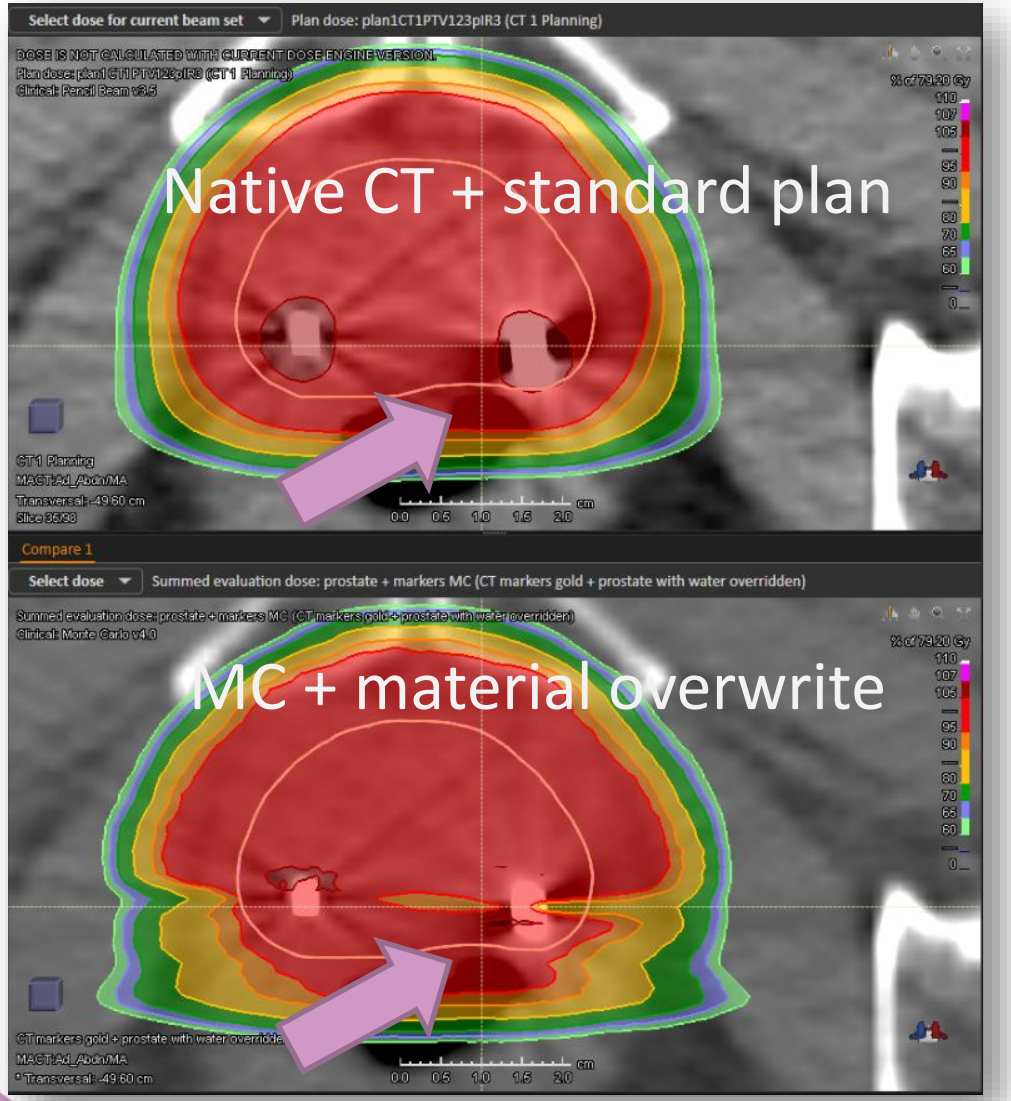


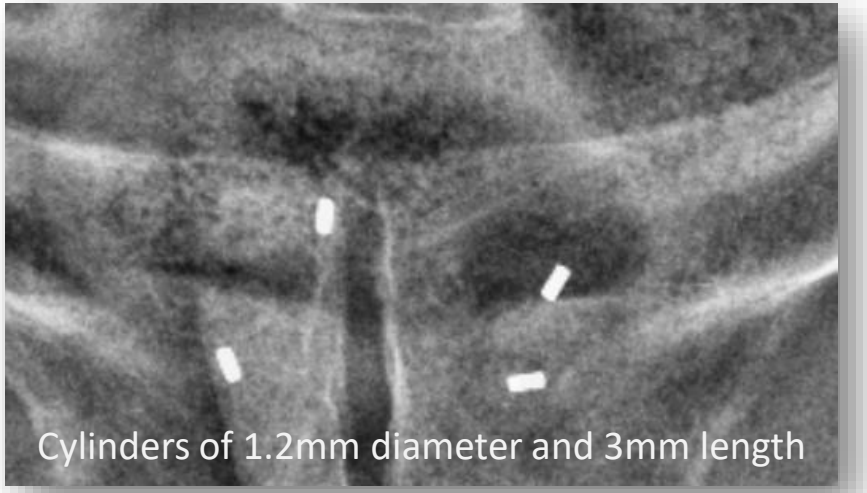


In case of less pronounced artefacts:

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

Prostate gold markers

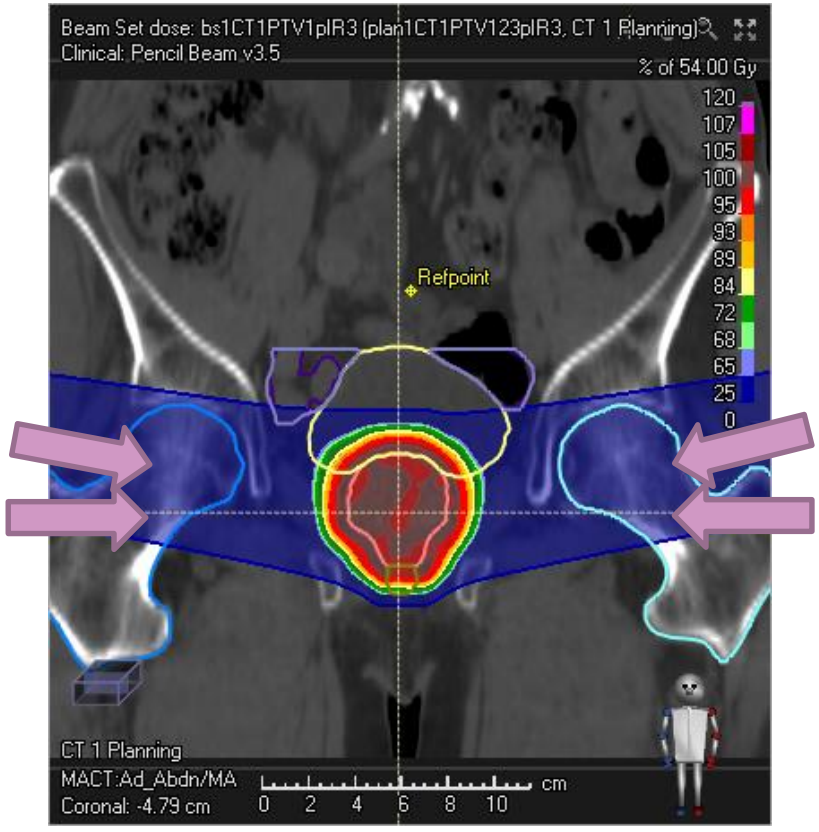


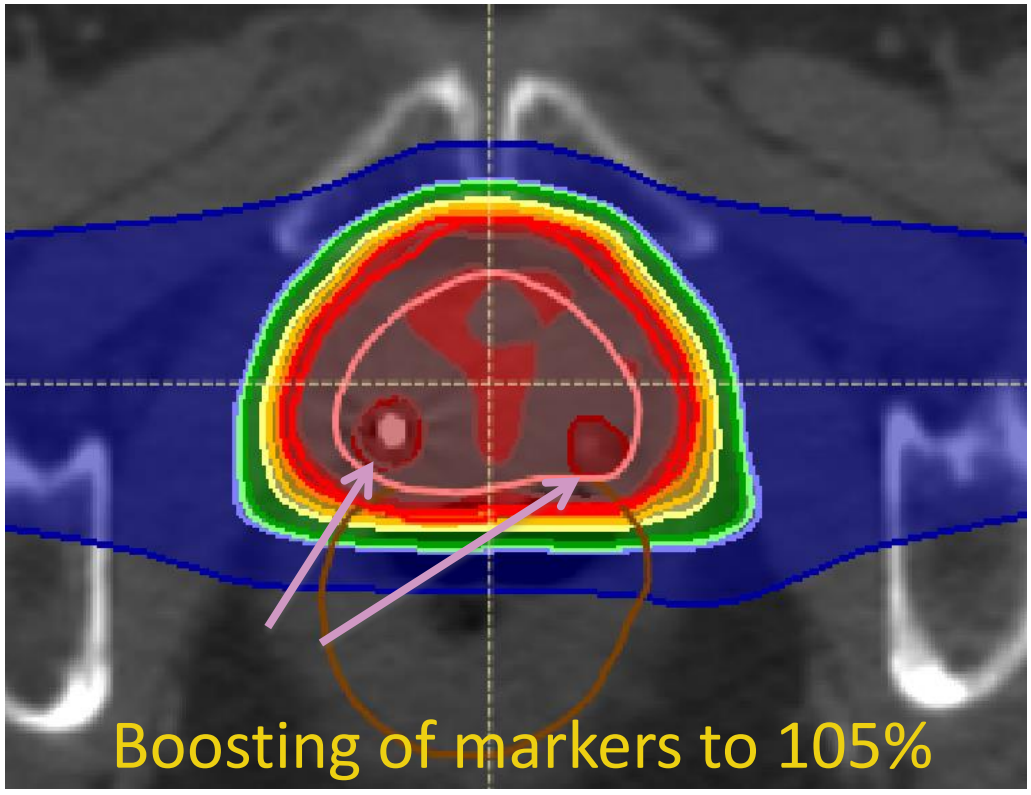


For a standard planning approach evaluated with material overwrite + MC to cause ‘dose shadows’

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

Prostate gold markers





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

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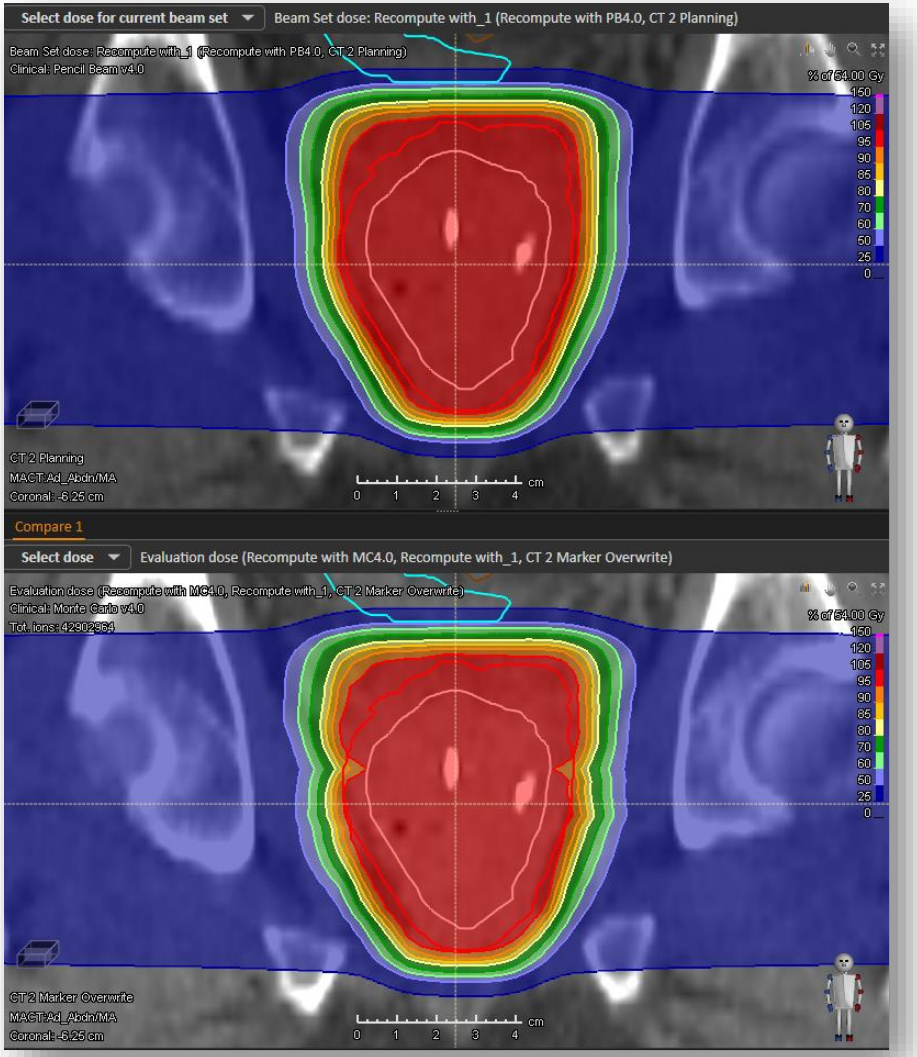
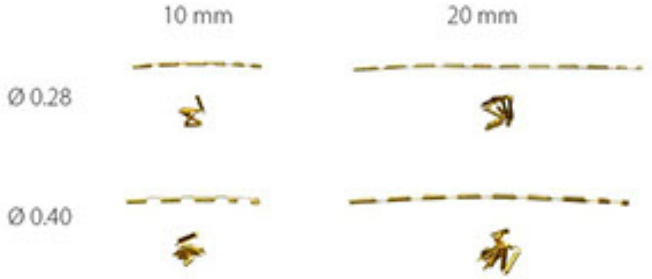
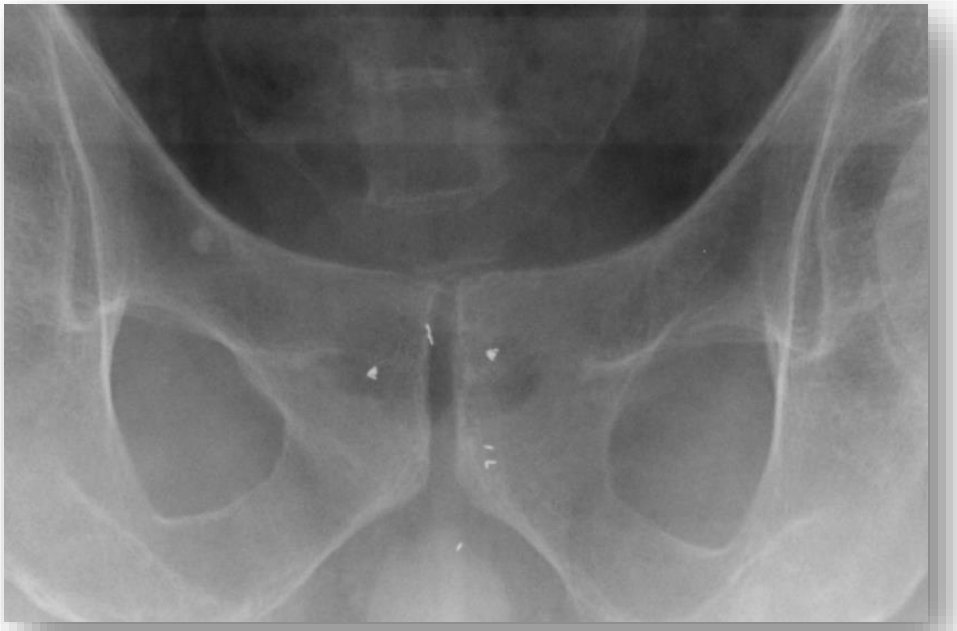
Impact of markers for PT







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

SBO (SFUD) and MBO (IMPT)

SBO: Single beam optimization

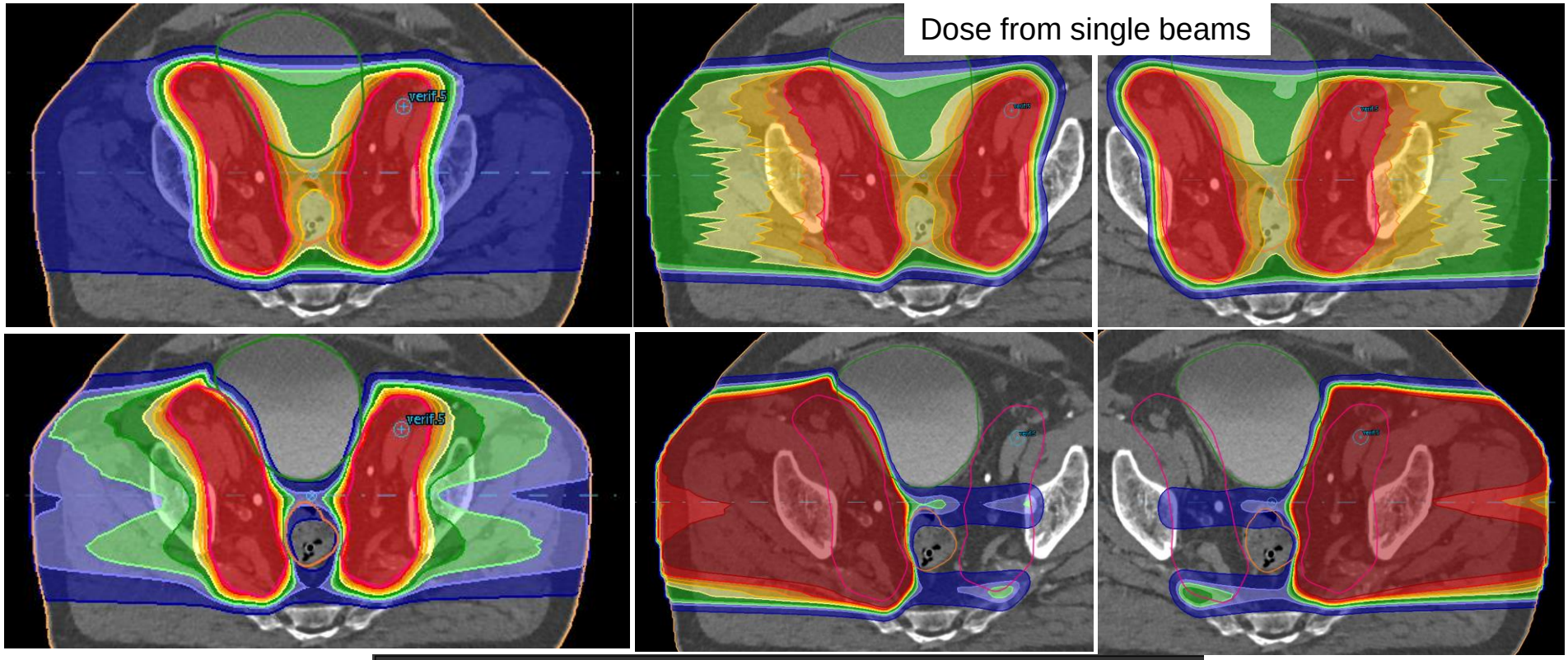
- Possible with passive scattering and active scanning technology
- Spots are weighted in order to achieve a homogenous target dose for every single beam
- OAR sparing only possible by using help structures
- More robust treatment plans

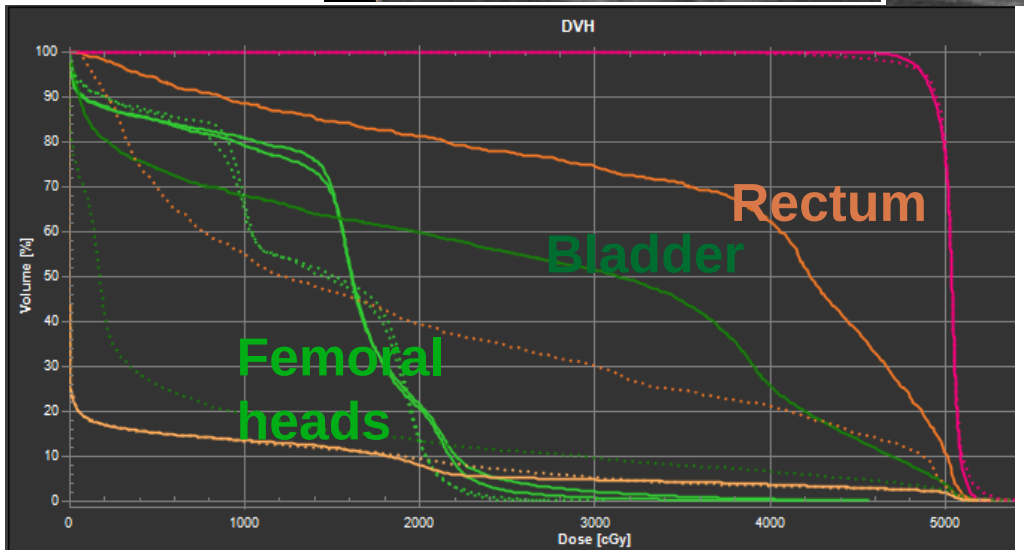
MBO: Multi Beam Optimization

- 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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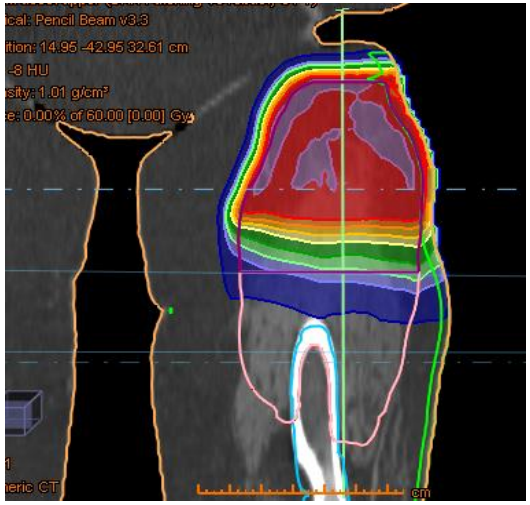
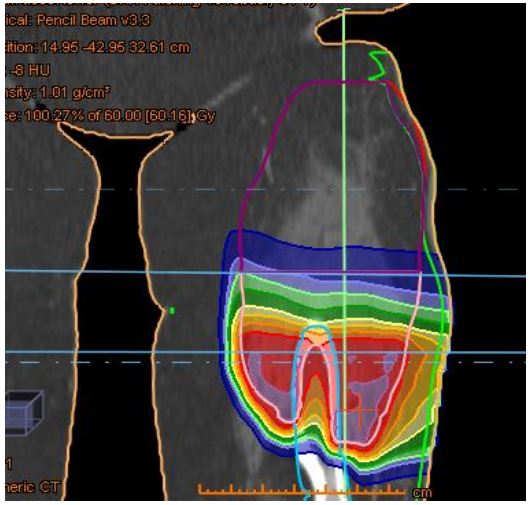
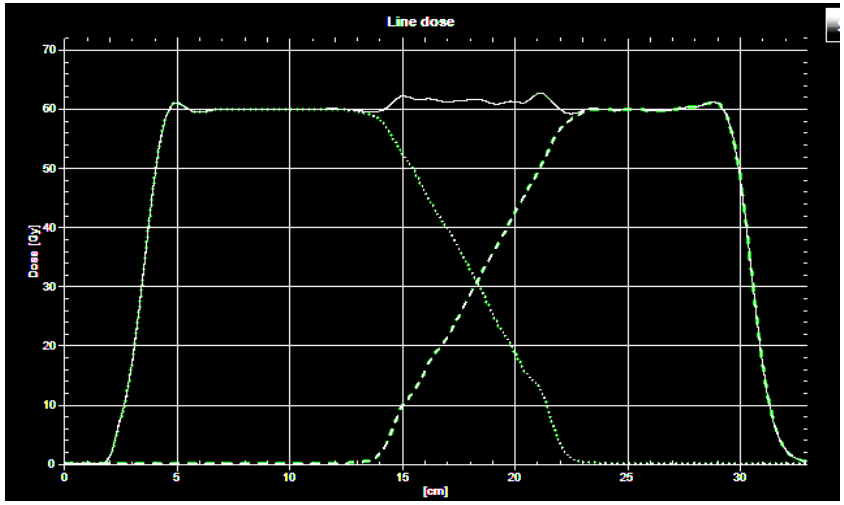
Field matching

- robust optimization for independent beams

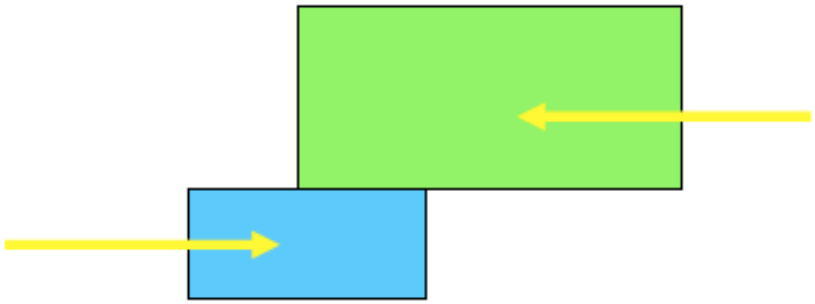






Particle planning basics

Abbuting fields

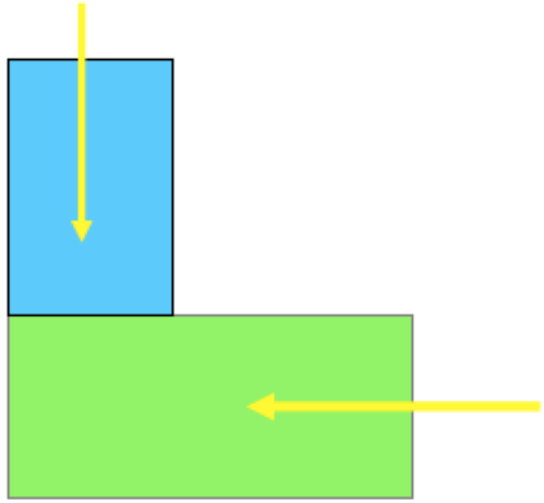


Lateral penumbra

+

Lateral penumbra

Patch fields



Distal penumbra

+

Lateral/distal penumbra

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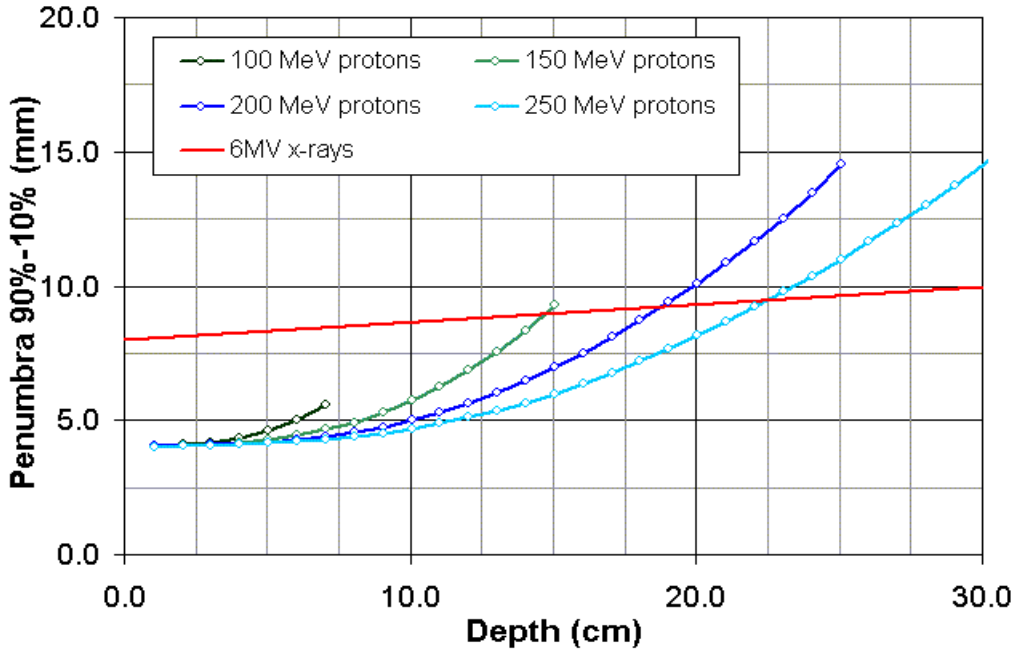
Penumbra

Lateral scattering:

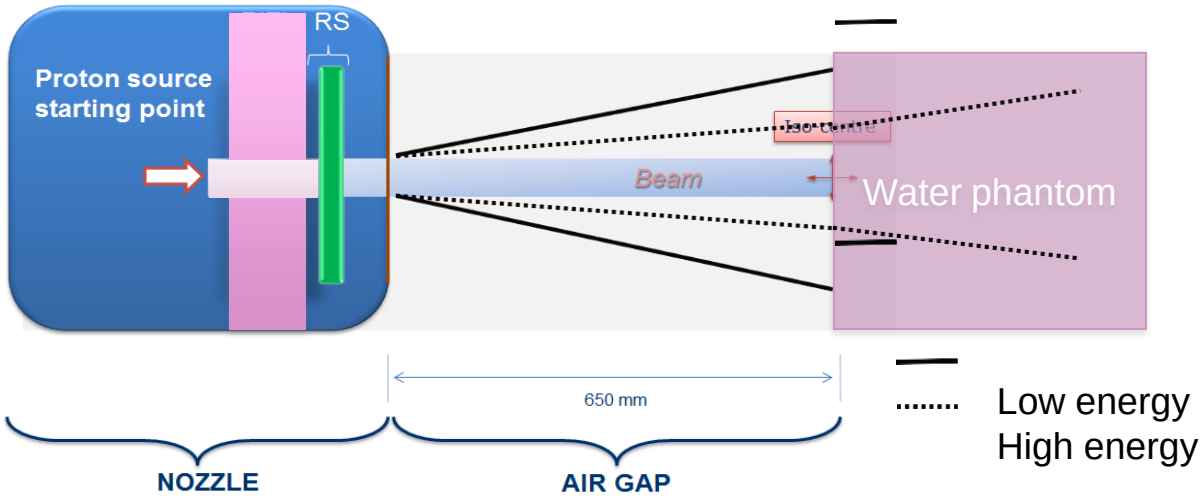
- MCS: penumbra increases with increasing penetration depth.
- Exceeds penumbra of photons at some point.



Courtesy Palmans 2006

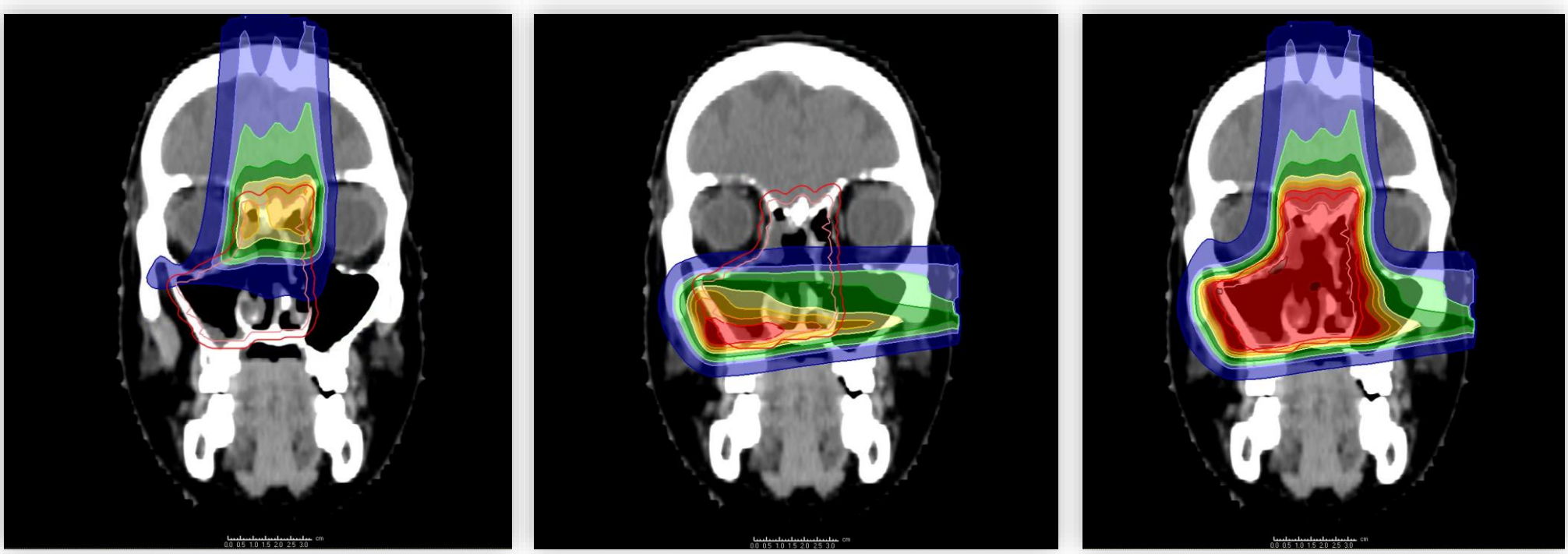
Presence of range shifter (combined with low energies):

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



Courtesy Grevillot 2014

Inter-Ocular Nasal Cavities with horizontal beam only



Patching with smooth matching-gradient + multiple beam sets

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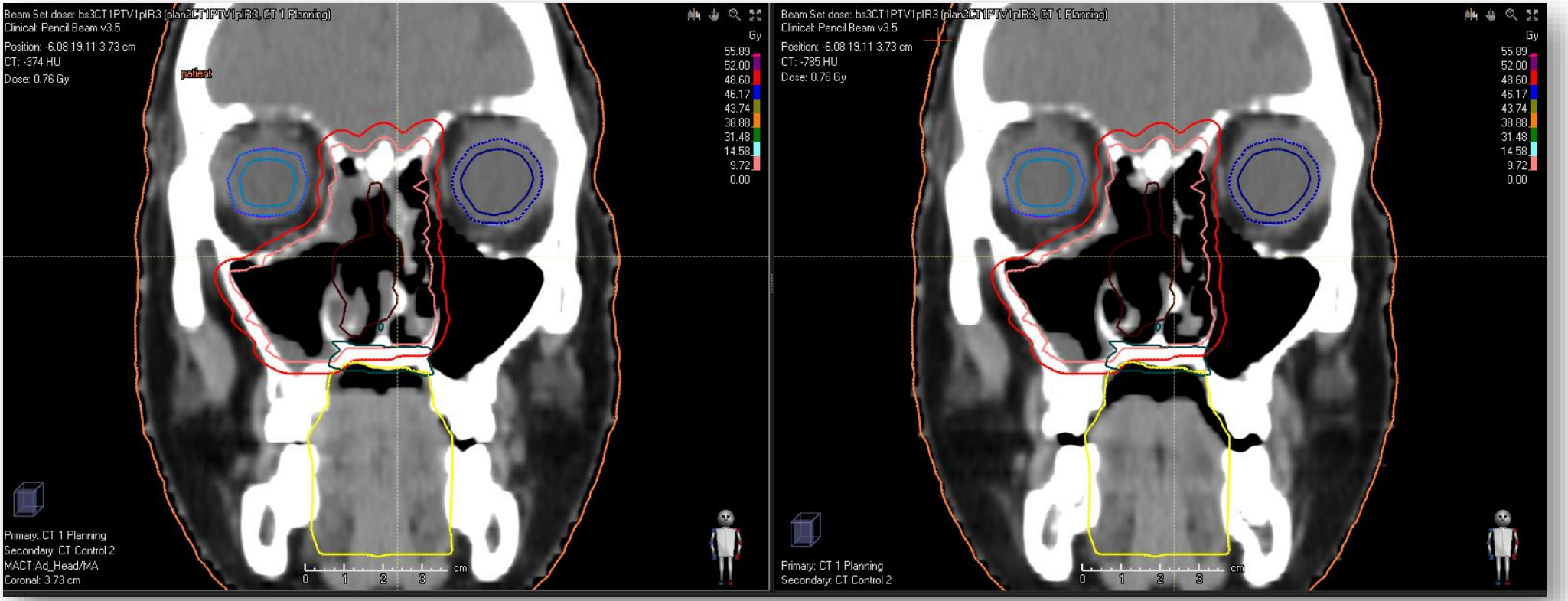
INTER-fx: Nasal Cavity Filling



Monitoring filling by control CTs + dose recomputation

Alters ranges and dose distribution?

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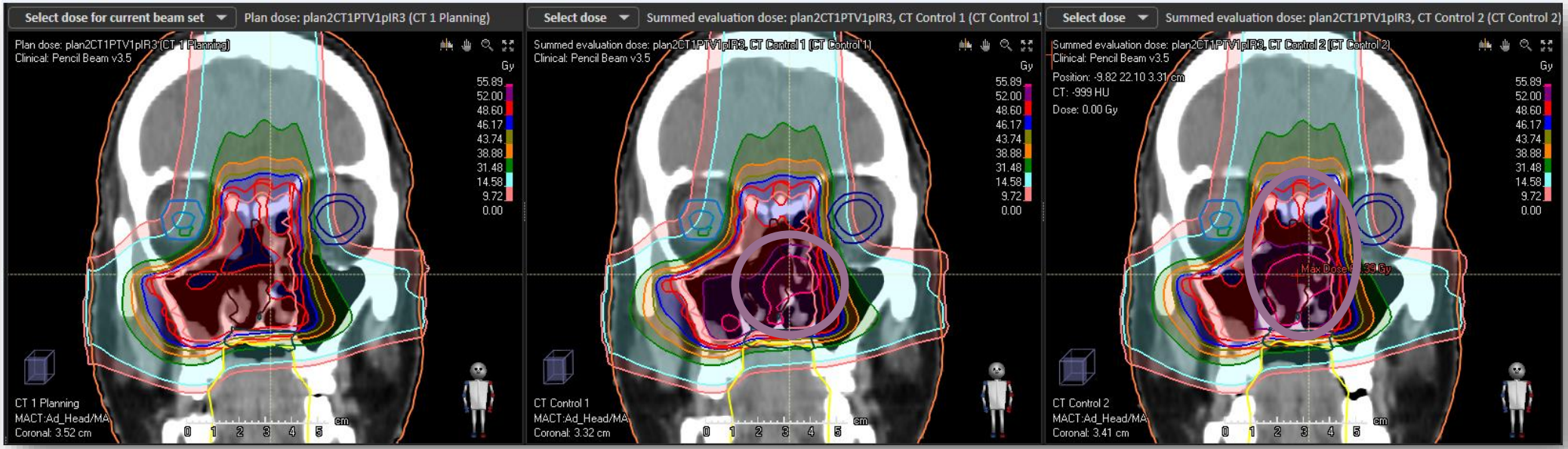
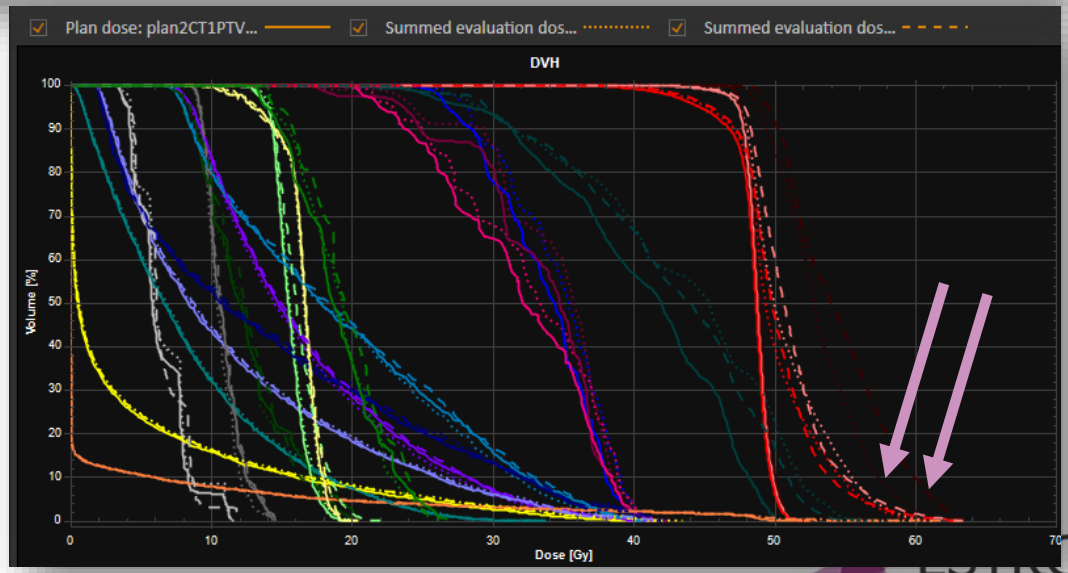
INTER-FX: Nasal Cavity Filling

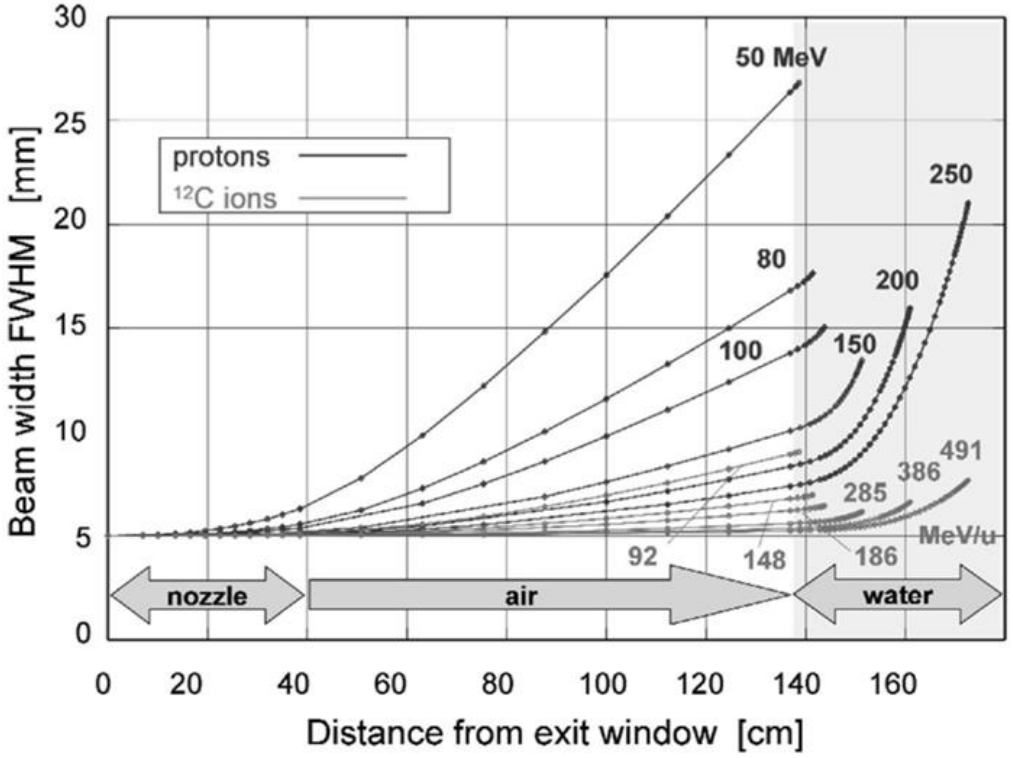




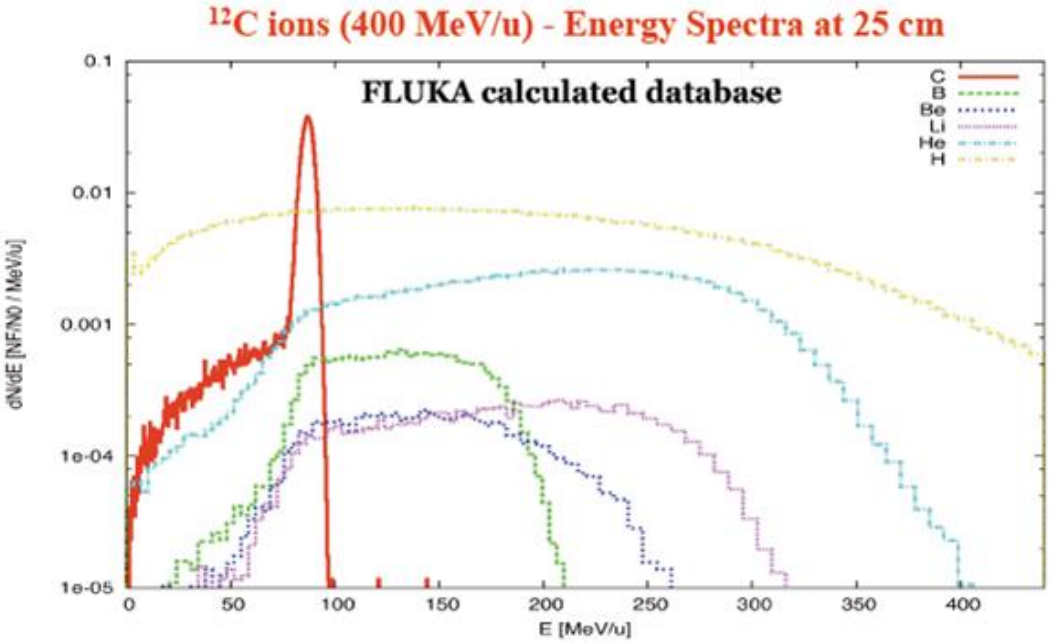
- Dosimetric impact evaluation
- Palate exposed to higher doses
- Plan adaption + compensation

CIBT wrt PT: Some important differences for TP

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

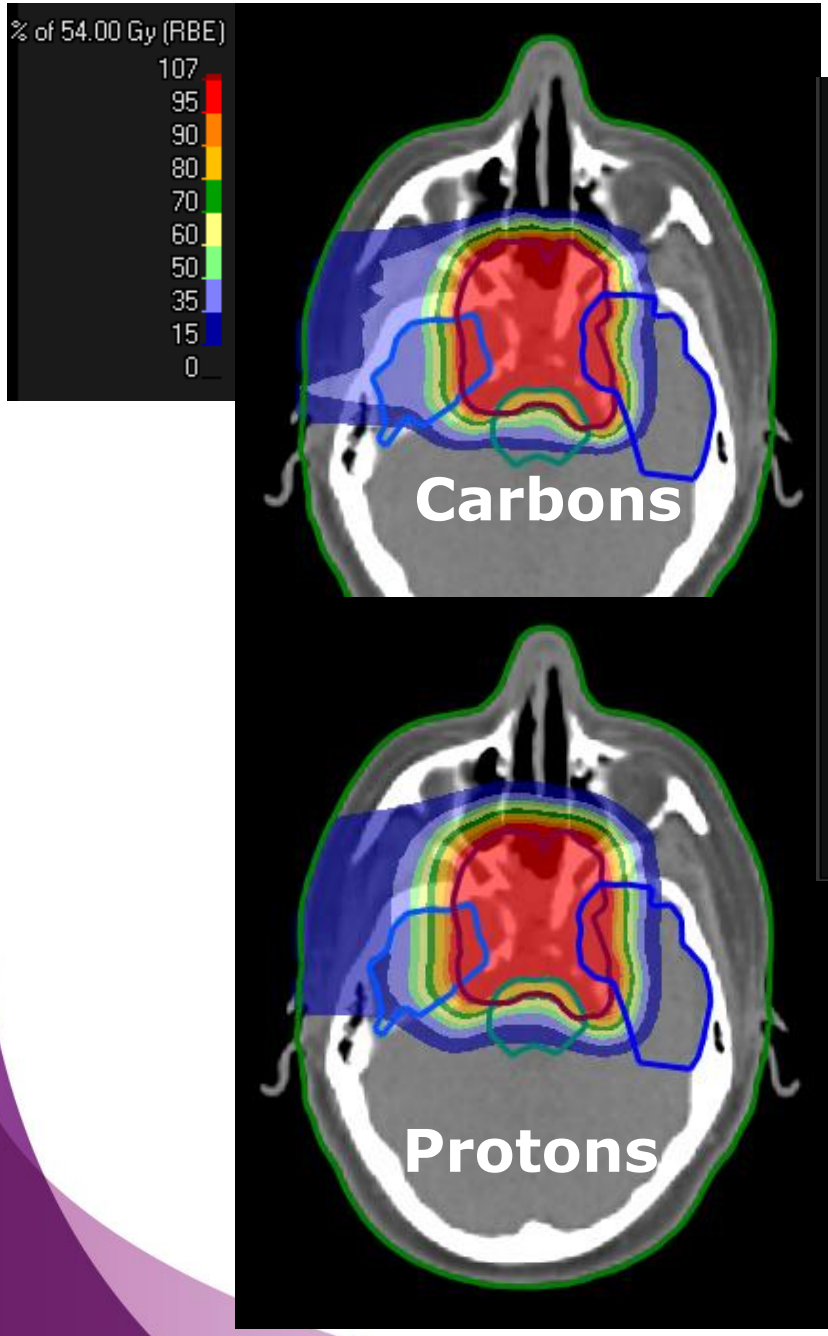


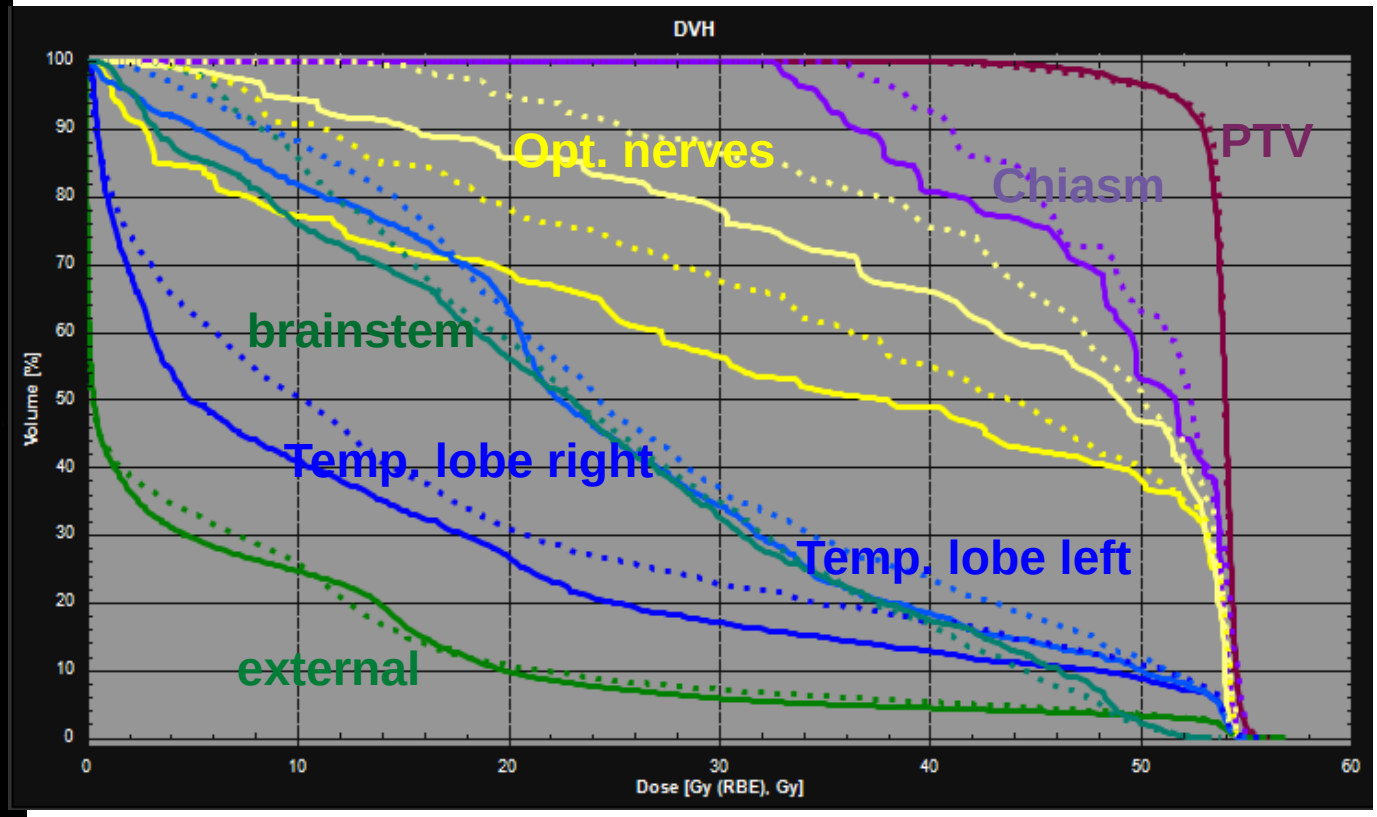
Weber and Kraft, *Cancer J* (2009) **15**(4):325–32



Mairani et al., PMB

C vs p: Skull base

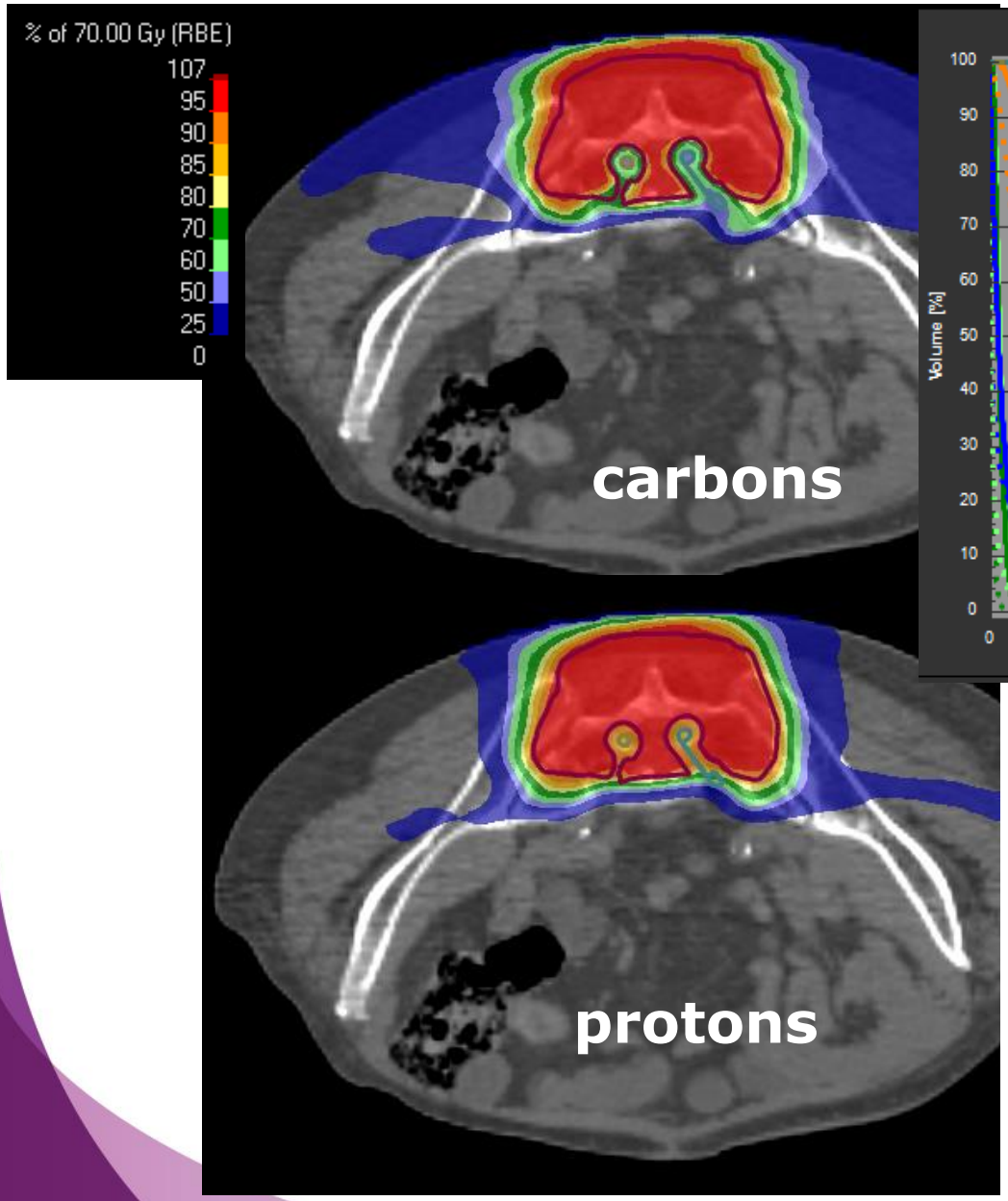


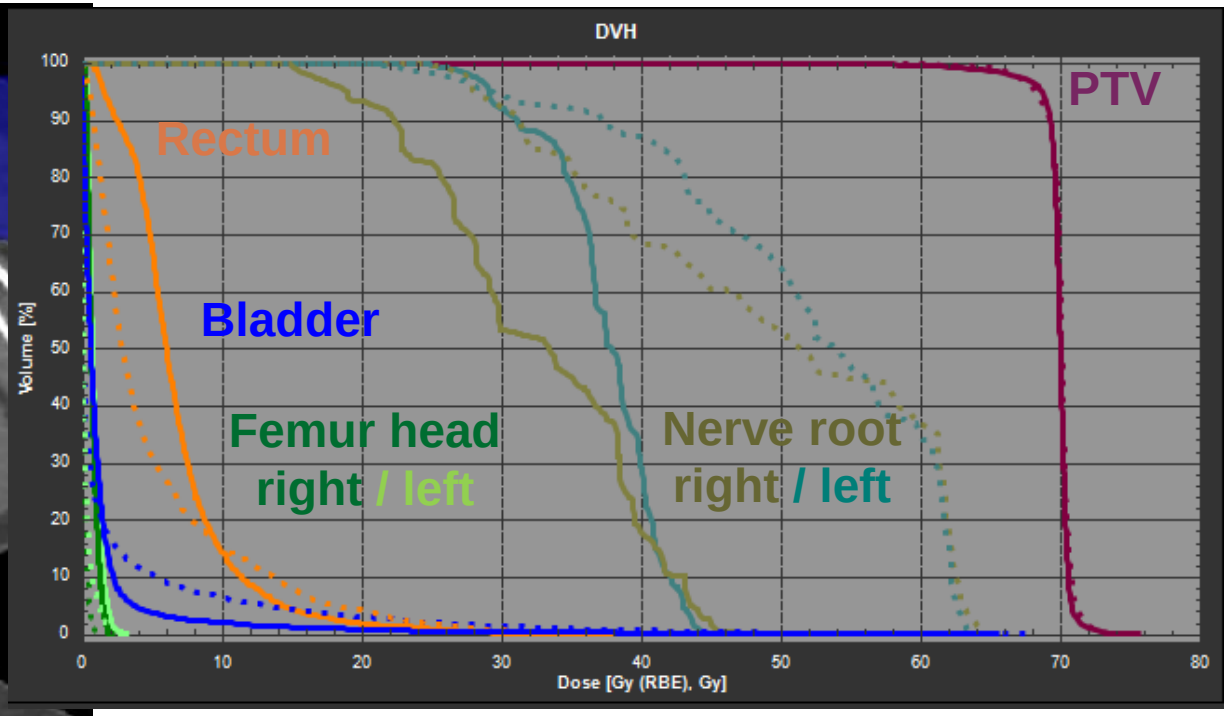


Solid: C

Dotted: p

C vs p: Sacrum





Solid: C

Dotted: p

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Early days at harvard cyclotron laboratory

- In 1973, the radiation oncology department commenced an extensive proton therapy program. The first patient was a 4-year old boy with a posterior pelvic sarcoma.

- The first large-field cancer patient treated at the HCL. Treatment was challenging due to the HCL's fixed horizontal beam when treating with posterior fields.

Some practical aspect in ion beam planning

For plan creation:

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

For plan quality assessment:

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

Conclusion

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

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Introduction Case 2: Brain (meningioma)

ESTRO ATP Athens

September 2018

Ms E, 51 years old

History:

- Partial resection 7 month ago: meningioma WHO grade I
- Partial re-resection 1 month ago: now WHO grade II-III

Histology:

- transition to atypical meningioma and malignant meningioma - WHO grade II-III
- 17 mitoses per 10 high power fields (HPF)

Ms E, 51 years old

Target:

- Residual tumour at left base of skull
- Tumour bed plus
- Margin for extension

Imaging available:

- Planning CT
- MR series (Pre, Post op)
- DOTATOC PET for boost

Ms E, 51 years old

- Complete closure of eye
- Cavernous sinus nerve involvement

- ‘Functionally’ blind in left eye

Not our patient

Courtesy of Google Images

Ms E, 51 years old

- Grade III (malignant or anaplastic) meningioma has a poor outlook

- WHO Grade — 5 year local control
  - I — 90 - 95%
  - II — 40 - 60%
  - III — 20 - 50%

- Grade III often transform from lower grade
- Metastasis seen in (only) 0.1% of cases, all grade III tumours

RT dose

- Some evidence of RT dose response

- Balance between
  - ‘Safe’ dose but with poor effectiveness
  - Higher dose with some risk but higher effectiveness

Imaging Available

Imaging Available

- Planning CT
  - Used for dose calculation and DRR generation for setup
  - CT can also show bone involvement

- MR series
  - Crucial to delineate tumour, but difficulty with ‘tail’

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Imaging Available

- Planning CT
  - Used for dose calculation and DRR generation for setup
  - CT can also show bone involvement
- MR series
  - Crucial to delineate tumour, but difficulty with ‘tail’
- DOTATOC PET for boost
  - Somatostatin analogue
  - Useful to show extent of tumour

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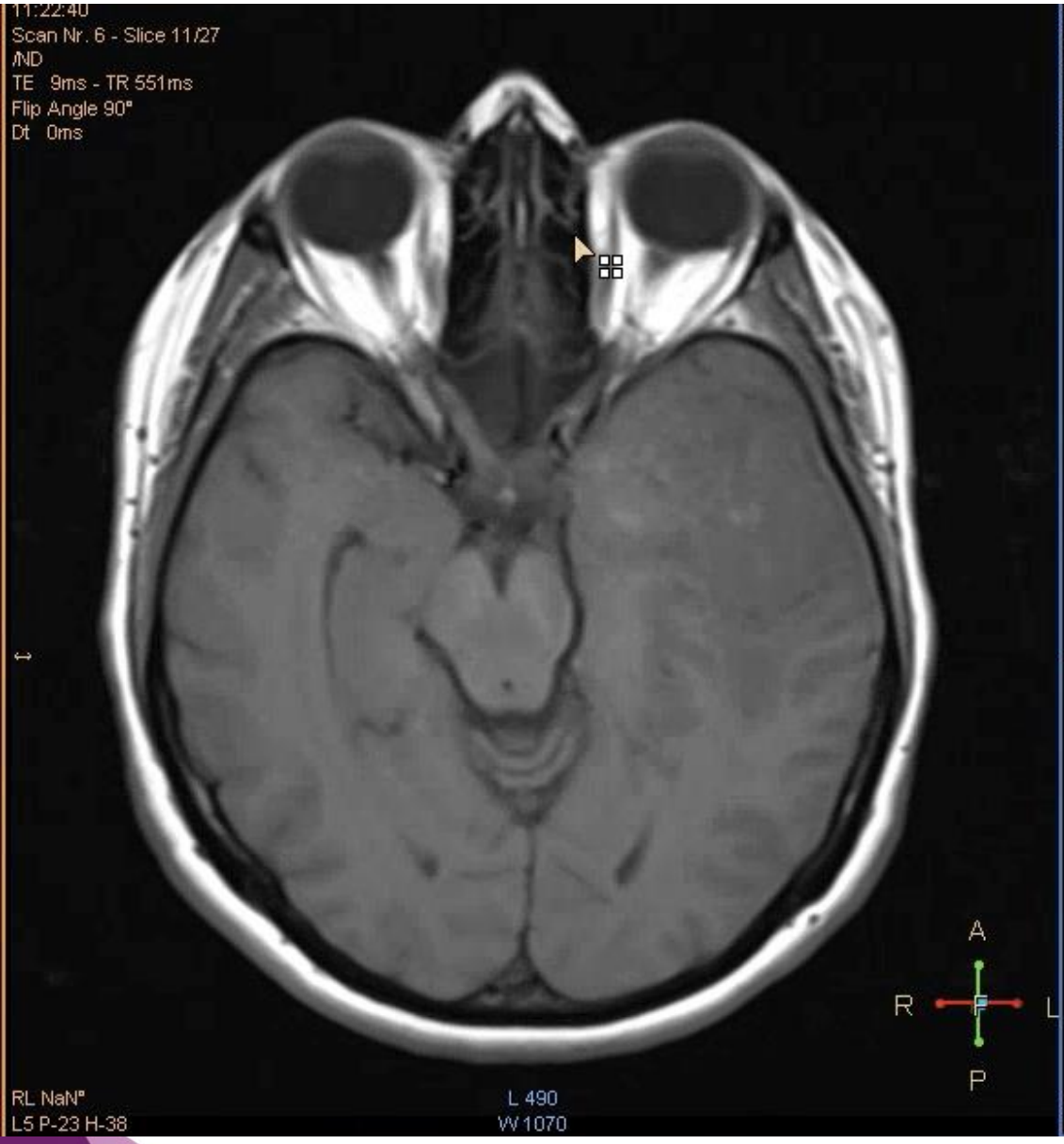
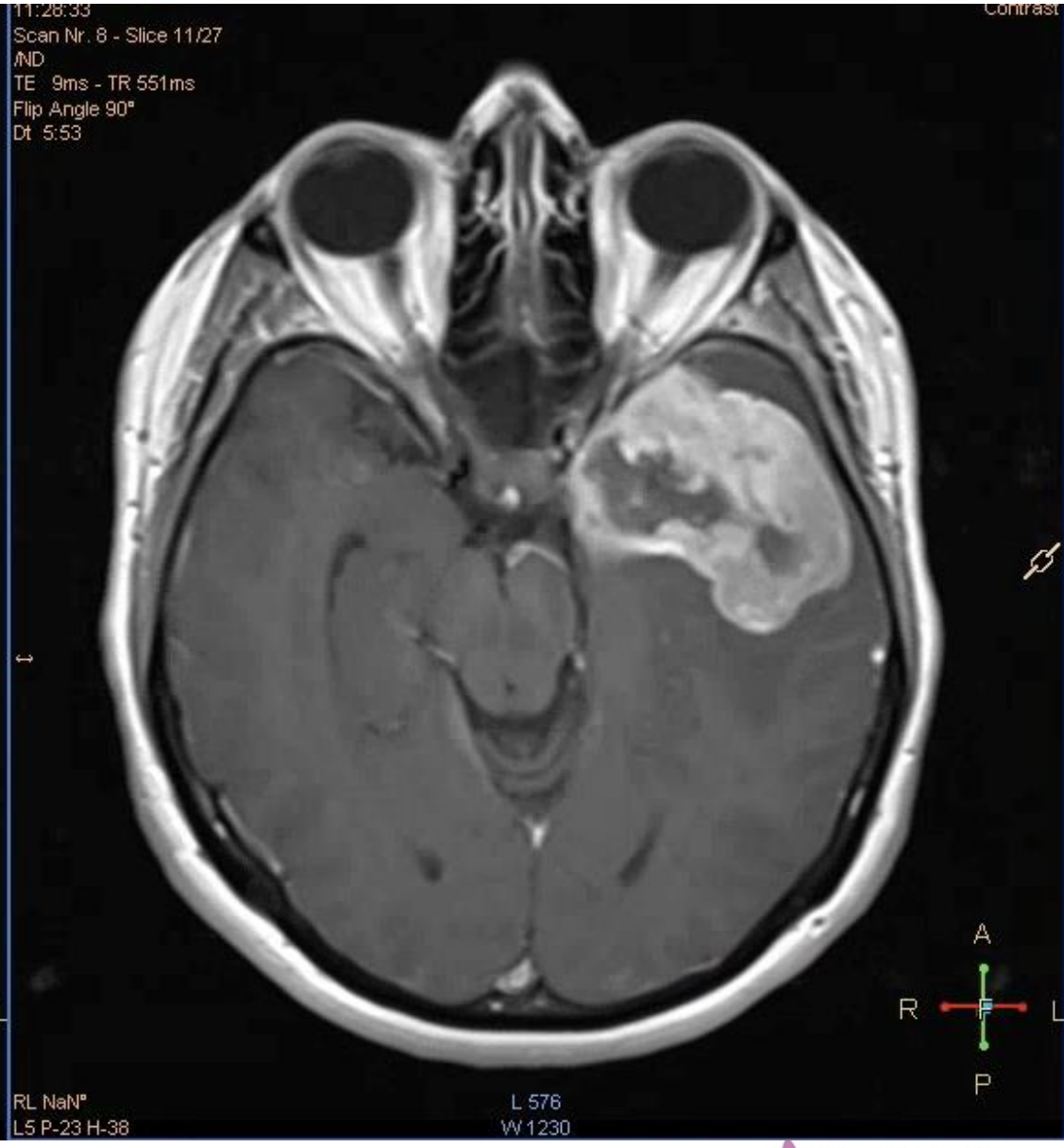
Pre-Operative Imaging





T1 Pre-Contrast

T1 Post-Contrast

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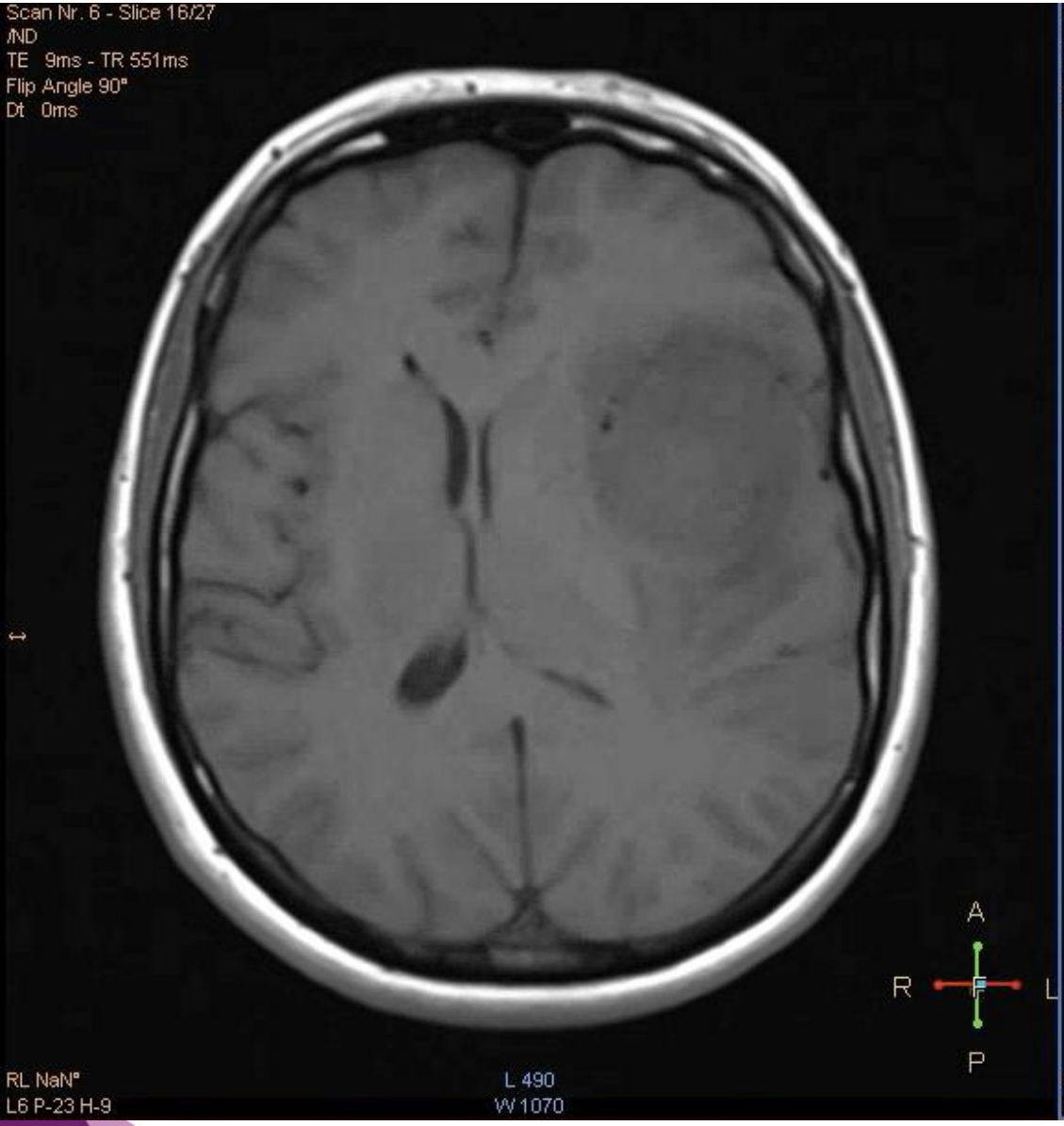
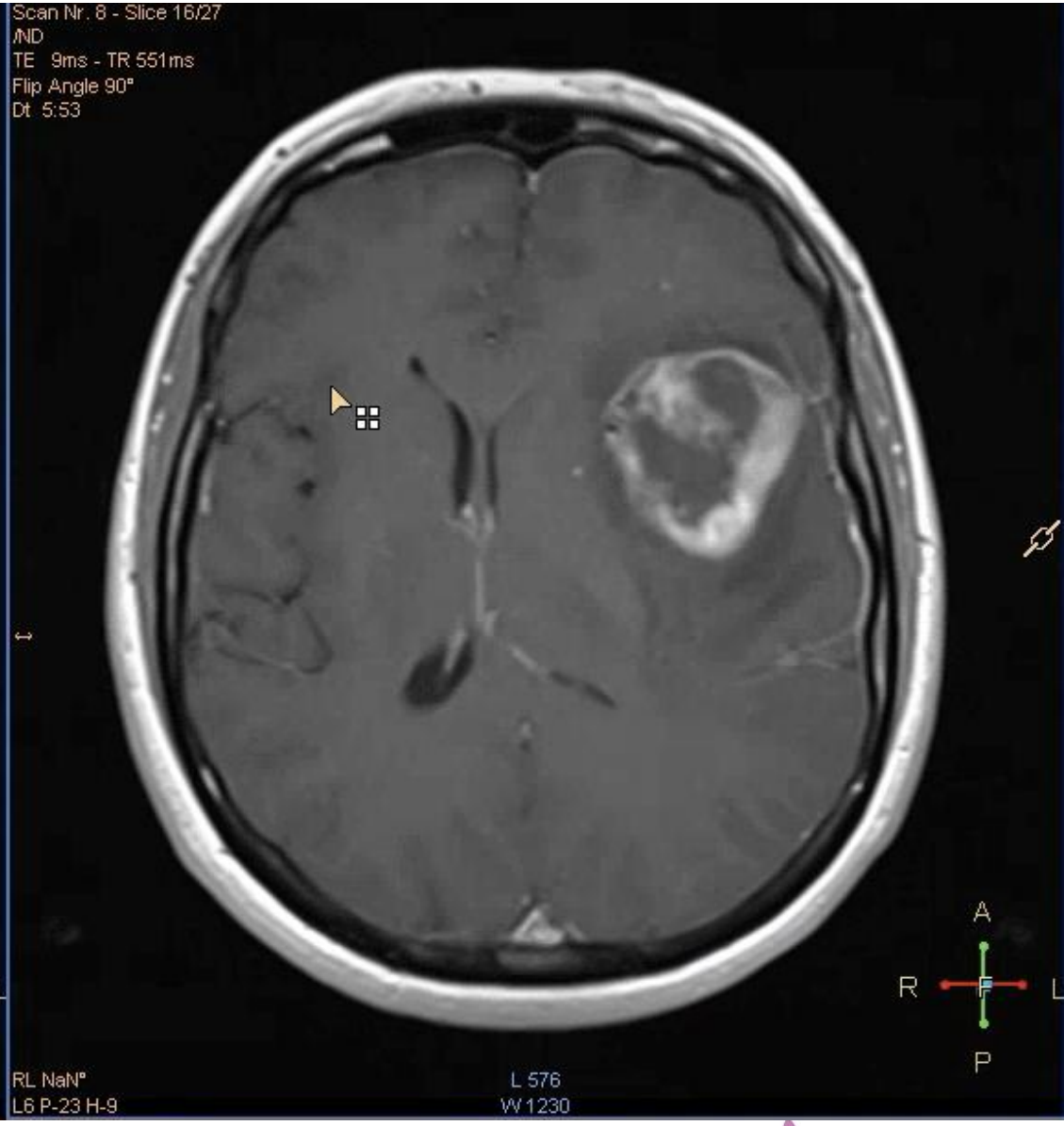
Pre-Operative Imaging





T1 Pre-Contrast

T1 Post-Contrast

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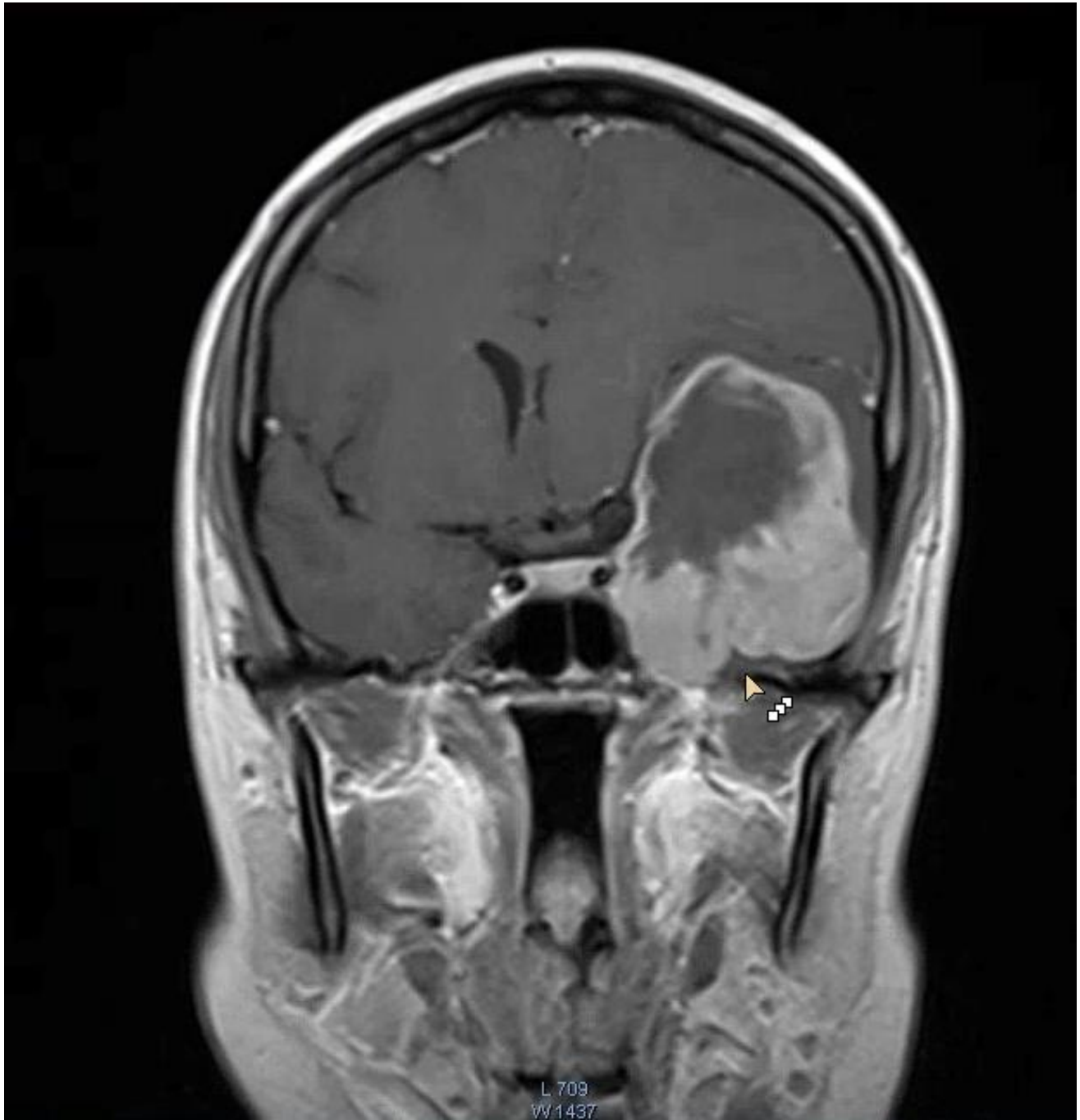
Pre-Operative Imaging



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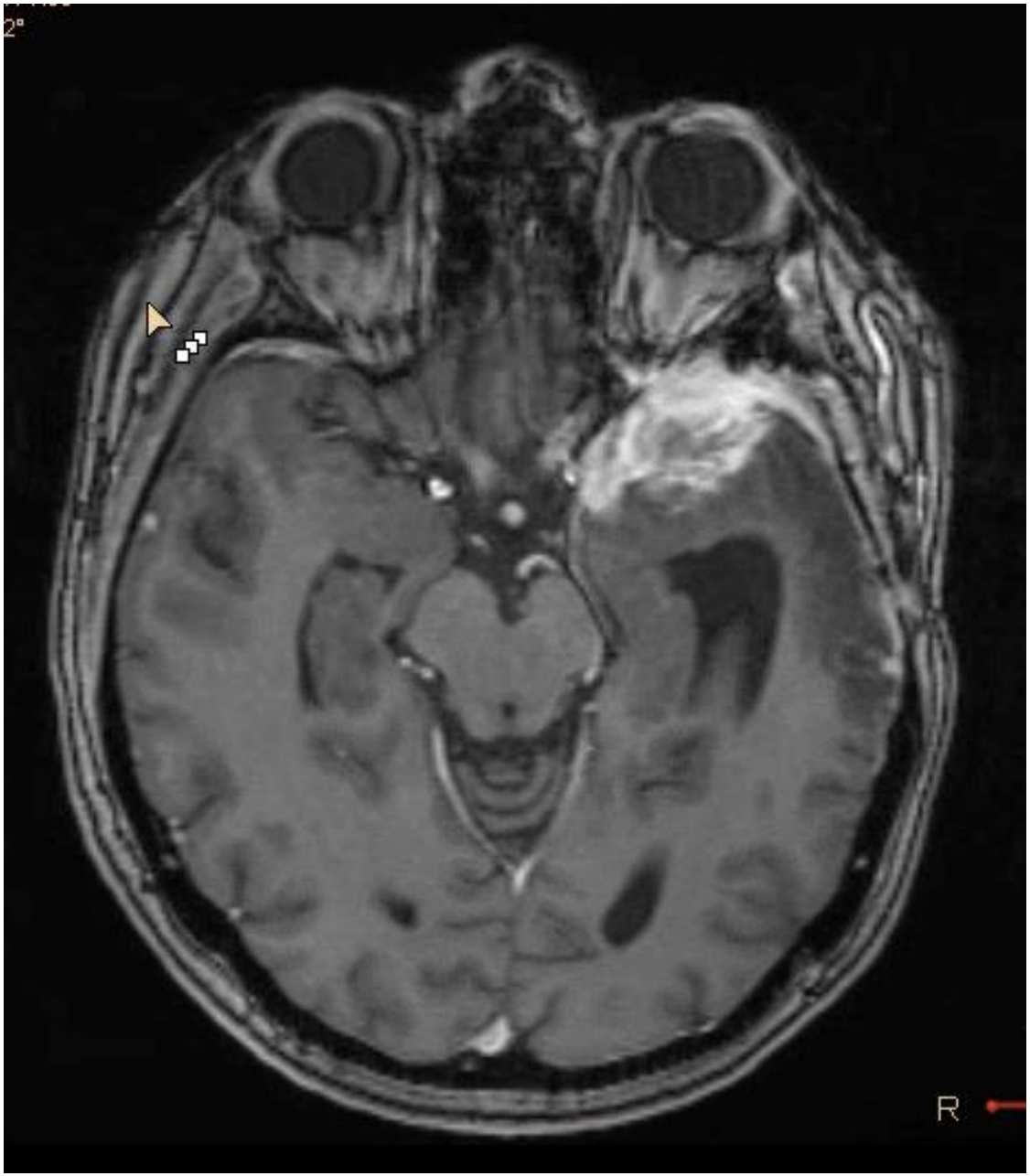
Pre-Second Operative Imaging



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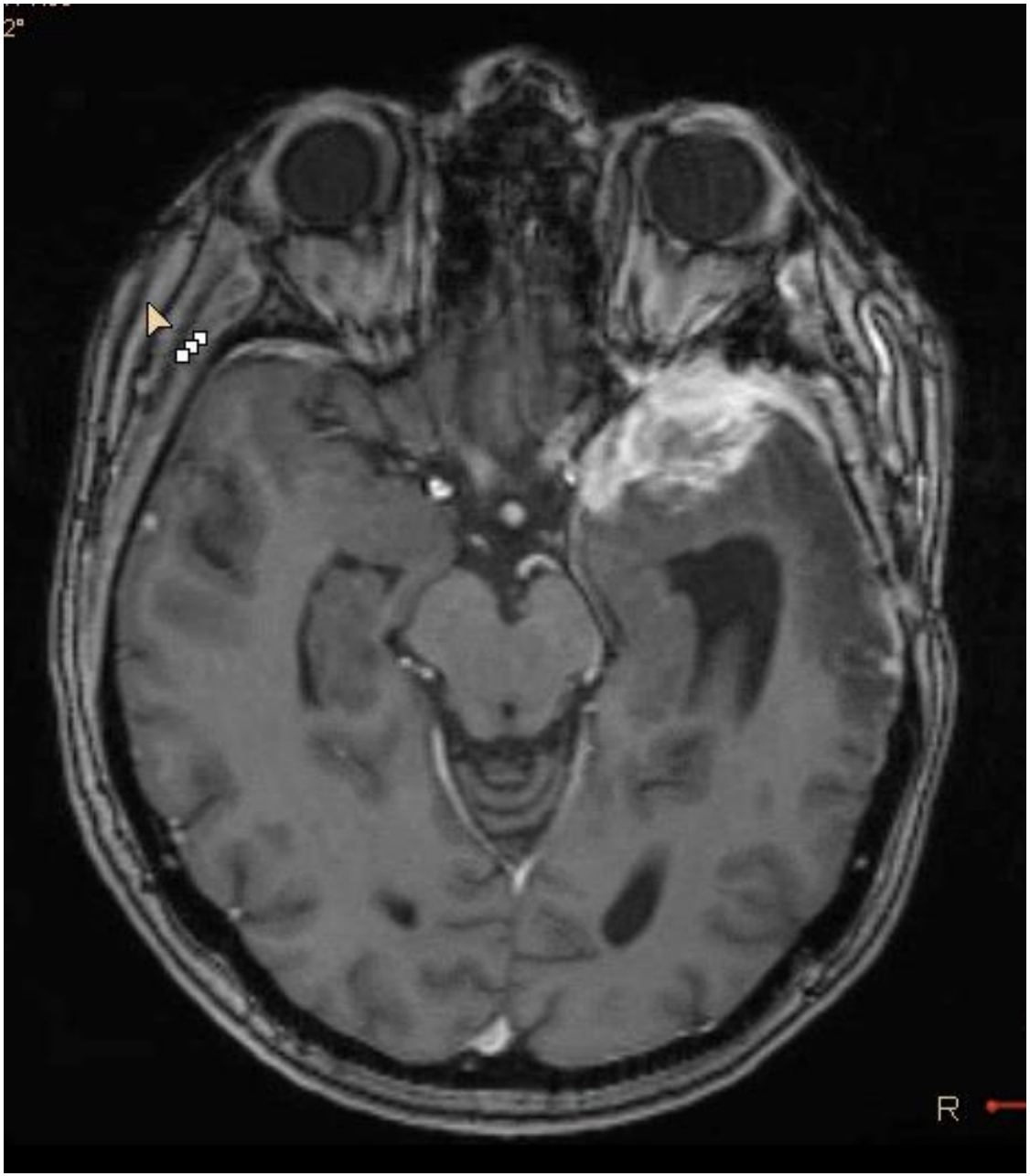
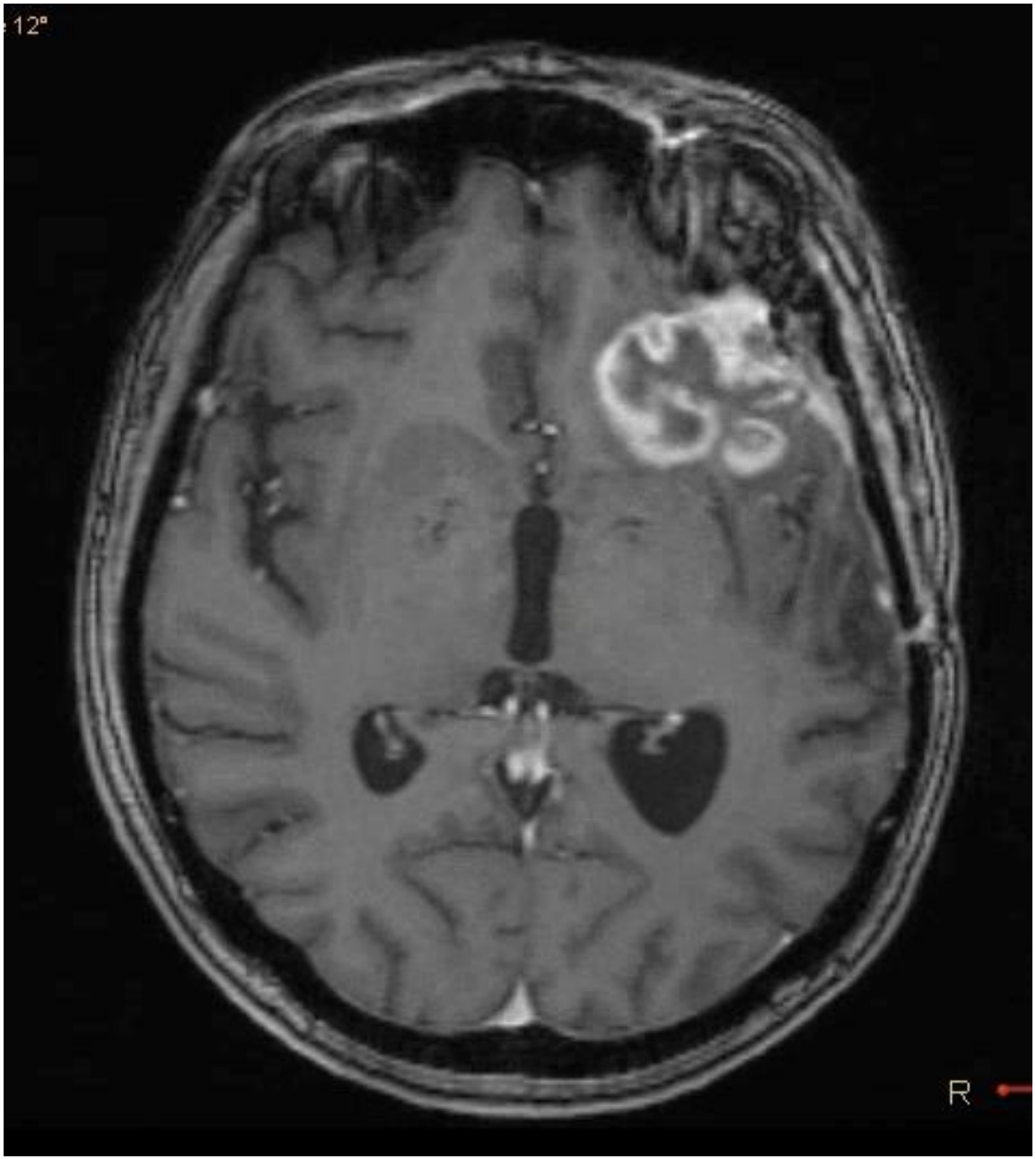
Pre-Second Operative Imaging



Pre-Second Operative Imaging



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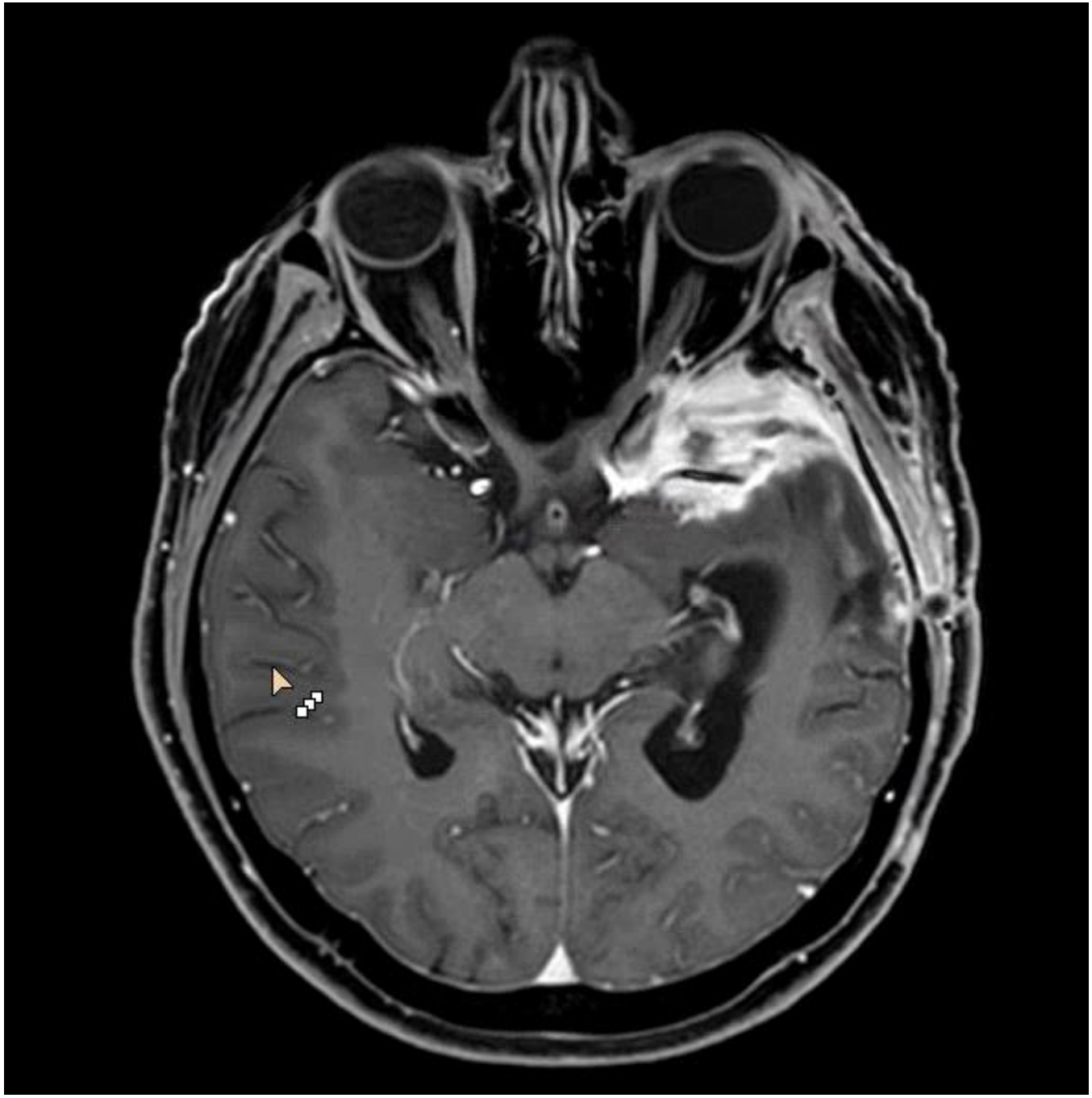
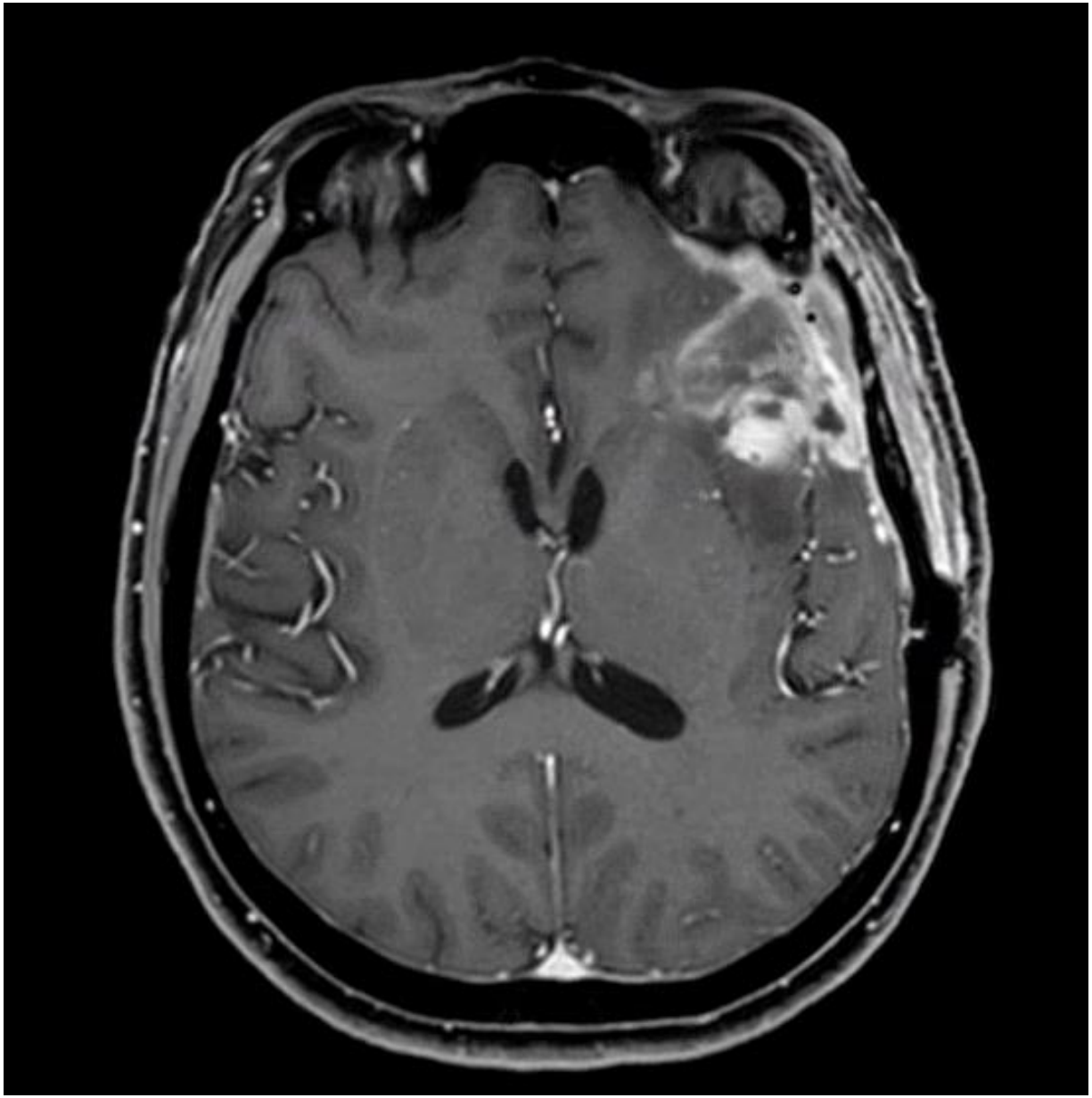
T1 – Planning Scan

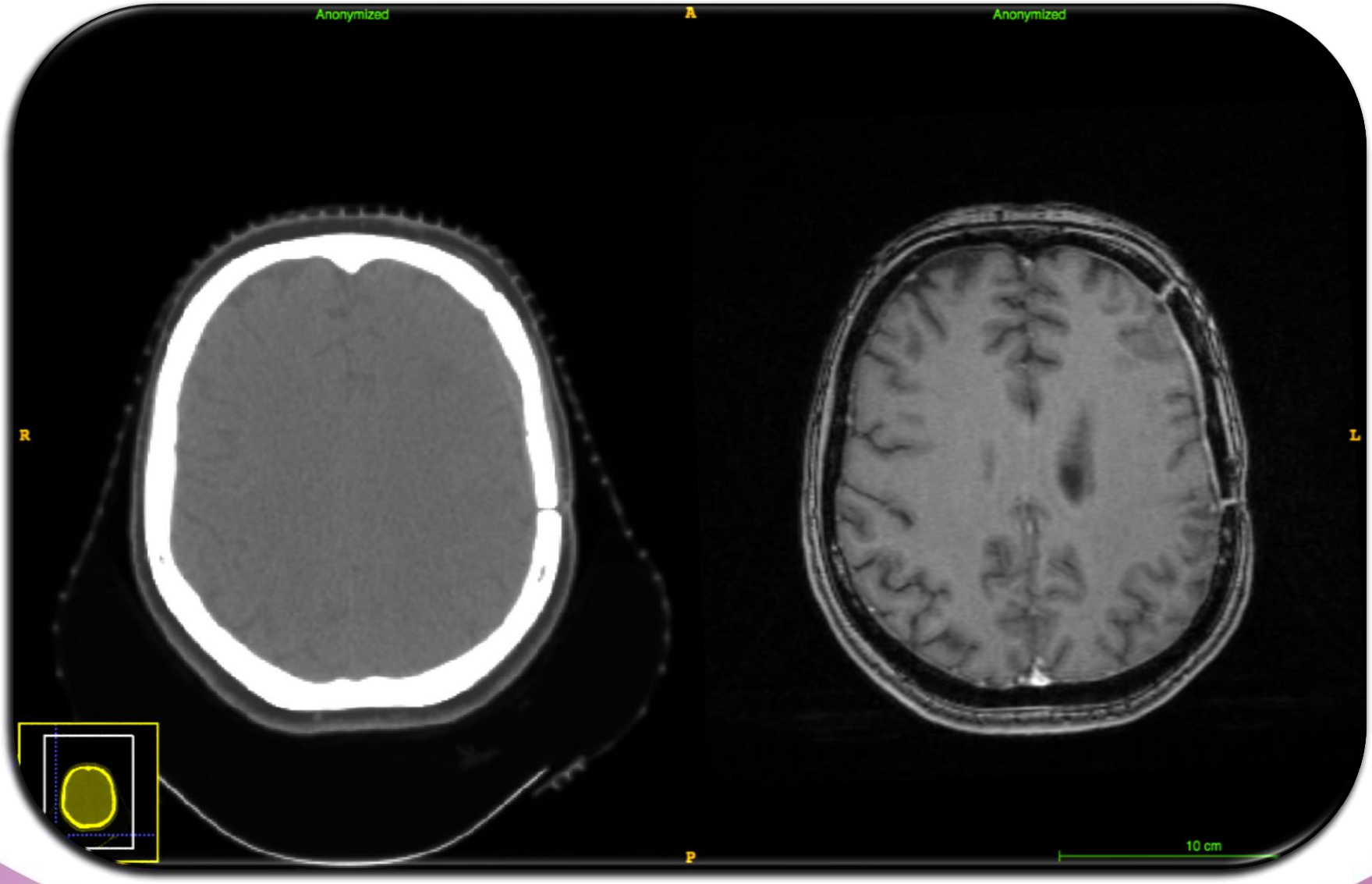


T1 – Planning Scan



Planning-CT and -MRI

CT MRI



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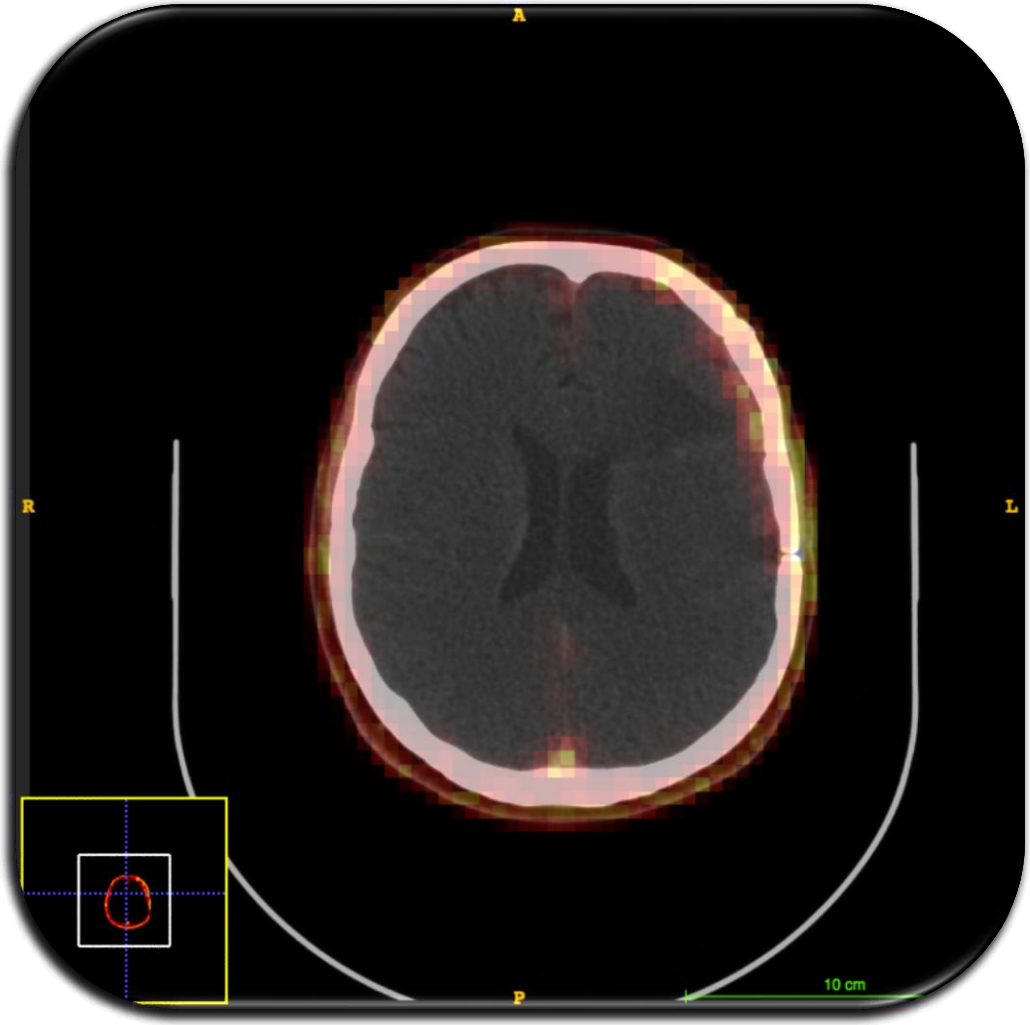
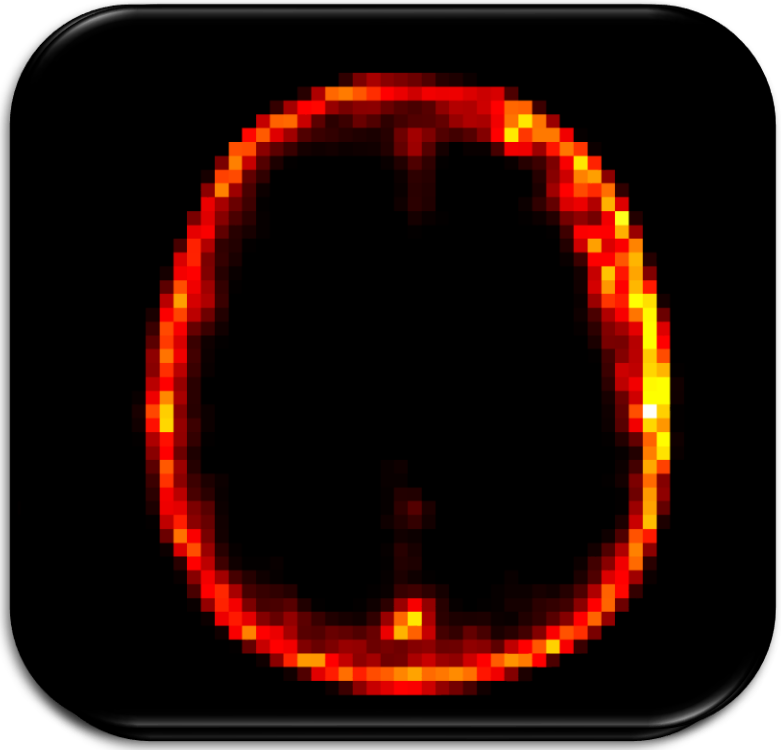
Functional Imaging – Dotatoc PET





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Risks of normal tissue damage

- Specify endpoint
  - Brain necrosis ≠ cognitive dysfunction

- Often 'extra' sparing by reduced dose/#

- Achieve reduced dose per fraction when give less than 100% to an OAR
  - Reduced total dose
  - Reduced dose/fraction

    → 'double sparing'

Meningioma RT – Organs At Risk constraints

Organ	Clinical Constraint PBT [IMRT]
Brainstem	D2% < 63 Gy [< 58 Gy]
Brainstem center	D2% < 54 Gy [=]
Spinal cord	D2% < 63 Gy [< 58 Gy]
Spinal cord center	D2% < 54 Gy [=]
Opticus L/R	D2% < 56 Gy [=]
Chiasm	D2% < 56 Gy [=]
Bulbus L/R	D2% < 45 Gy, Dmean < 30 Gy

NB constraints apply to 39#

Organ	Clinical Constraint
Skin	D20cm^2 < 60 Gy (surface dose)
Temp Lobe L/R	D2cm^2 < 72 Gy
Cochlea R	Dmean < 30 Gy
Parotis L/R	Dmean < 26 Gy
Larynx	Dmean < 50 Gy; V50 Gy < 30%
Mandible	D2% < 70 Gy
Hippoc. L/R	D100% < 10 Gy; D2% < 16 Gy
Lacr.gl. L/R	Dmean < 26Gy
Retina L/R	D2%<45Gy

Meningioma RT – session objectives

PTV				
		PTV1	PTV3	
Prescription (GY(RBE)) ($D_{RBE, 50\%}$)		54.0 Gy	70.2 Gy	
Number of fractions		39	39	
$V_{95\%}$	= 100%	100 %	100 %	
$D_{RBE, 98\%}$	≥ 95%	>95%	>95%	
$D_{RBE, 2\%}$	< 107%	<107%	<107%	
CTV				
$V_{95\%}$	= 100%	100%	100 %	
$D_{RBE, 98\%}$	≥ 95%	>95%	>95%	
$D_{RBE, 2\%}$	< 107%	<107%	<107%	

- Techniques:
  - IMRT
  - VMAT
  - Tomo
  - Protons

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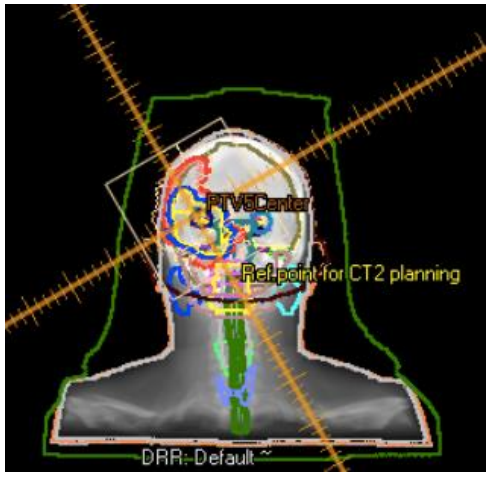
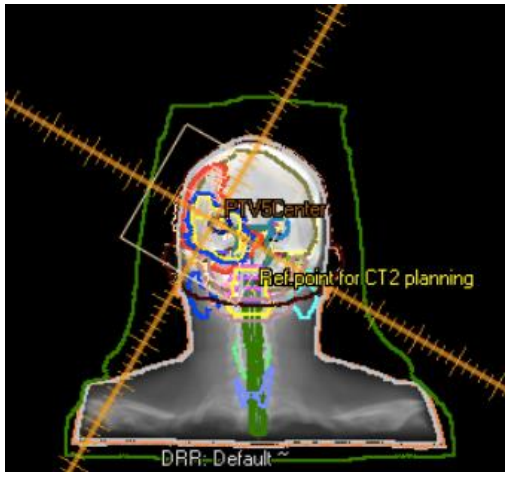
Suggestions

- Single phase (i.e. SIB) - 54Gy to PTV1, 70.2Gy to PTV3 in 39#
  - (original as 2 phase plan - 54/30# to PTV 1 + 16.2/9# to PTV3)
- S&S IMRT : 9 beams (maybe non-coplanar ?)
- VMAT: at least 2 full arcs for PTV1 & PTV3 or sequential half arcs for PTV3
- Put priority on PTV coverage
- Slightly turn collimator (20-30 degrees)





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

Good luck!

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Extra slides in case of questions

Meningioma RT – Organs At Risk constraints

Organ	Clinical Constraint PBT [IMRT]	Alpha:beta ratio
Brainstem	D2% < 63 Gy [< 58 Gy]	2.5
Brainstem center	D2% < 54 Gy [=]	2.5
Spinal cord	D2% < 63 Gy [< 58 Gy]	0.89
Spinal cord center	D2% < 54 Gy [=]	0.89
Opticus L/R	D2% < 56 Gy [=]	1.6
Chiasm	D2% < 56 Gy [=]	1.6
Bulbus L/R	D2% < 45 Gy, Dmean < 30 Gy	
Brain		2.9

NB constraints apply to 39#

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Basic principles of rotational IMRT planning

Gert Meijer

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Rotational IMRT not really new

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

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

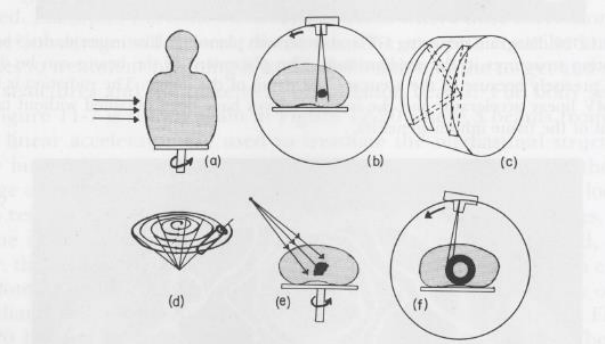

Figure 12-22. Diagrams illustrating the various types of rotation therapy.

Courstesy of Dirk Verellen

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

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

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

(An invited contribution for the Diamond Jubilee Number)

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

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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

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

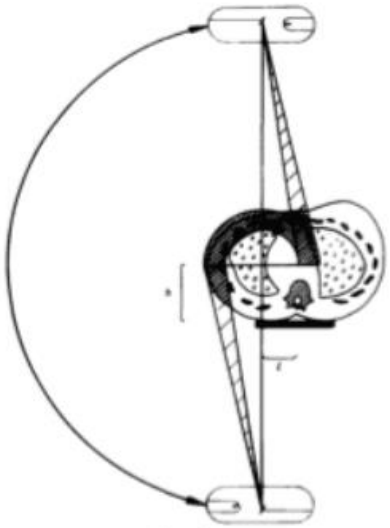


FIG. 1.

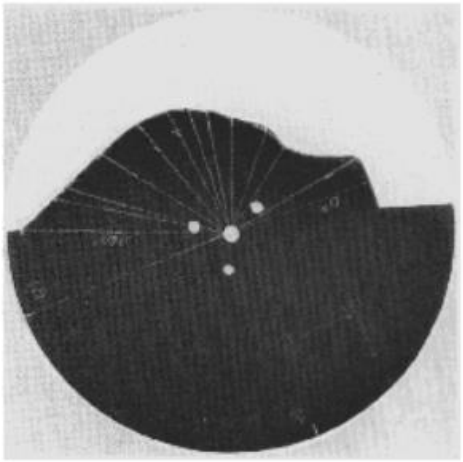


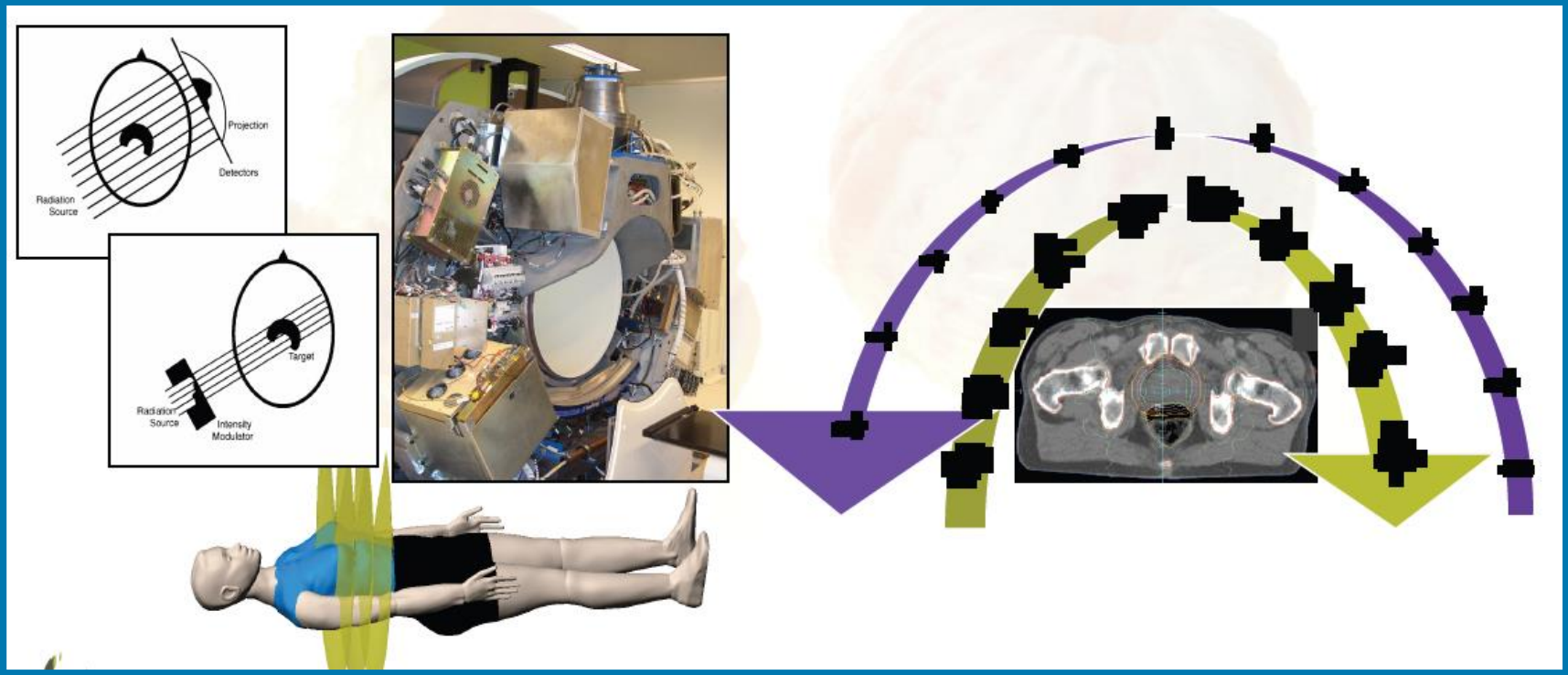
FIG. 2.

British Journal of Radiology, 1956

(1944, Wachsmann, Pendulum unit)

Courstesy of Dirk Verellen

fan beam vs VMAT



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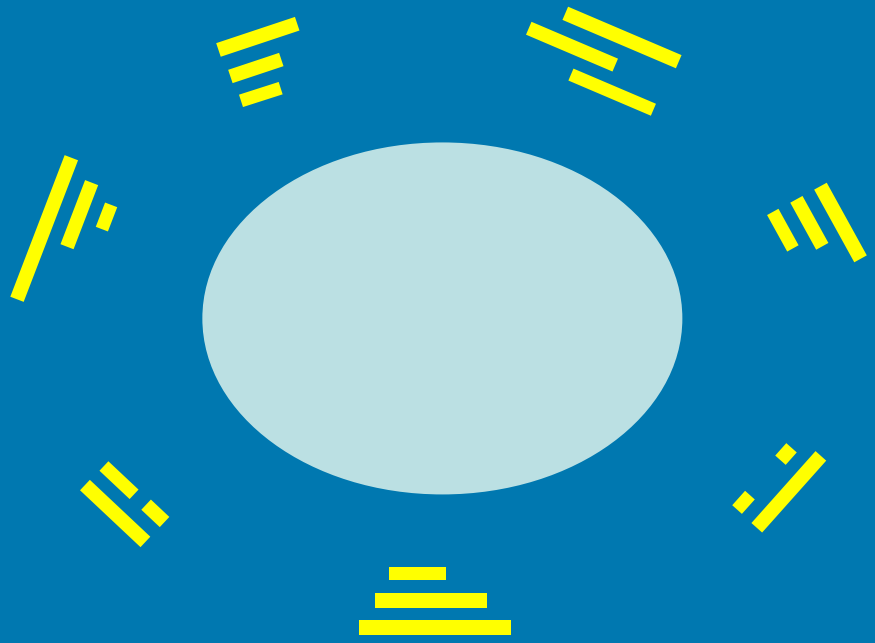
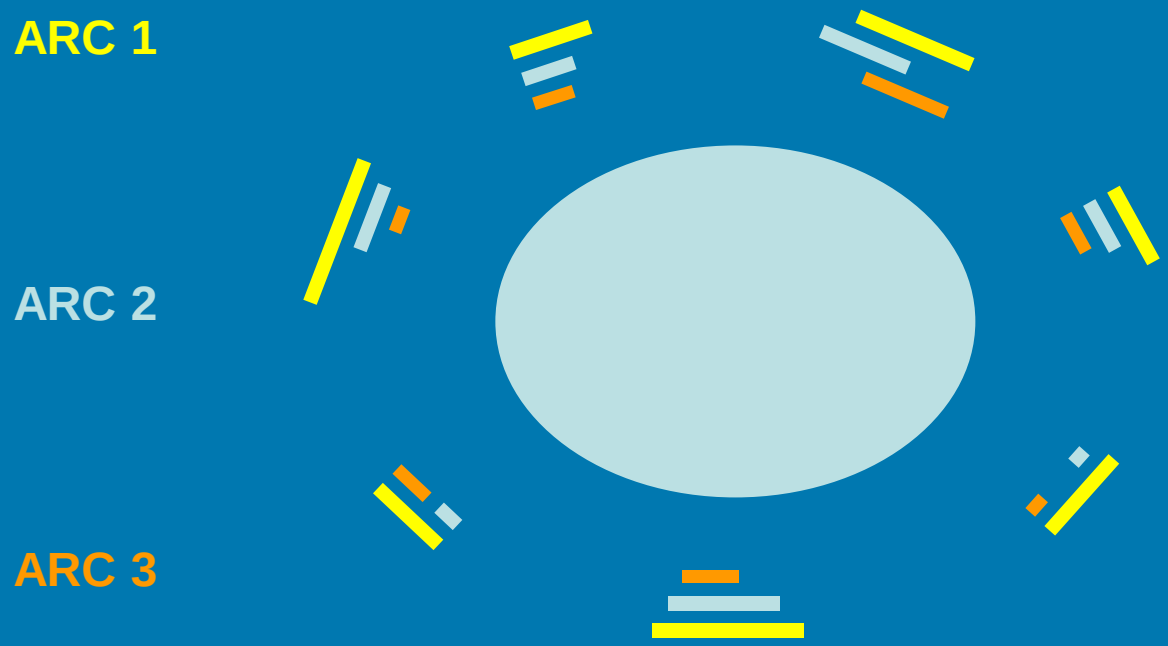
IMRT

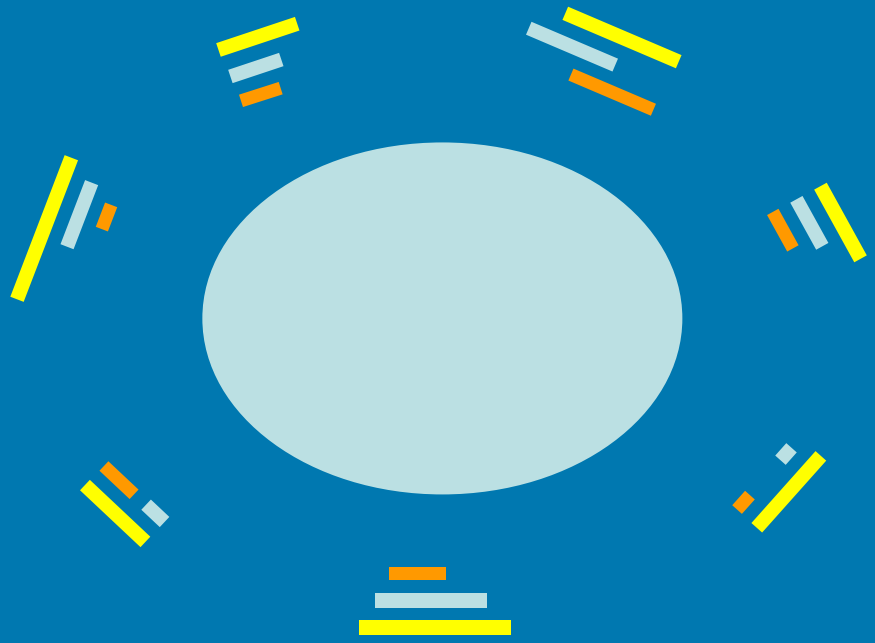


IMAT



from 3 arcs to a single arc

moving from stacked to spaced



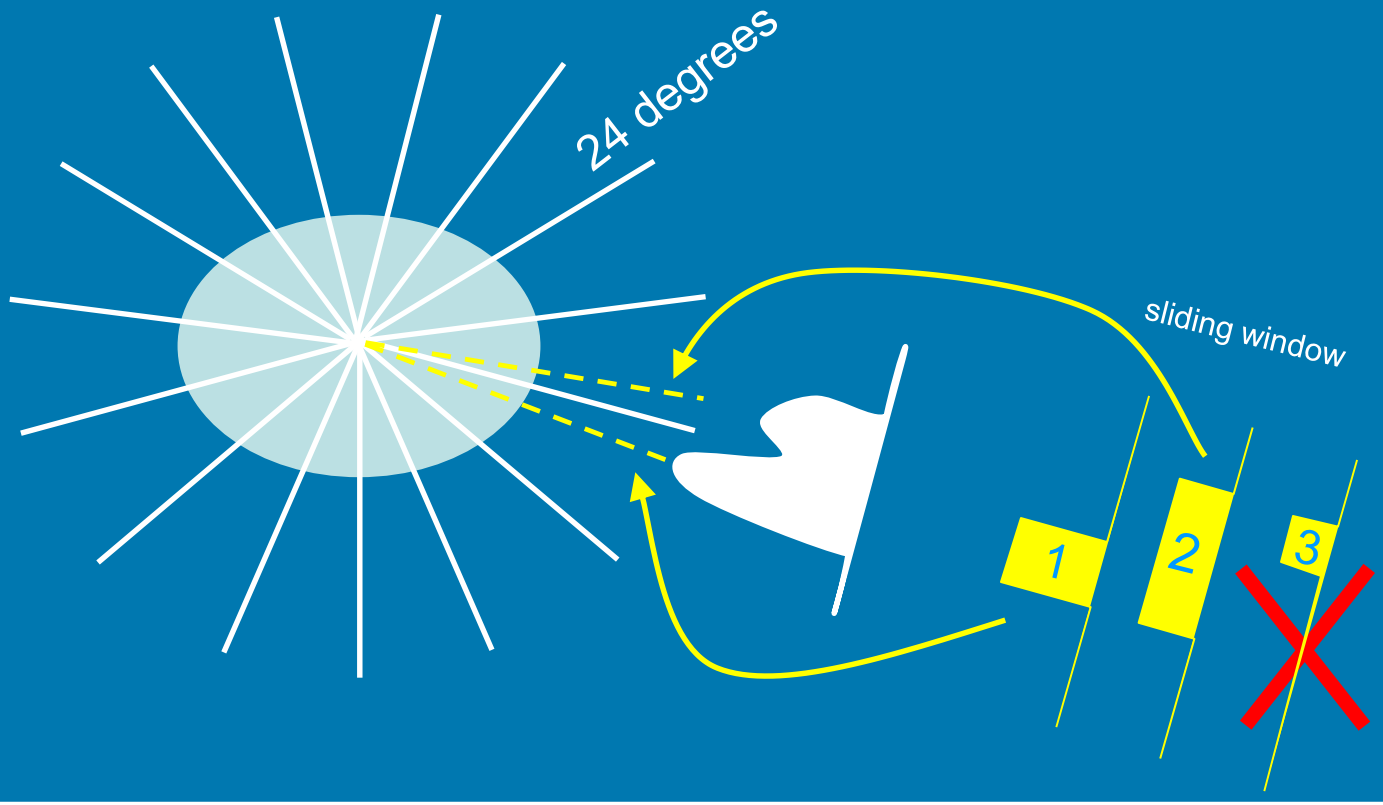
Tang *et al.* (IJROBP 2007)

So….

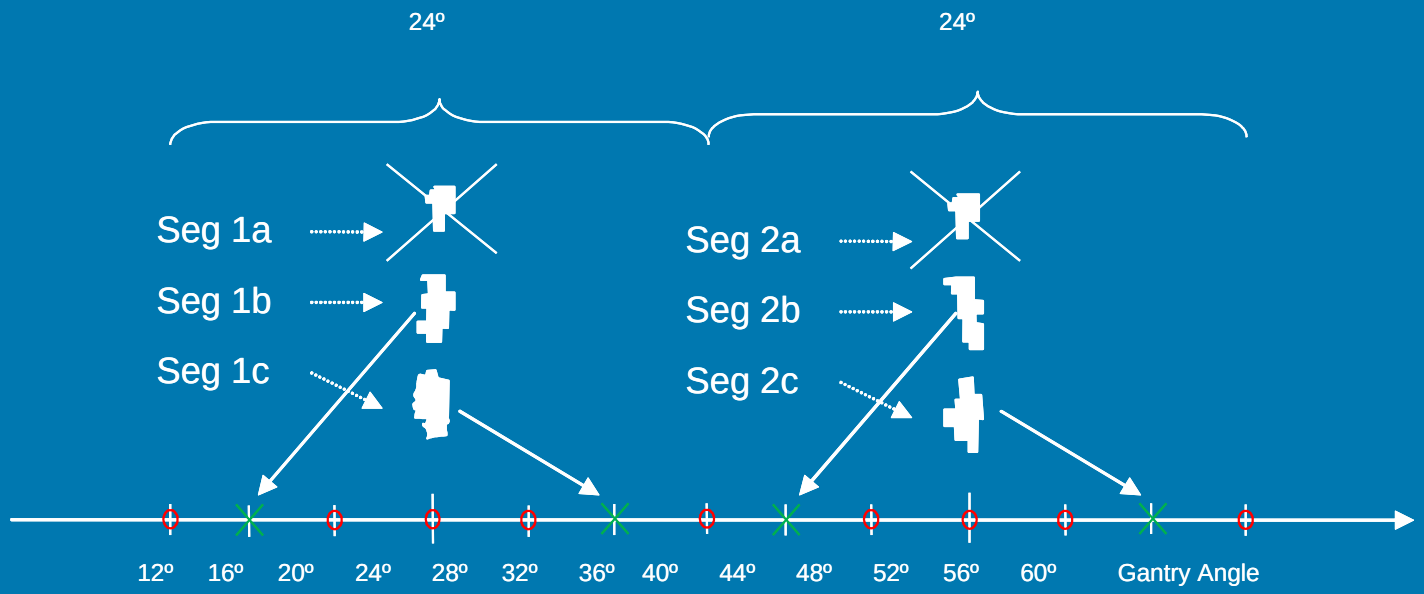
rotational therapy is rather insensitive to angle deviations

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

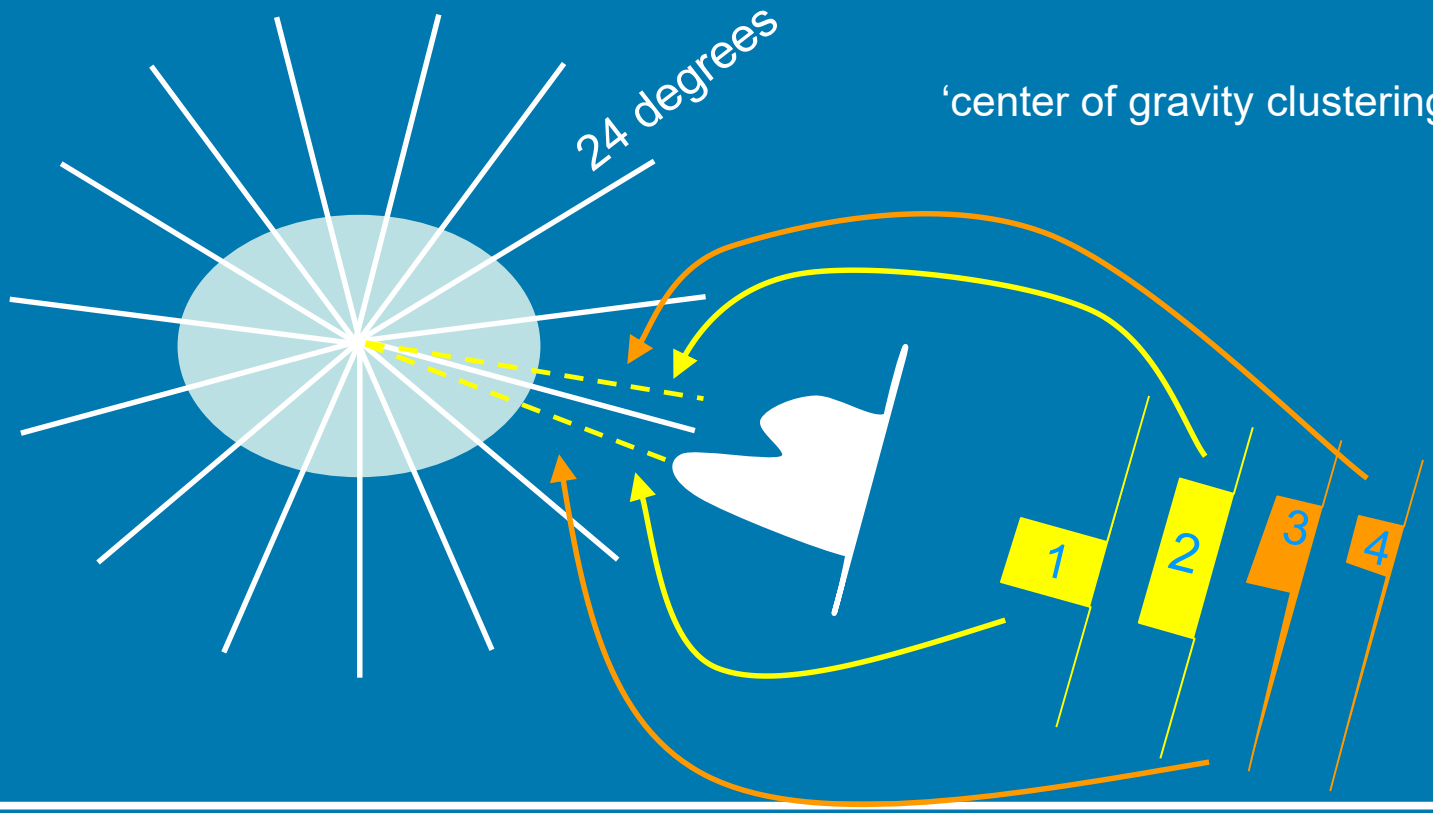
So how does is work in practise?



Segmentation



How about dual arcs?




IMRT
VMAT

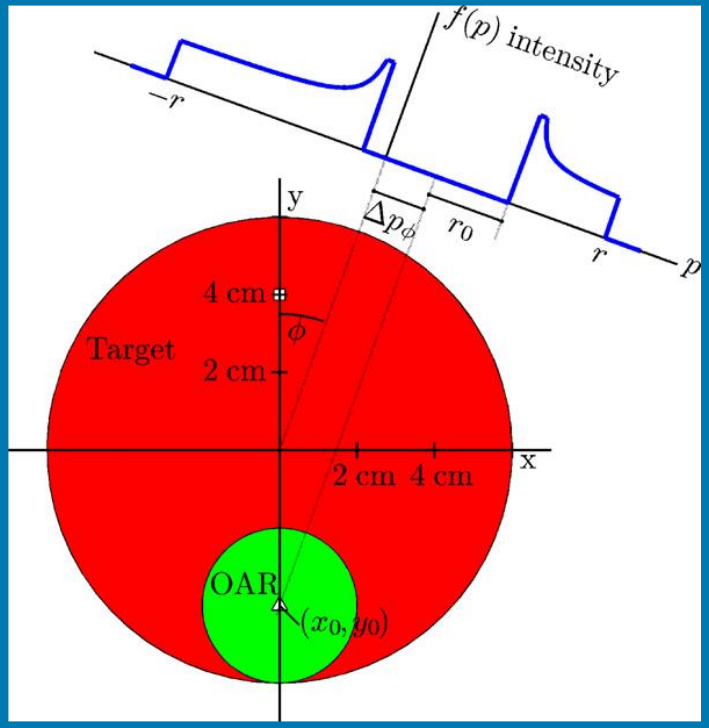
Static IMRT vs VMAT - Conceptual issues

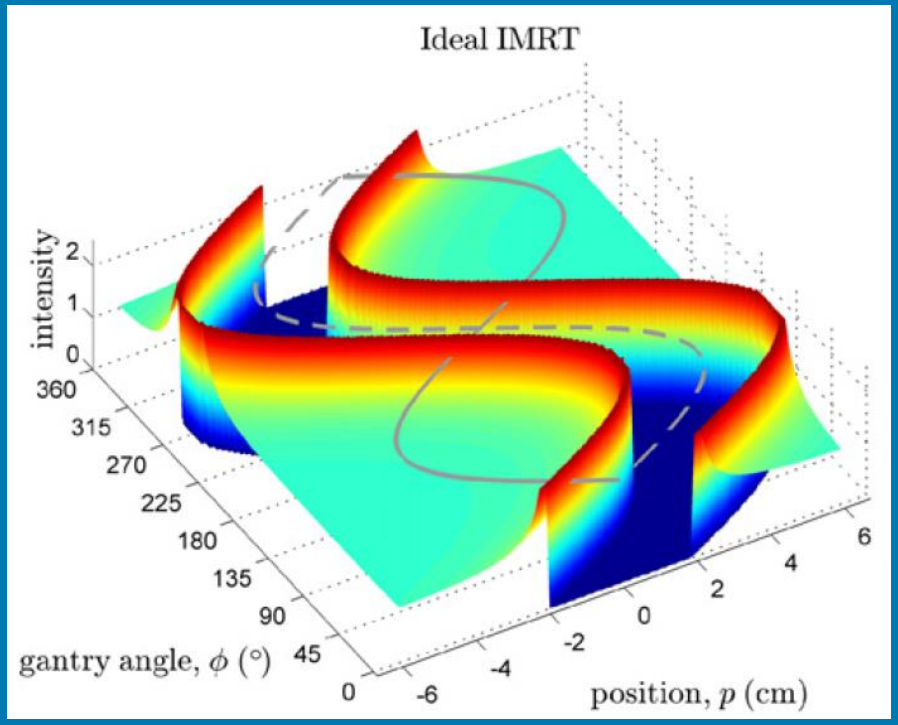
Is there any difference between static IMRT and VMAT?

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

Courstesy of Jochem Wolthaus

IMRT vs. VMAT - Conceptual differences

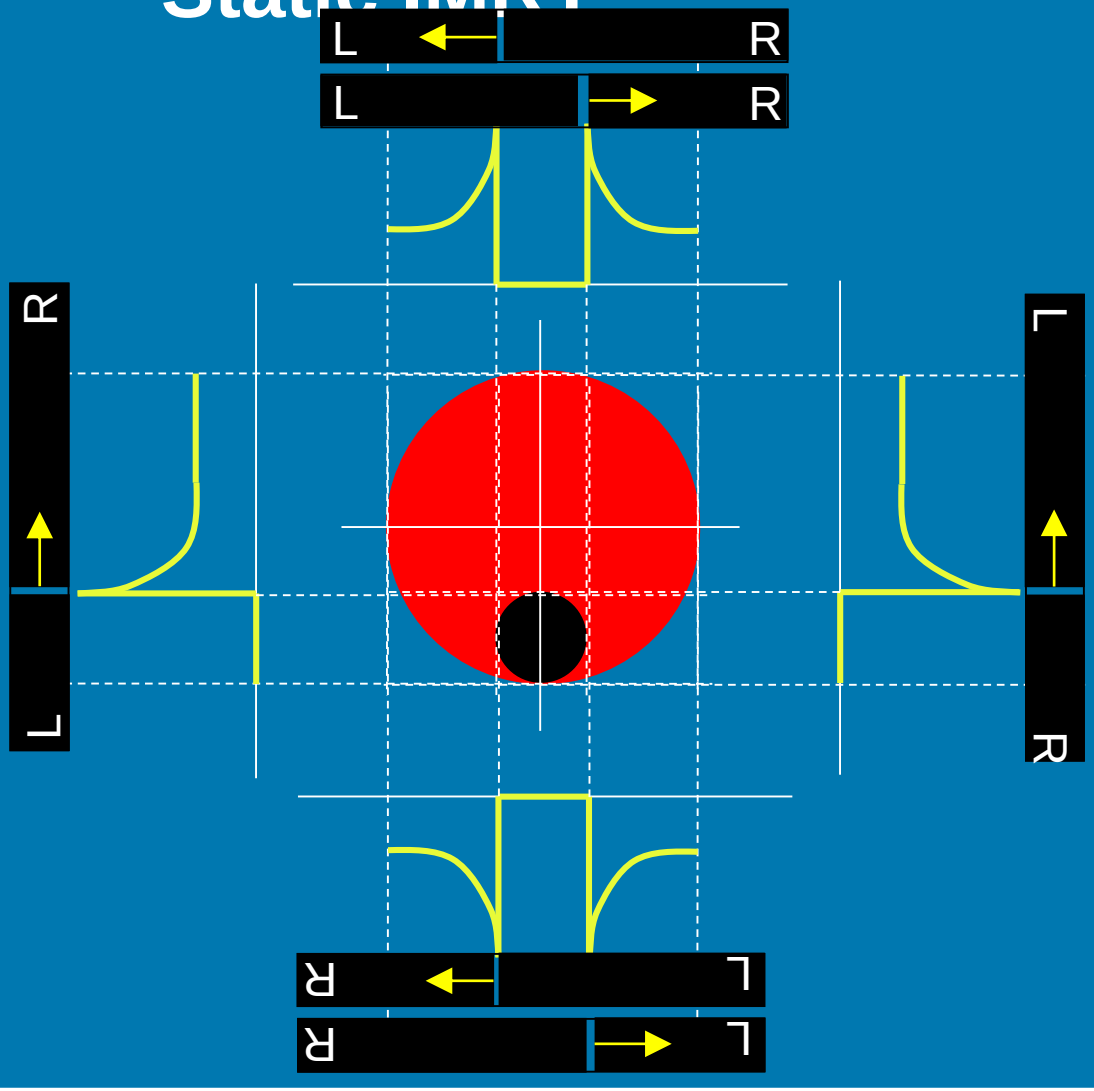


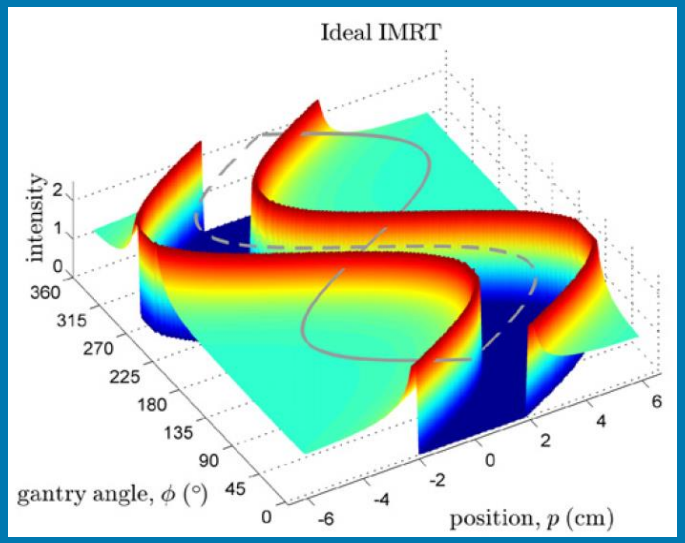


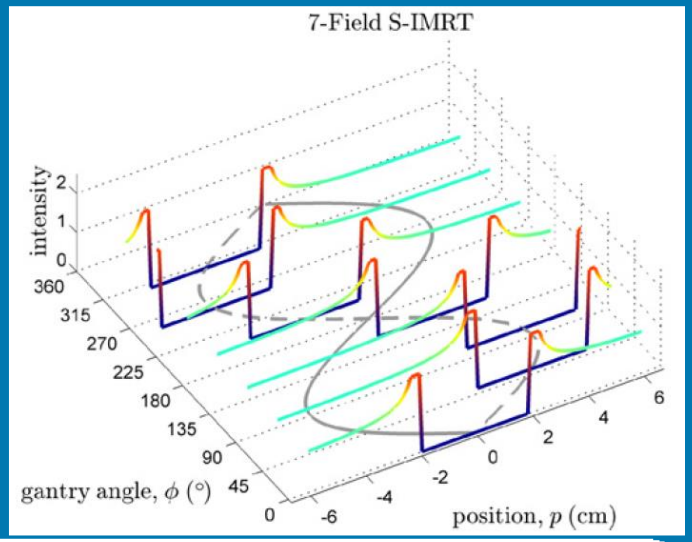
Bortfeld and Webb (2009) explaining VMAT by Brahme's IMRT case (1982). Target volume is wrapped around an OAR. Analytical solution is known

Courstesy of Jochem Wolthaus

Static IMRT







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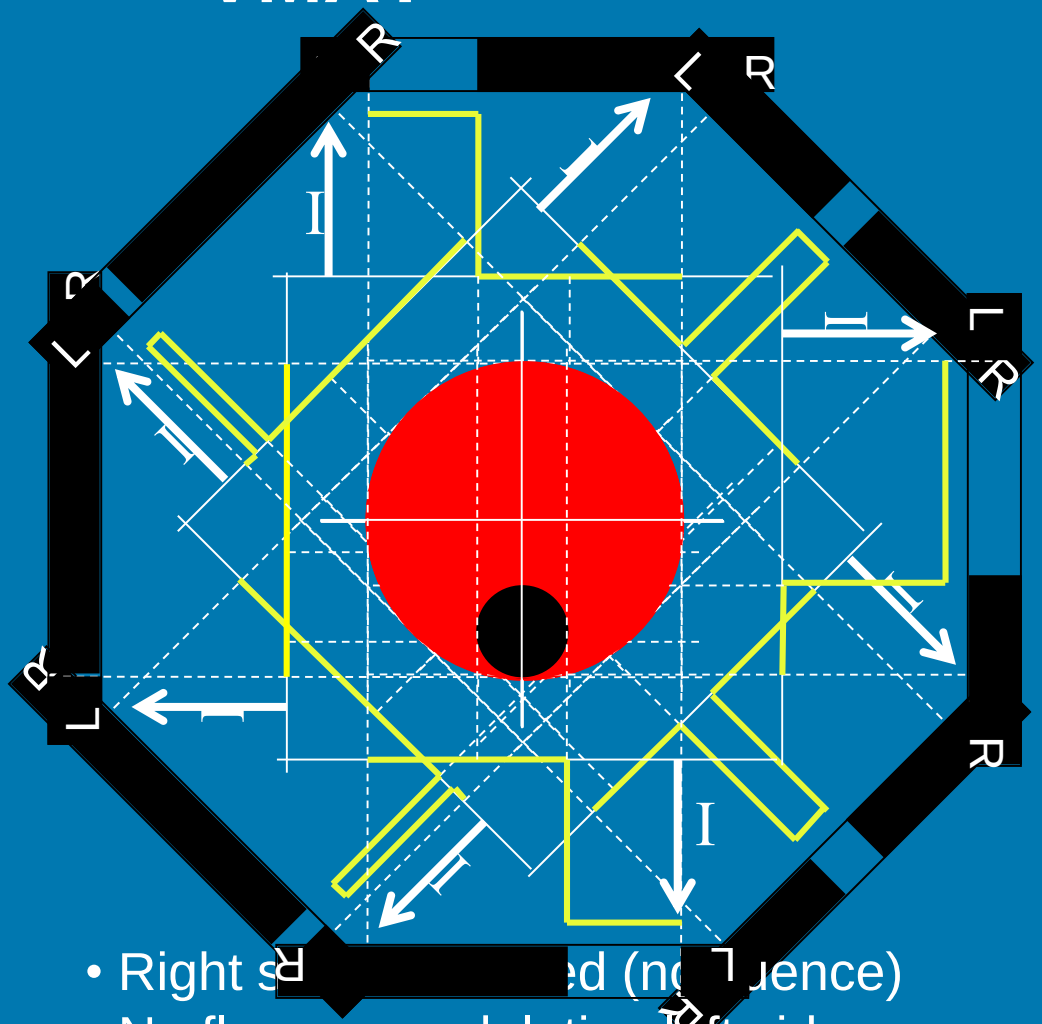
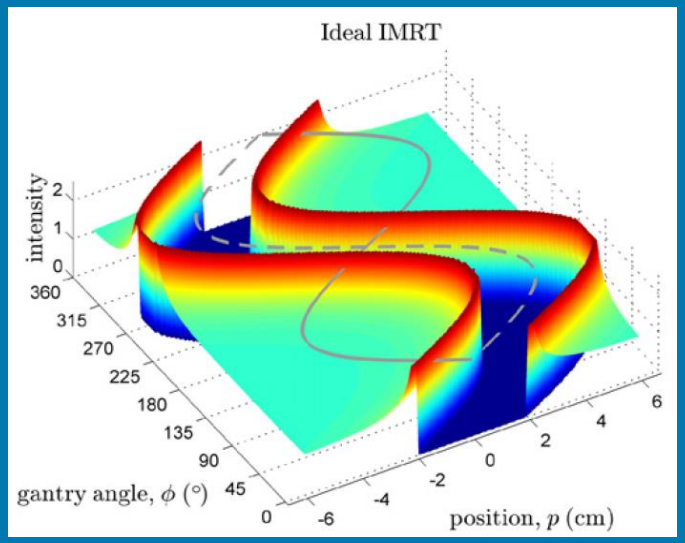
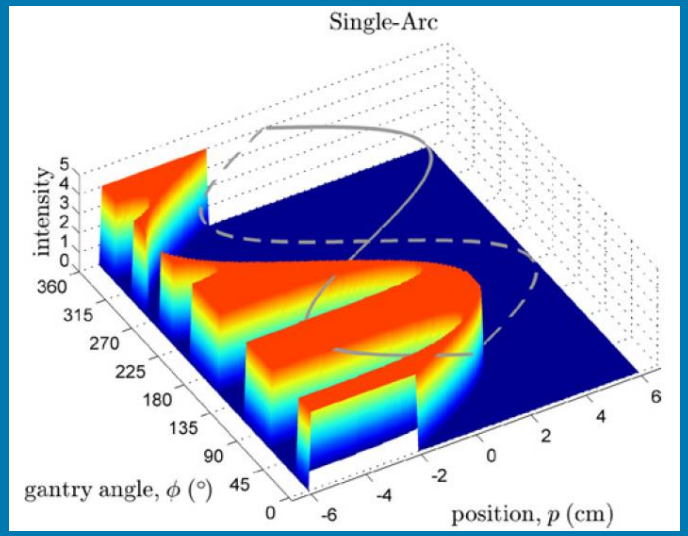
VMAT







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

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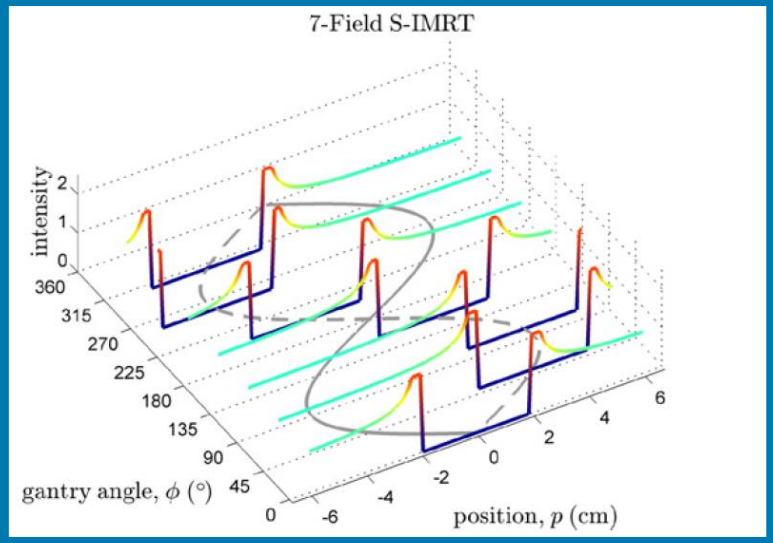
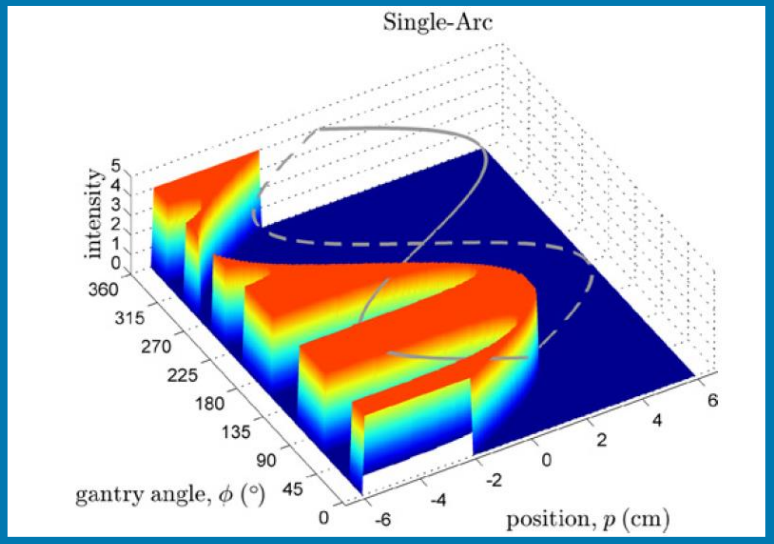
IMRT vs. VMAT - Conceptual differences



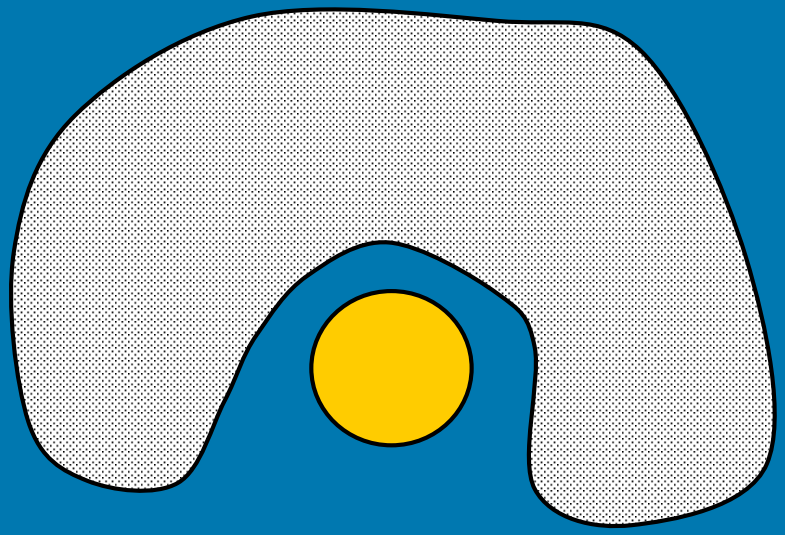


Compromises in different areas:

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

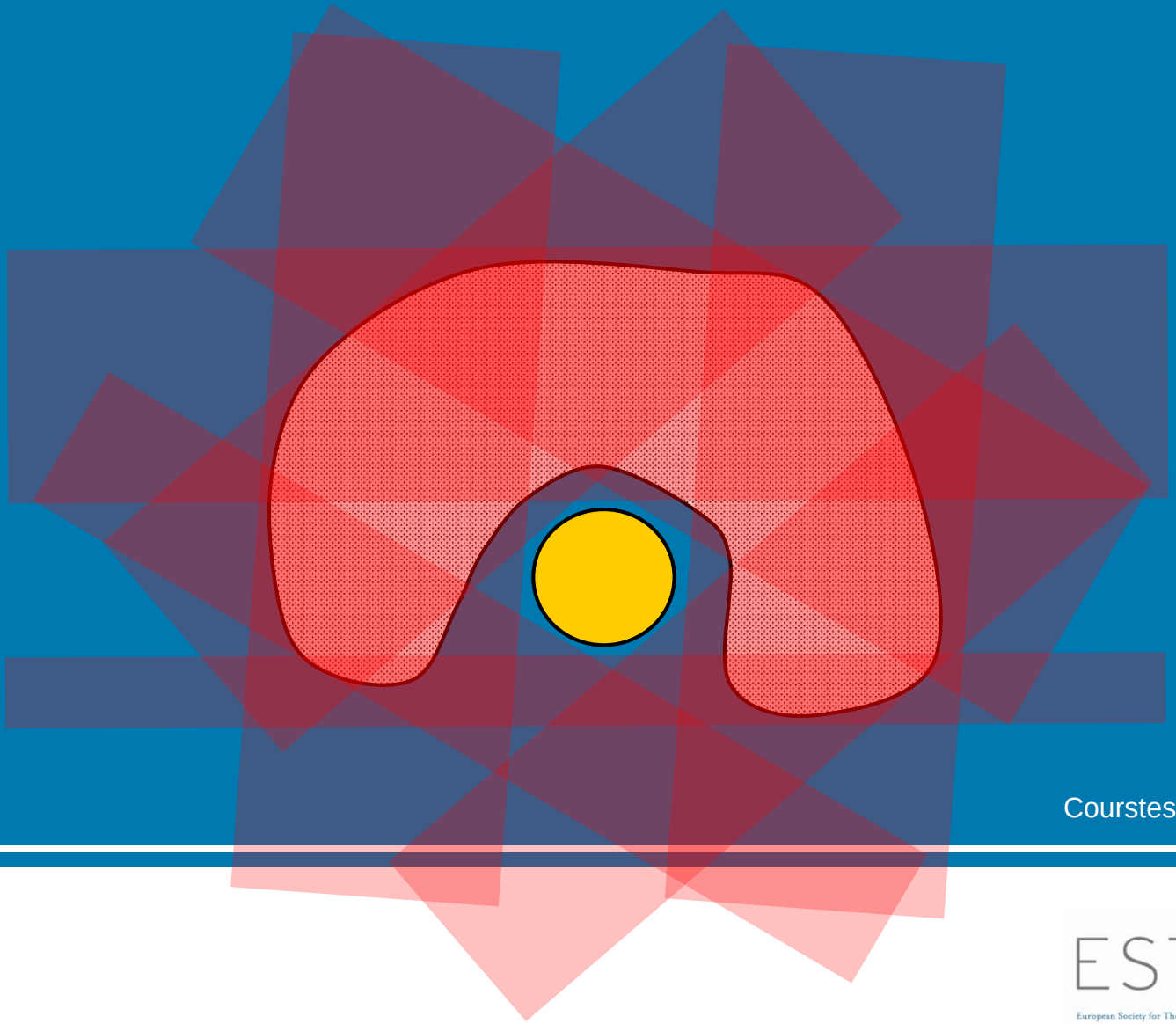
Courstesy of Jochem Wolthaus

Why need multiple arcs??



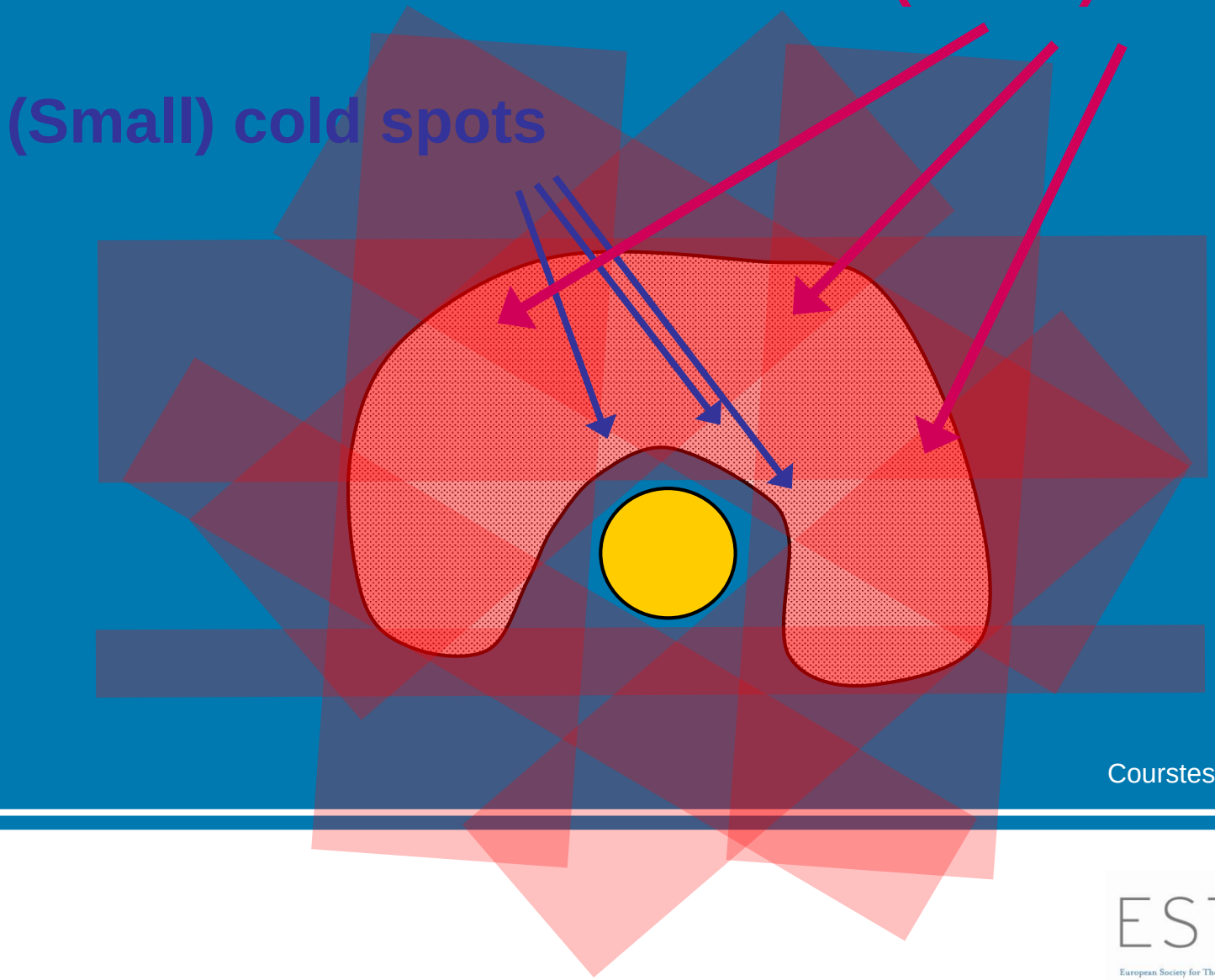
Courstesy of Markus Alber

Start with 4 beam angles



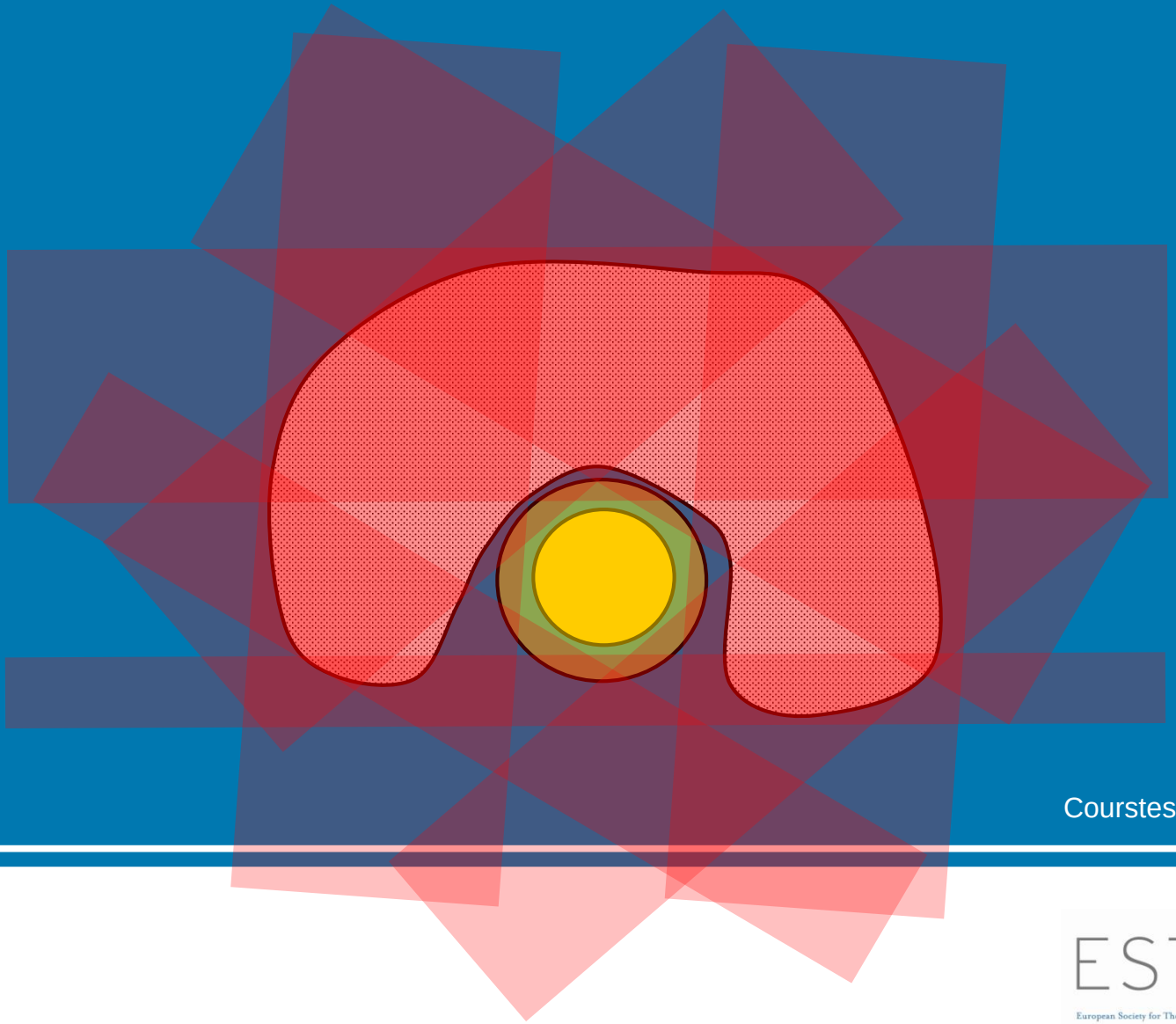
Courstesy of Markus Alber

Start with 4 beam angles



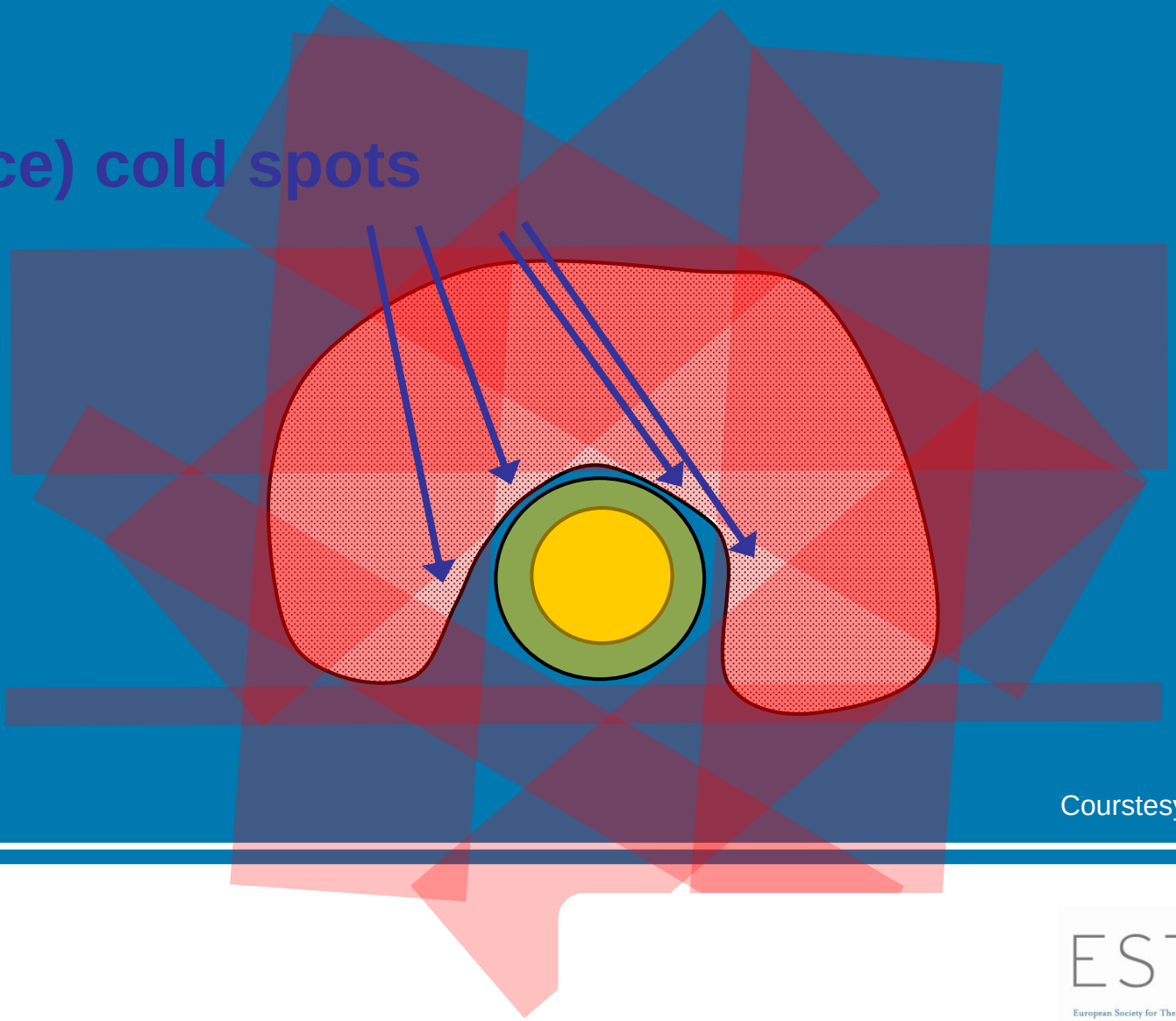
Courstesy of Markus Alber

What if the gradient has to be tighter?



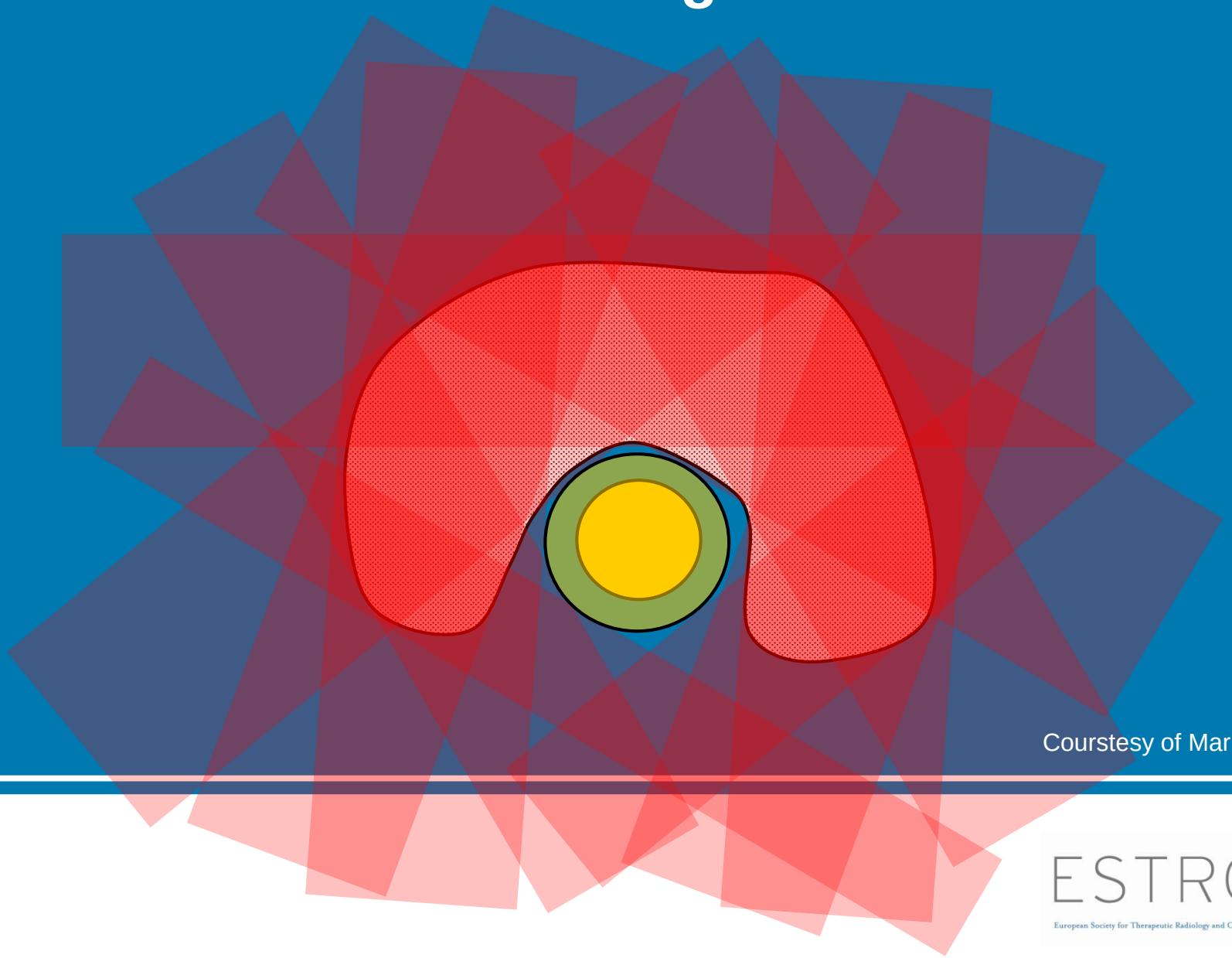
Courstesy of Markus Alber

What if the gradient has to be tighter?



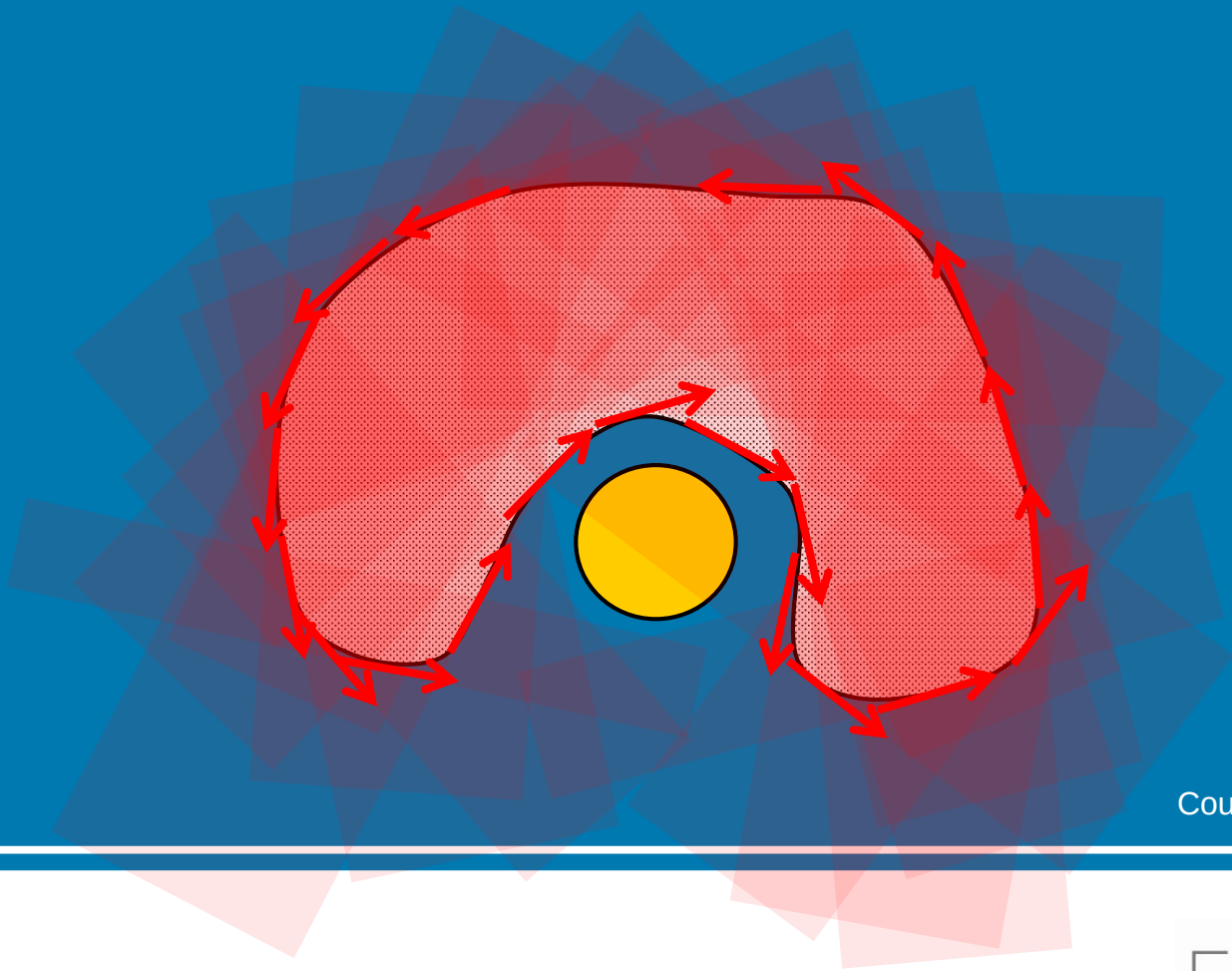
Courstesy of Markus Alber

Use more beam angles!



Courstesy of Markus Alber

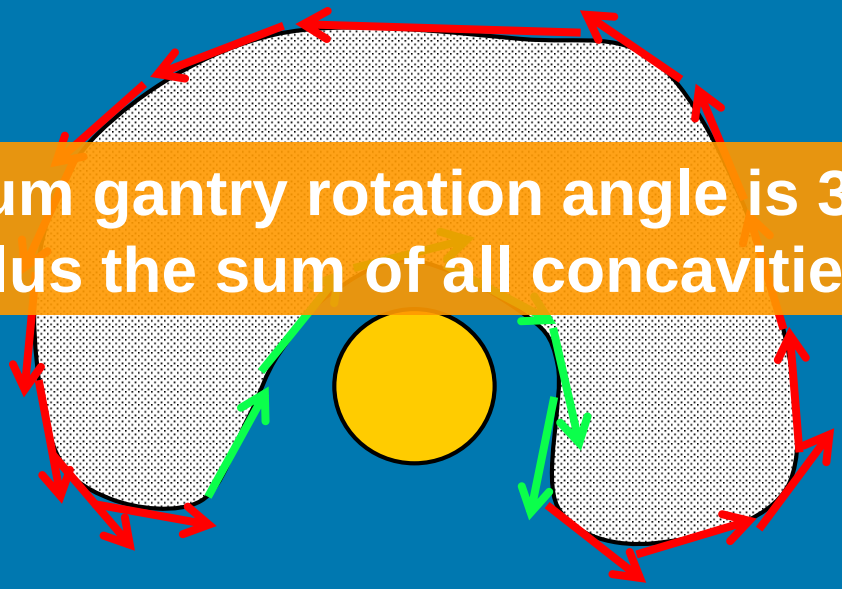
What is the maximum gantry rotation angle needed to paint all gradients for this target??



Courstesy of Markus Alber

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

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

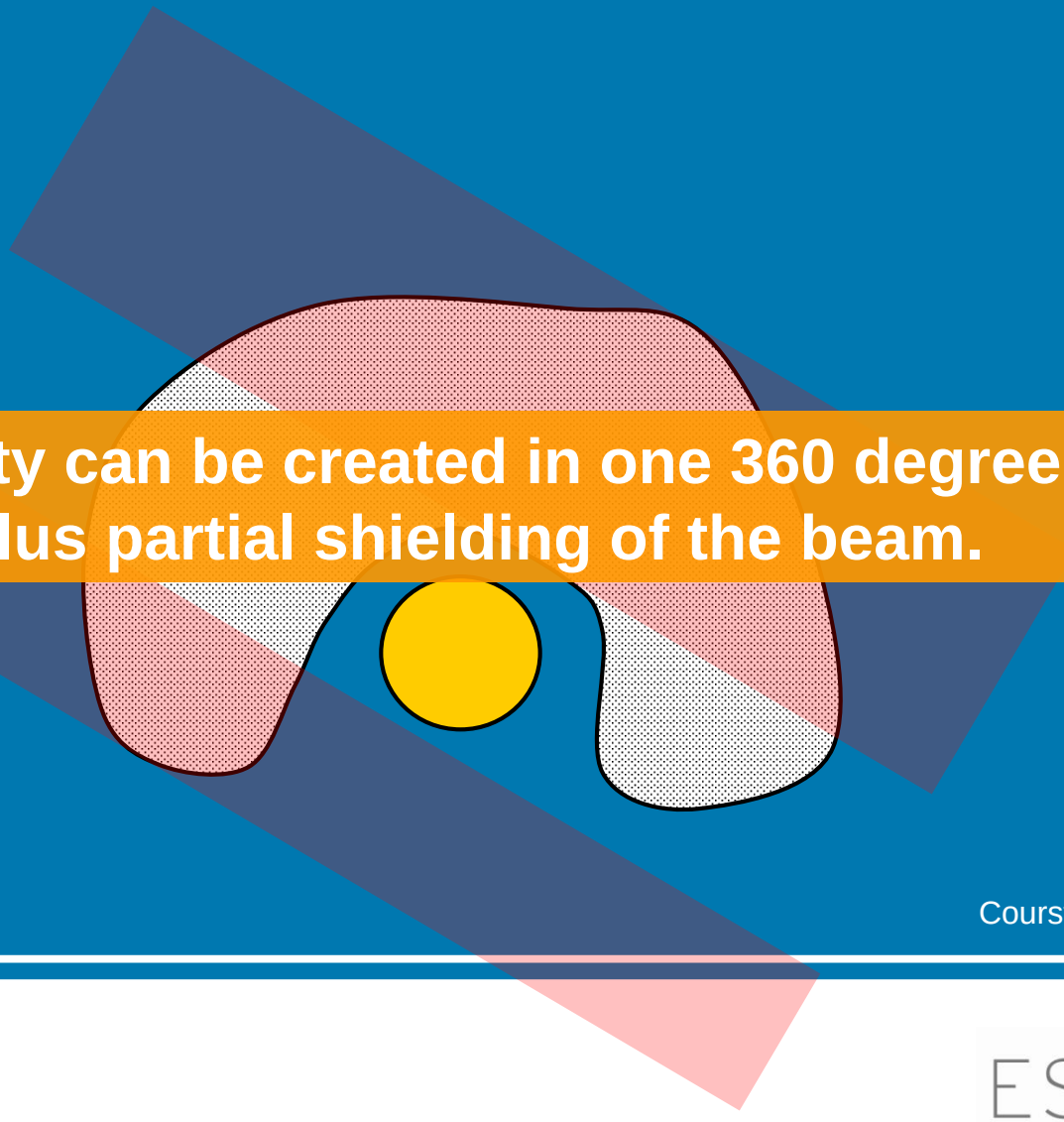


The maximum gantry rotation angle is 360 degrees plus the sum of all concavities

The sum of all red angles is 360 degrees.

Courstesy of Markus Alber

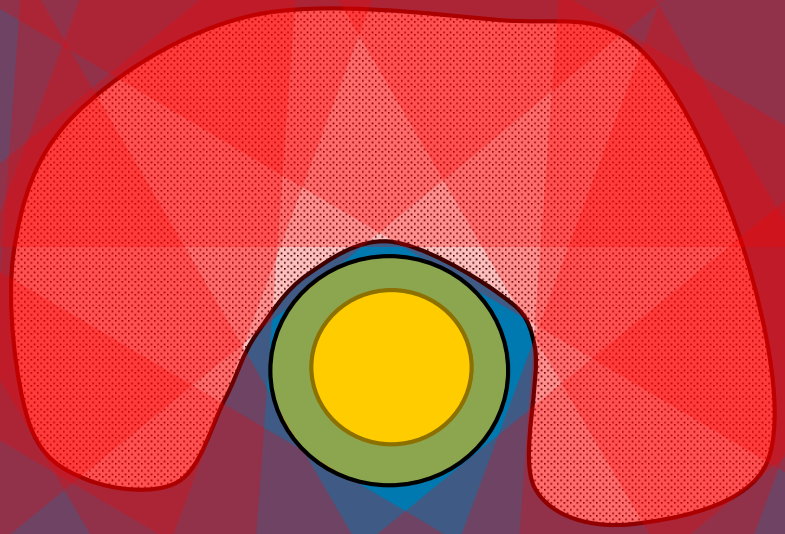
Alternatively:



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

Courstesy of Markus Alber

Alternatively:



Courstesy of Markus Alber

So .....

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

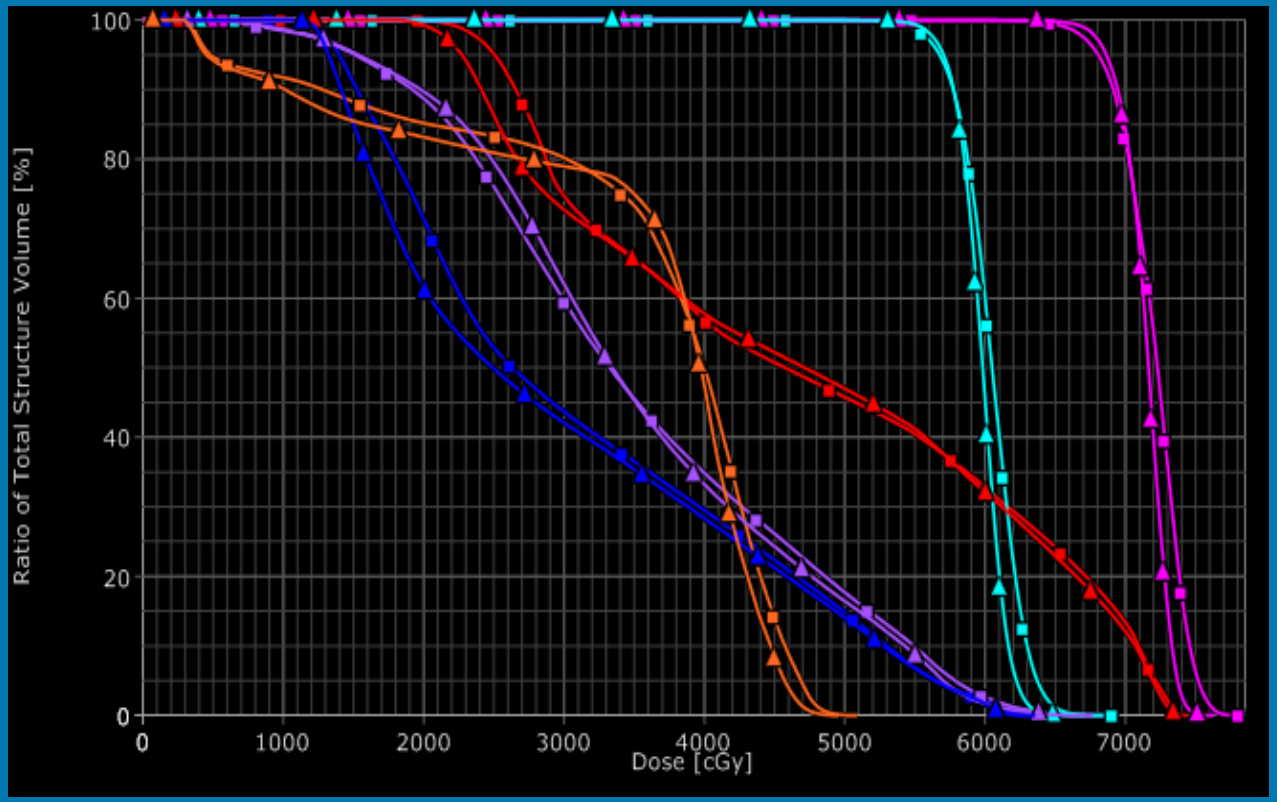
This is the *VMAT* way. It is analogous to the step and shoot technique in static gantry IMRT.

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

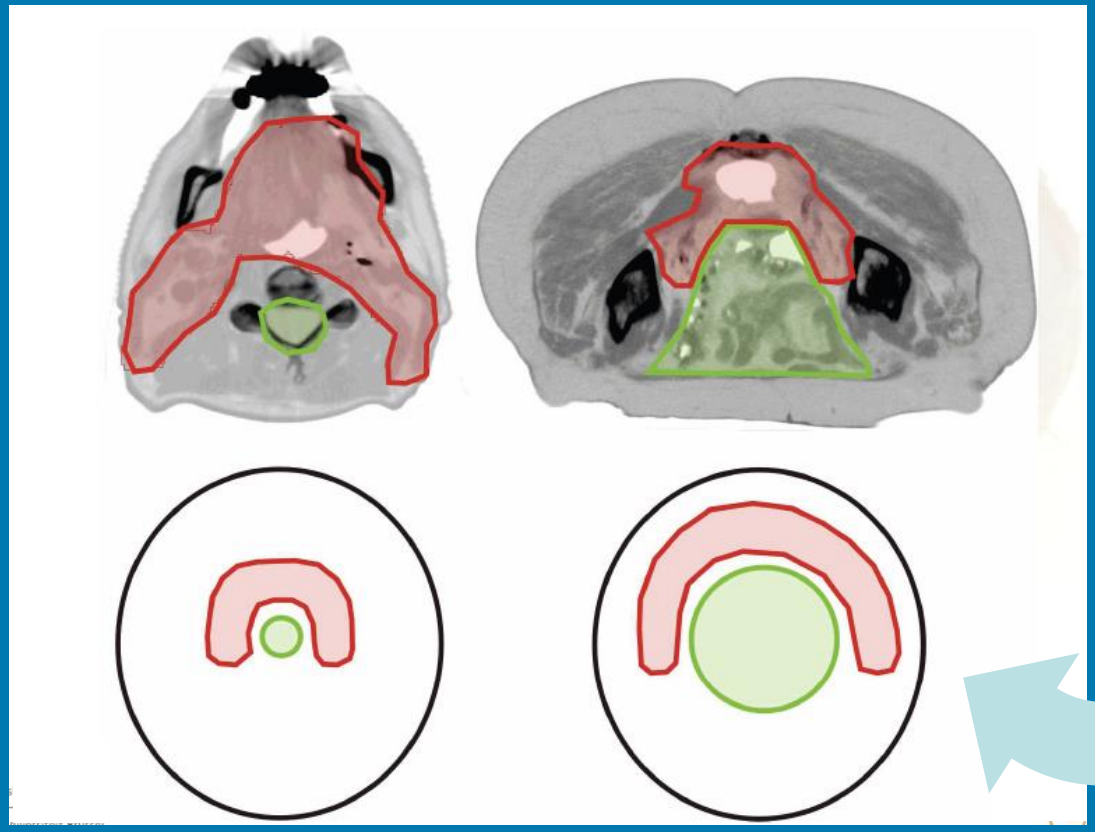
This is the *tomotherapy way*. Emulating it with a cone-beam MLC means large leaf travel and is wasteful in terms of primary radiation. (Notice, tomotherapy is also wasteful for narrow fan-beams and long target volumes)

Courstesy of Markus Alber

RapidArc single arc versus double arc

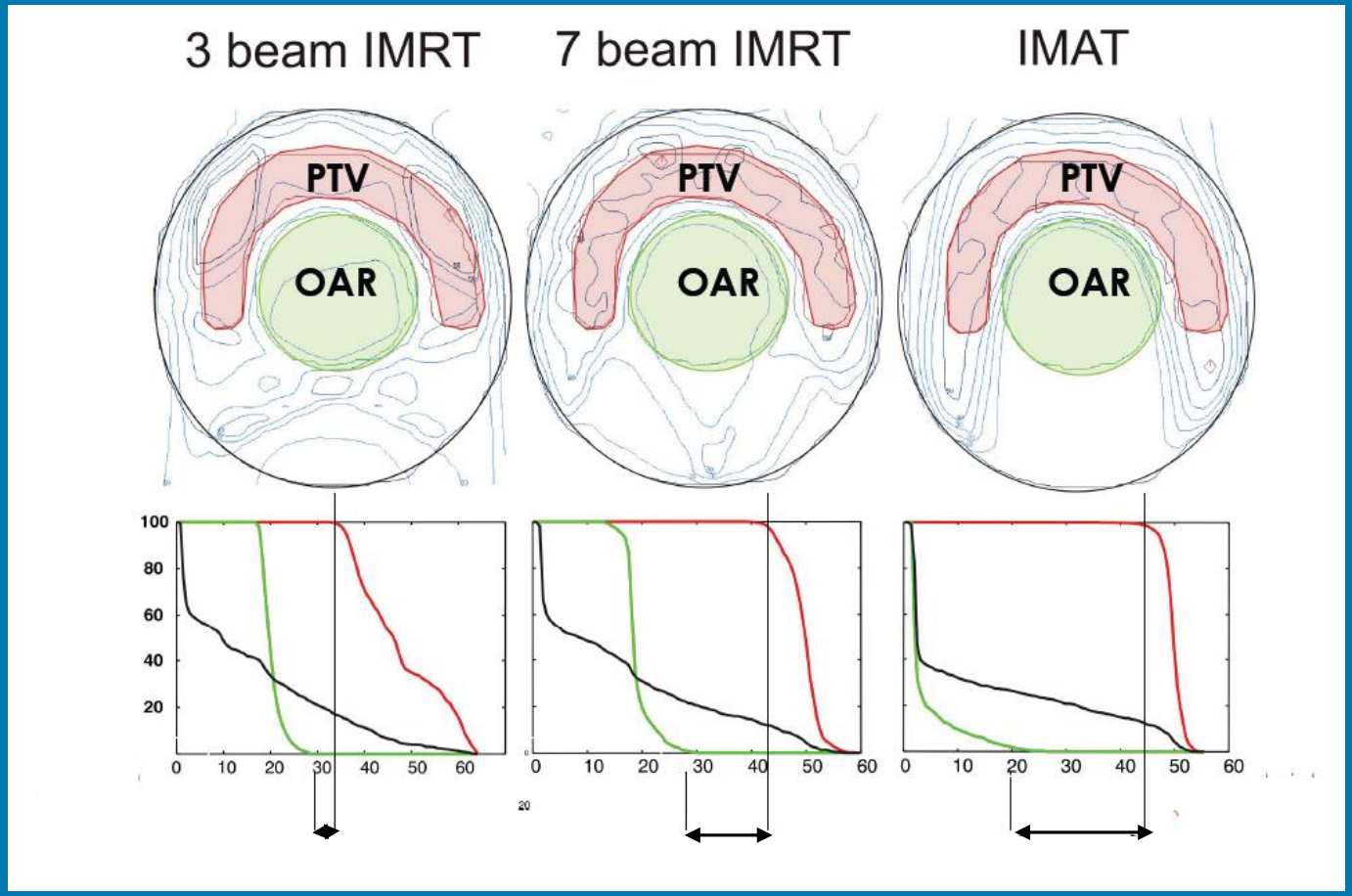


Courtesy of Wilko Verbakel



rotational IMRT generally does a better job at large concavities

De Meerleer *et al.*



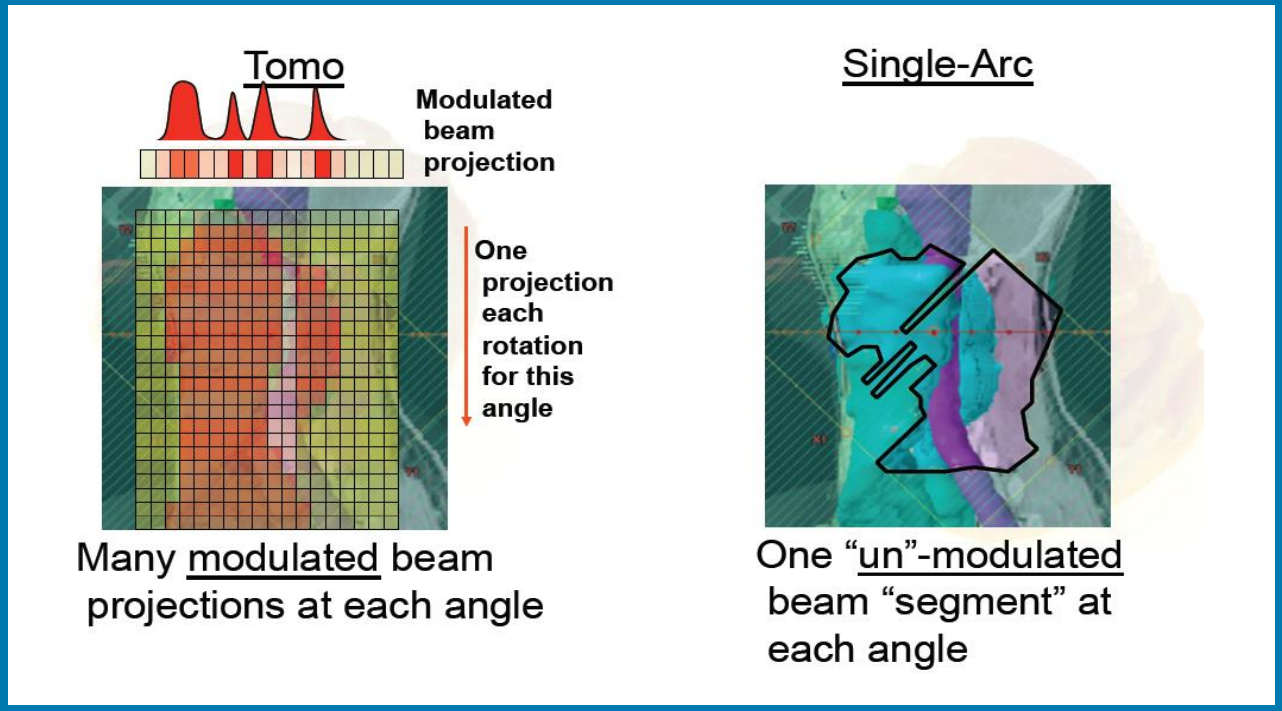
De Meerleer *et al.*

rotational cone beam IMRT vs static IMRT

- faster delivery
- comparable plan quality

fan beam IMRT offers more modulation than cone beam IMRT

(but comes at cost of longer irradiation time?)



Courstesy of Dirk Verellen

Conclusions

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

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

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

ESTRO School

Adaptive radiotherapy

Marcel van Herk

Includes slides by Michael Sharpe, Alan McWilliam and Corinne Johnson

Institute of Cancer Sciences

Manchester University

The Christie NHS Trust

(Formerly at the Netherlands Cancer Institute)

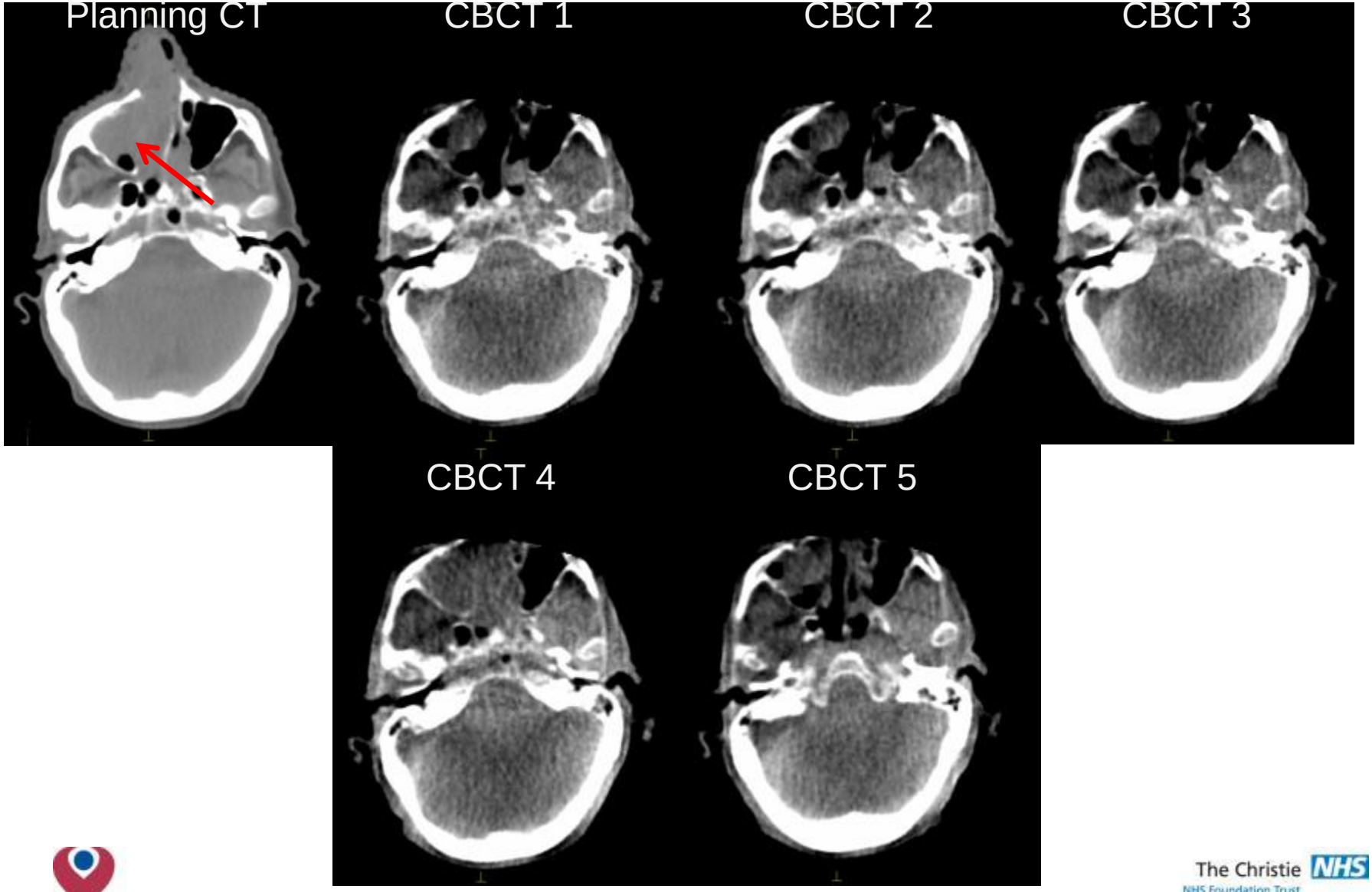
types of adaptive radiotherapy

- Ad-hoc
- Planned
- Geometry based
- Dose accumulation-based

Ad-hoc adaptive radiotherapy

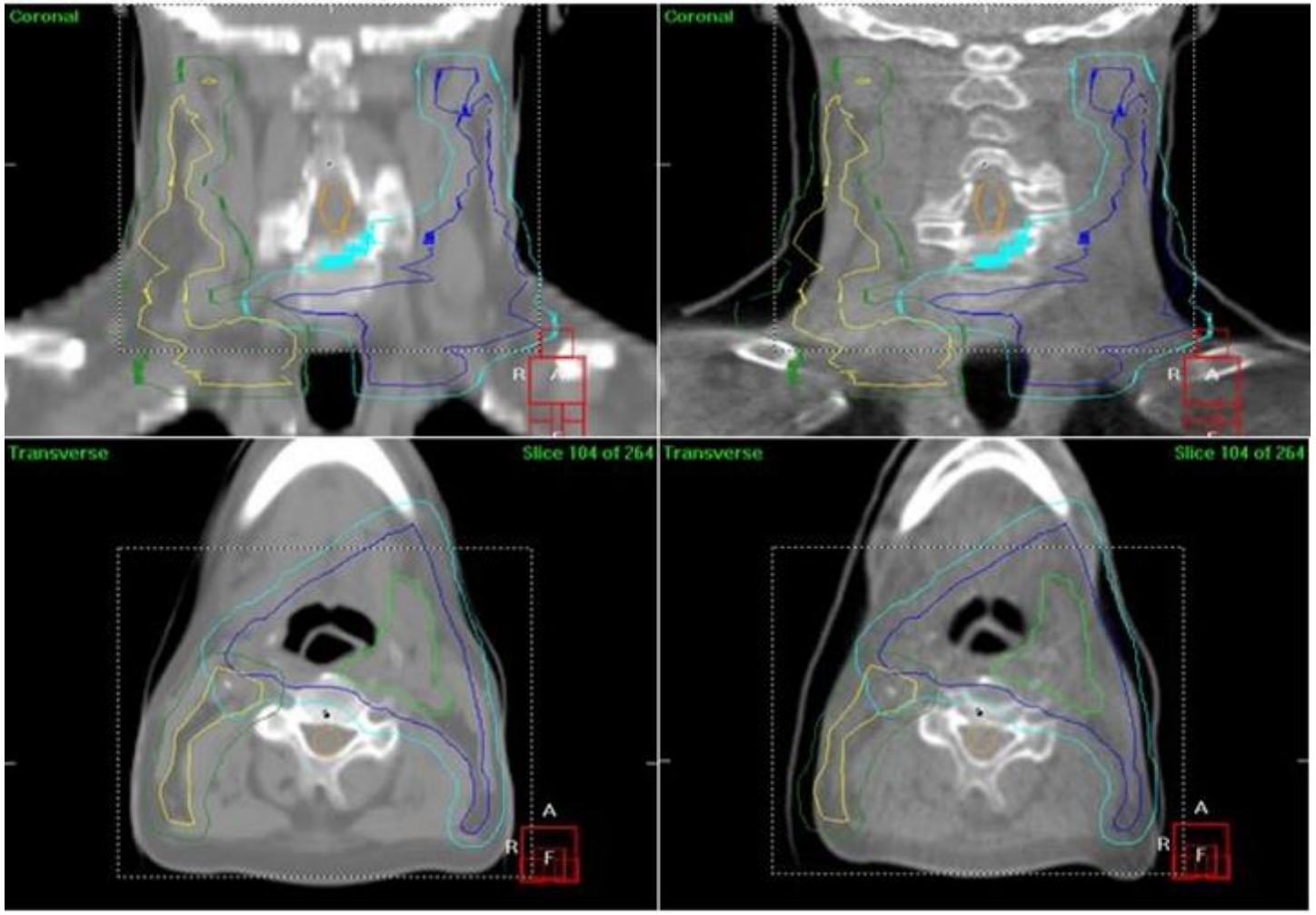
- In the Christie dose is recalculated on CBCT (with density override) based after visual analysis in ~7% of patients
  - mostly lung and H&N
- Actual adaptation in ~1% of patients
  - taking a new CT scan
  - independent new plan
- No special software is used to do this in the clinic – just the planning system

Sinus filling and emptying



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

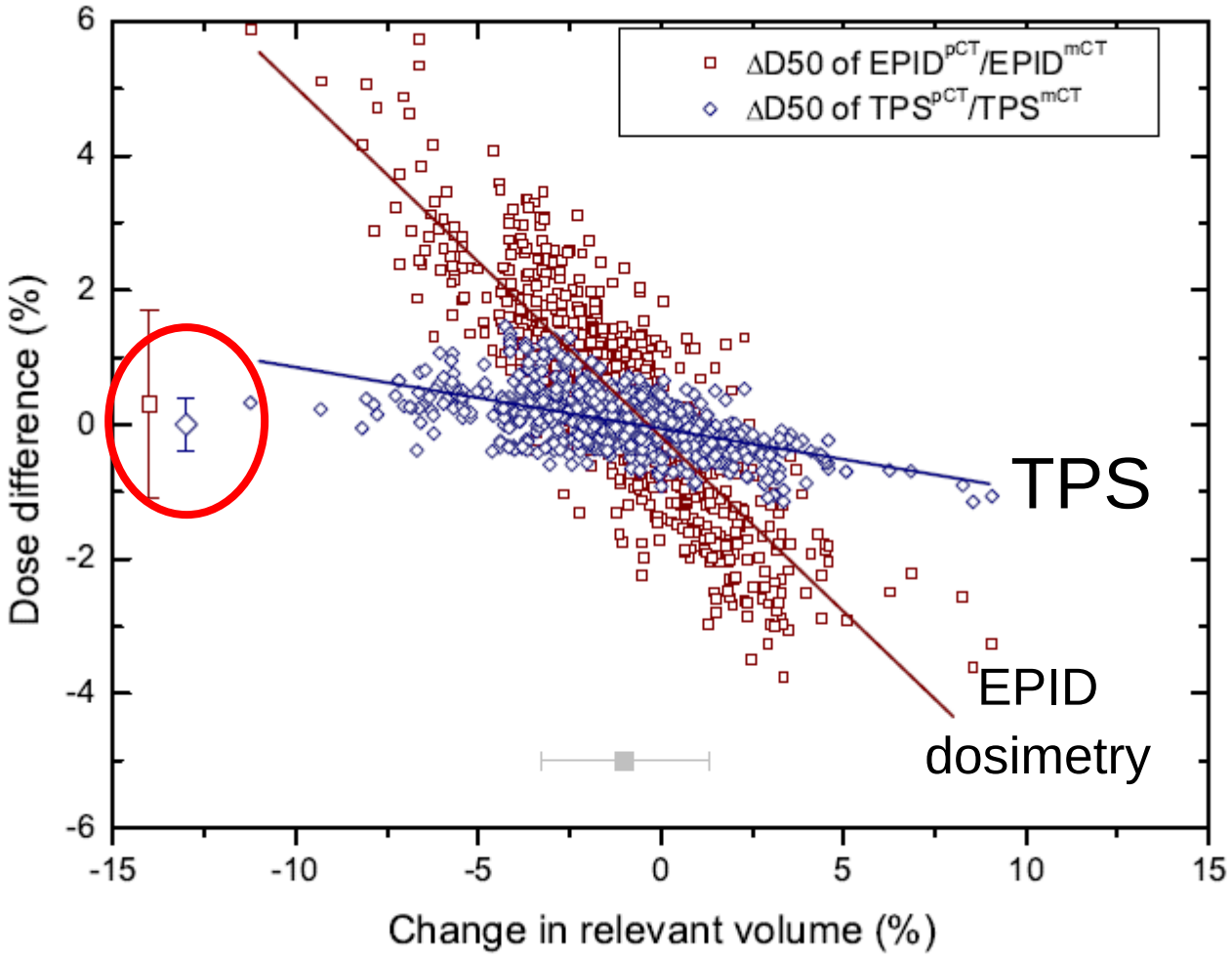
The Christie NHS
NHS Foundation Trust

Effects of anatomical changes

- Dosimetric effect
  - Extremely minor for photons

- Geometric effect
  - Organs and targets move relative to the dose distribution

Effect of weight loss on dose



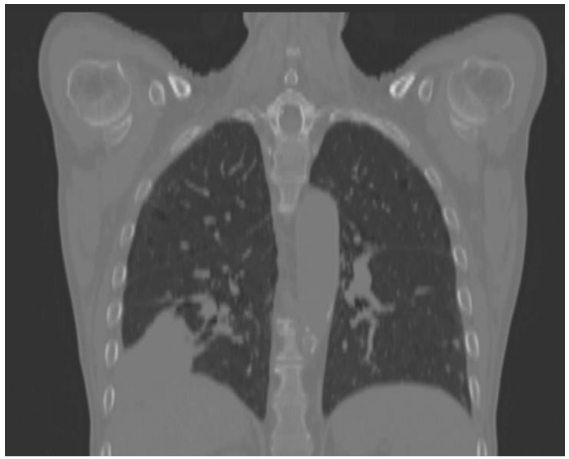
- Rozendaal et al, R&O 2015

Software for adaptive RT

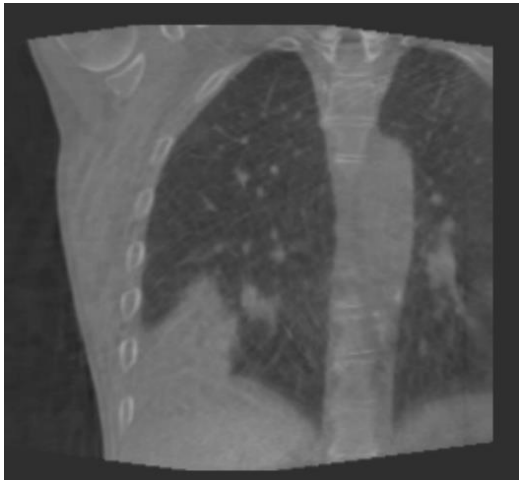
- To fix the HU of CBCT
  - Density override
  - Deform planning CT to CBCT
  - Shading correction based on planning CT

Modify CT to CBCT anatomy

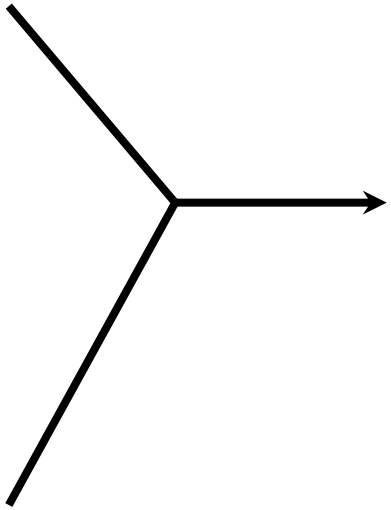
CT



CBCT

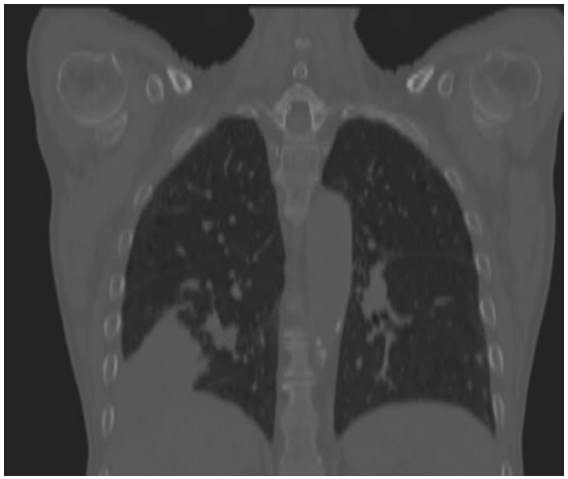


Deformable image registration



modified CT (mCT)

(CT numbers + CBCT anatomy)

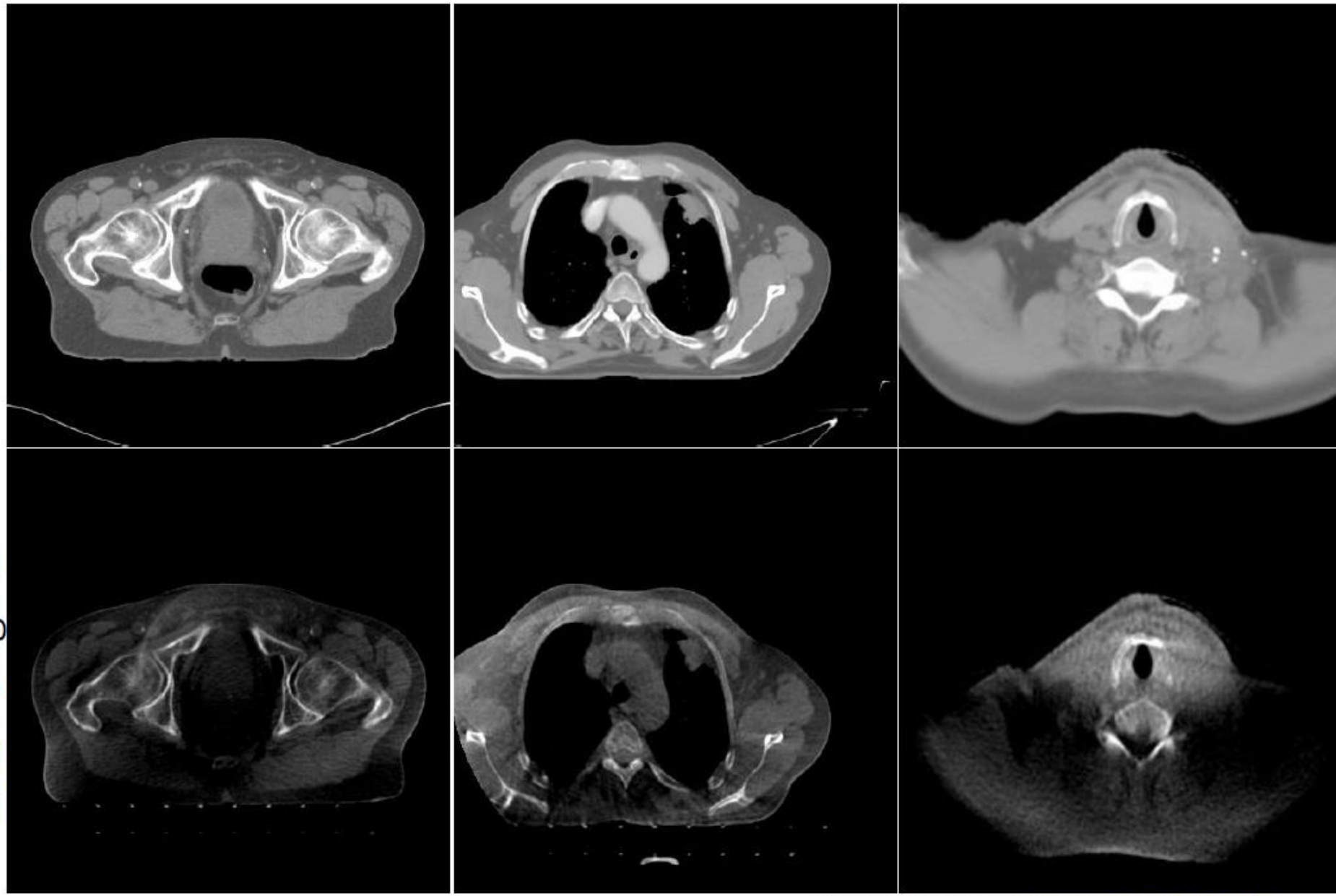


Make CBCT suitable for dose calculation

Szeto et al, NK1I 2016

The Christie NHS
NHS Foundation Trust

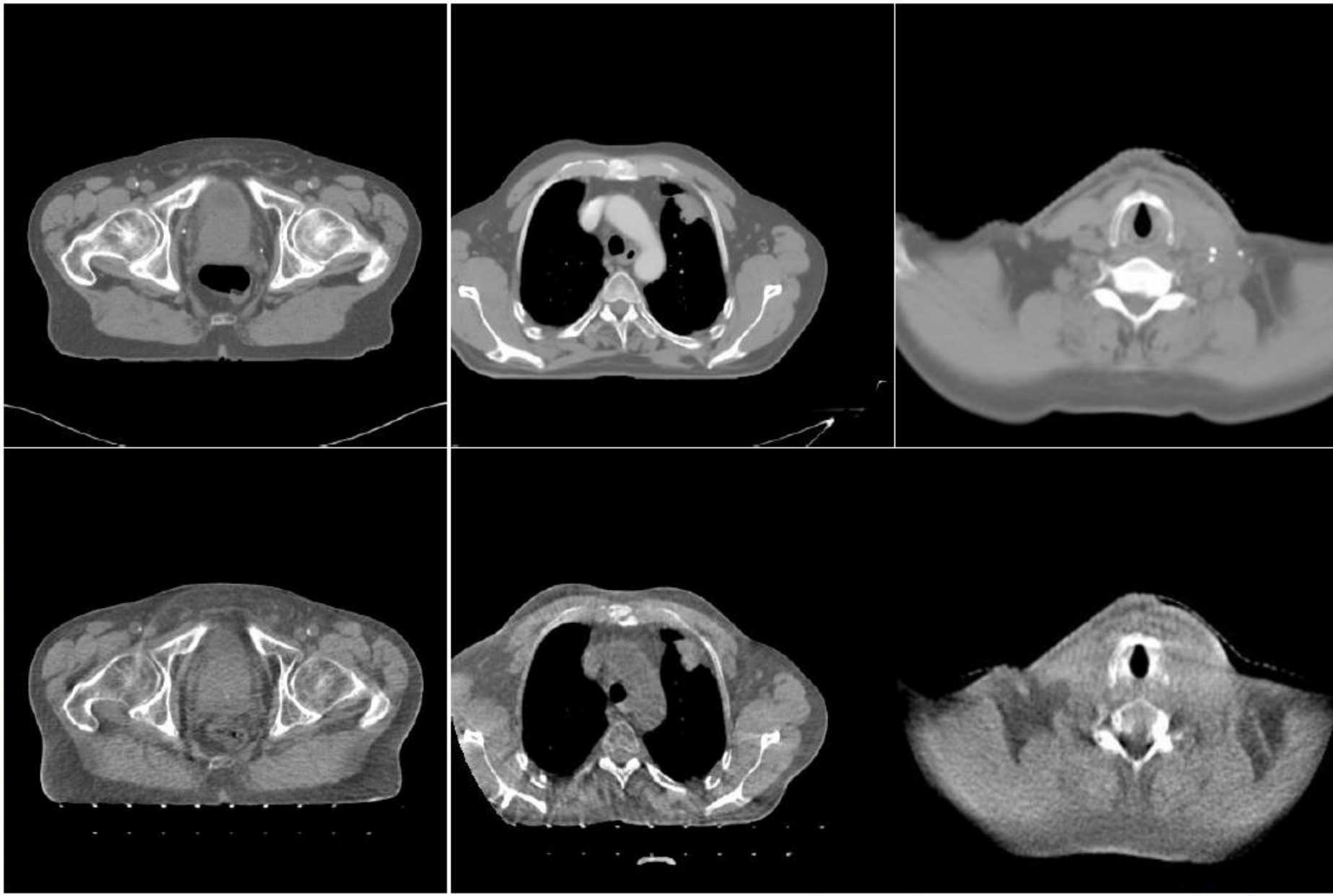
Shading correction examples



- Marchant and Yoshi, SPIE 2017

Examples at www.cscart.tech

Shading correction examples



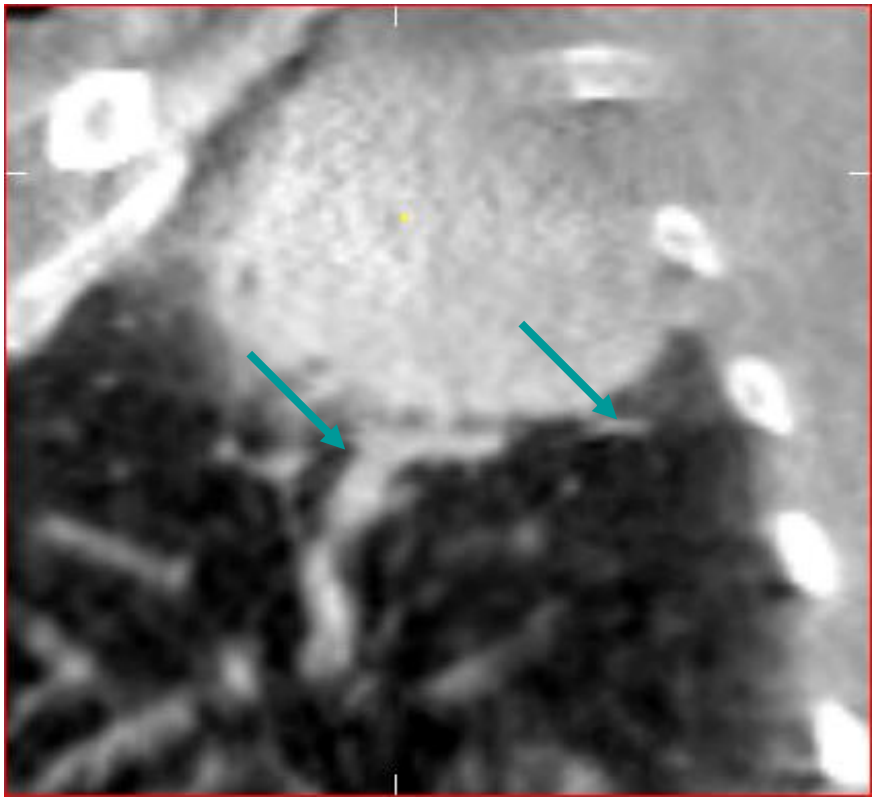
- Marchant and Yoshi, SPIE 2017

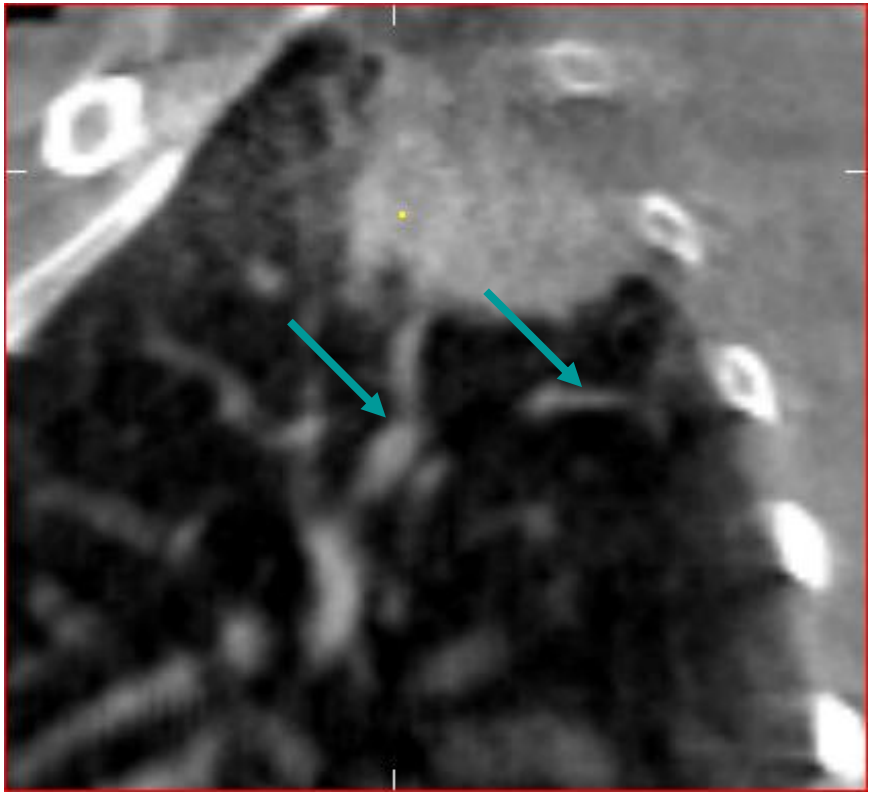
Examples at www.cscart.tech

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

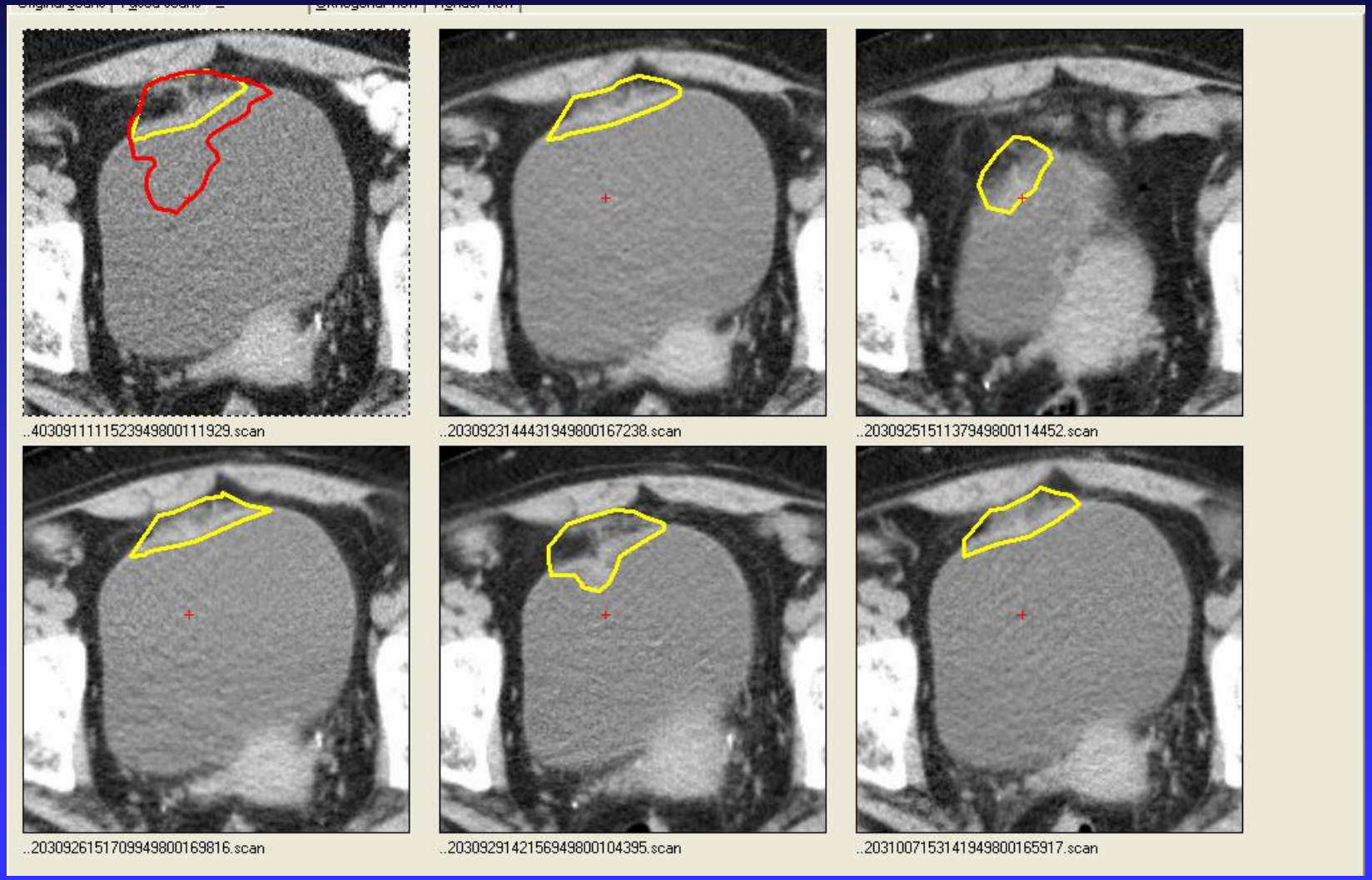




Geometrical adaptive radiotherapy

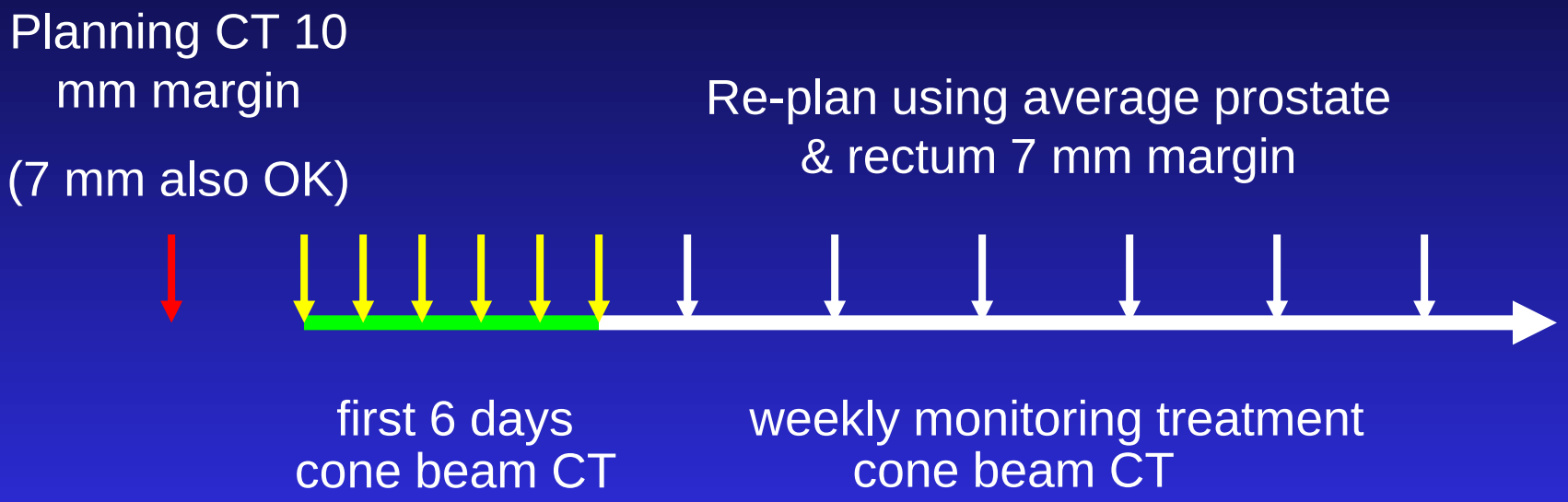
- ITV methods
- Mean methods
- Dose prescription per fraction methods

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



Pos et al 2005

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

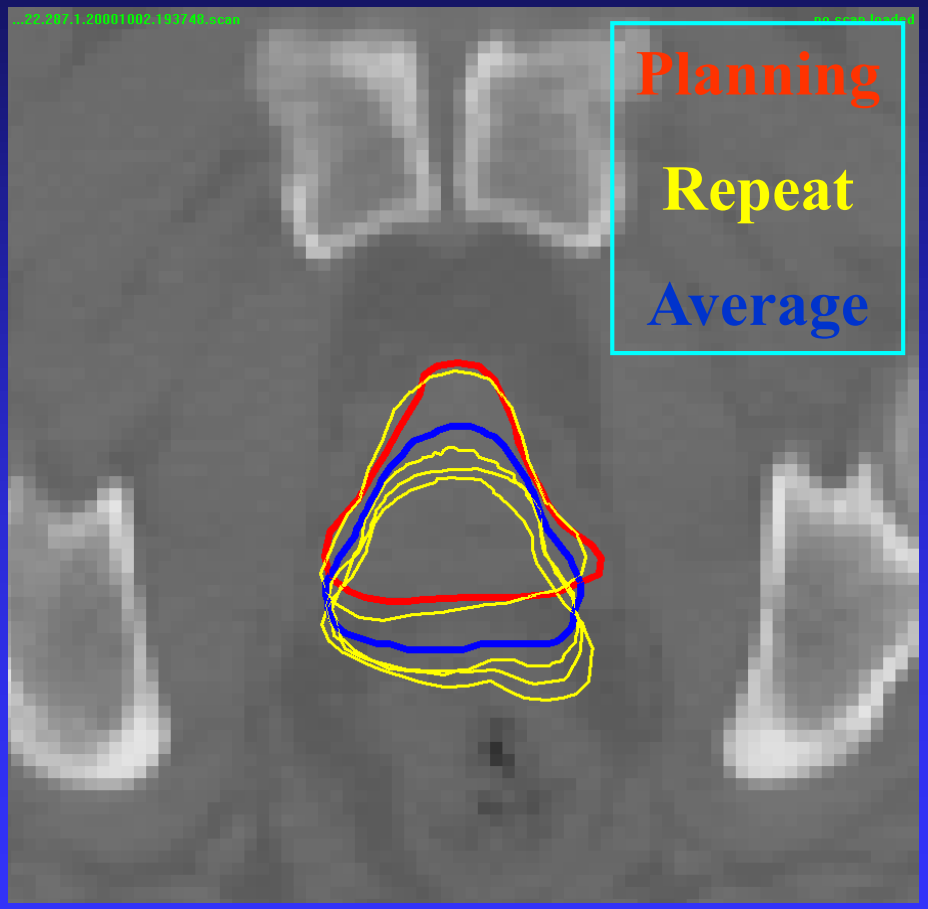
Methods: average prostate (rigid registration based)

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

T_{AVG} / R_{AVG}

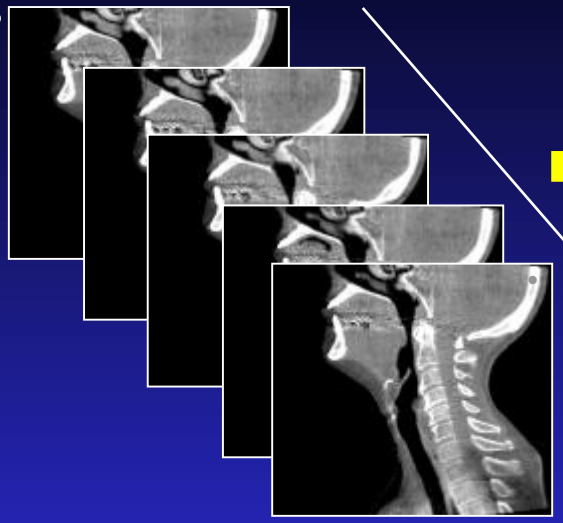
T_{AVG} / R_{AVG} puts prostate from plan CT in average position

- With this CTV the margin can be safely reduced from 10 mm to 7 mm

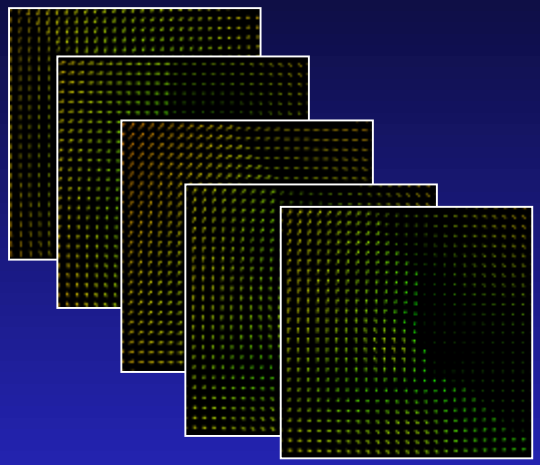


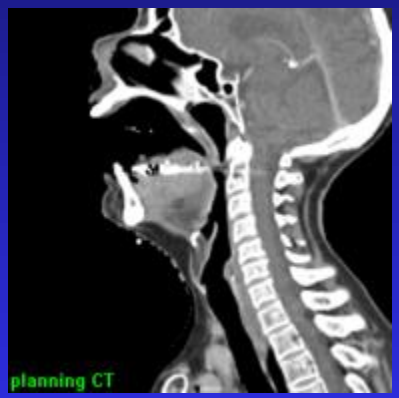
Adaptive replanning on average anatomy

- daily CBCTs

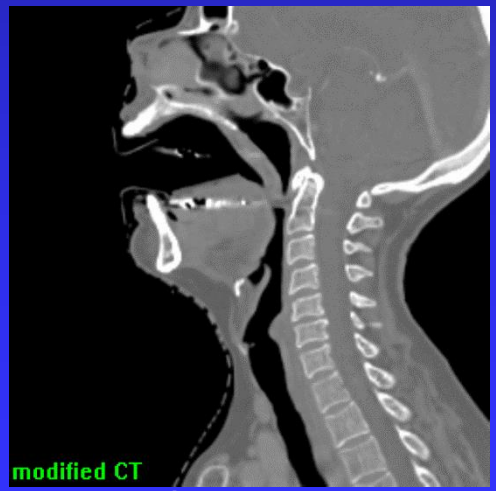


- deformation vector fields

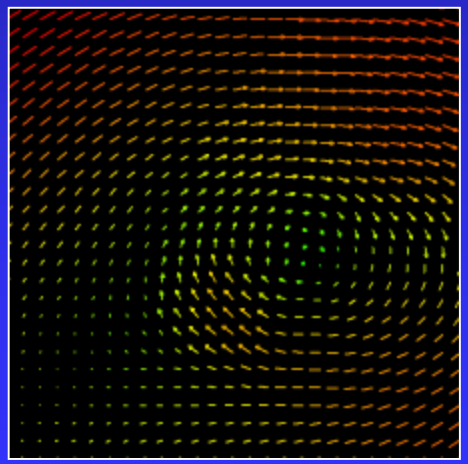




- Planning CT



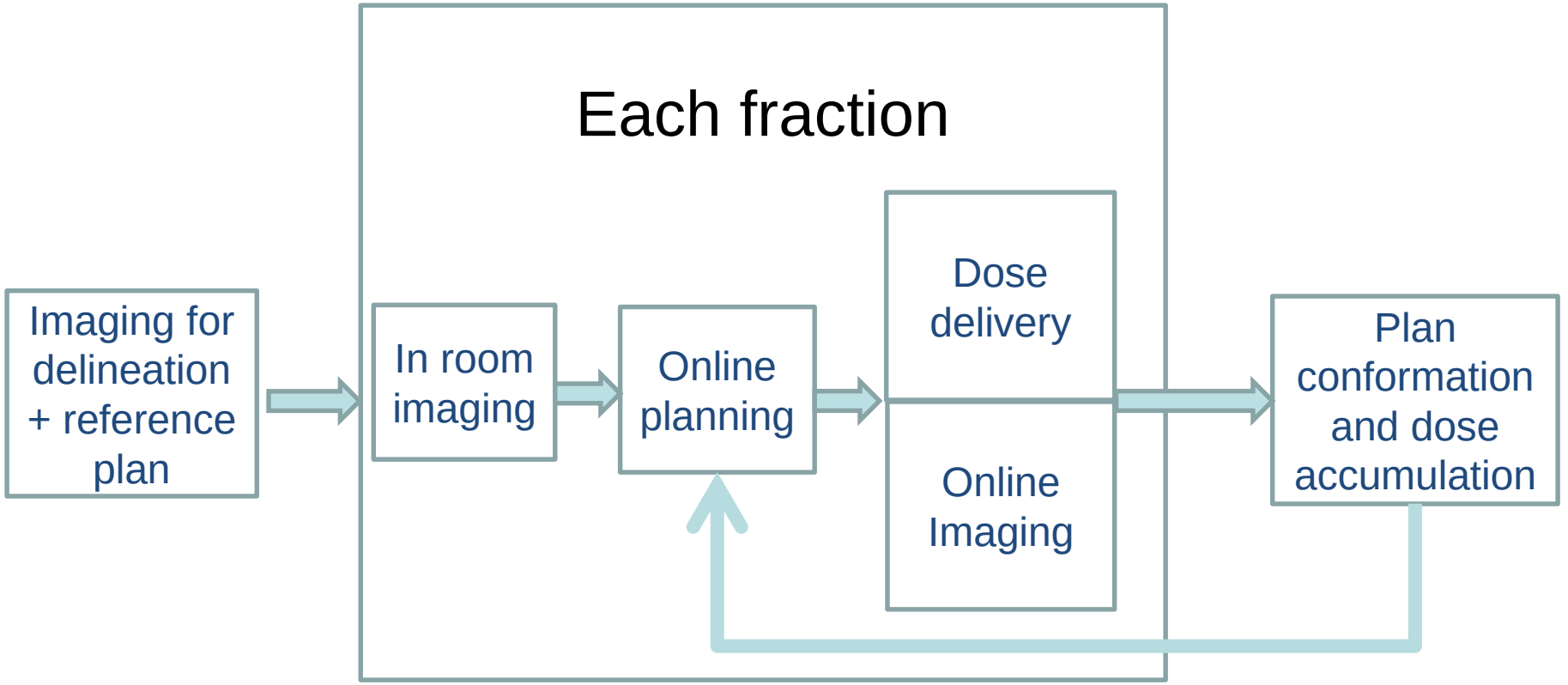
- Average anatomy



- systematic deformations

Kranen et al, IJROBP 2016

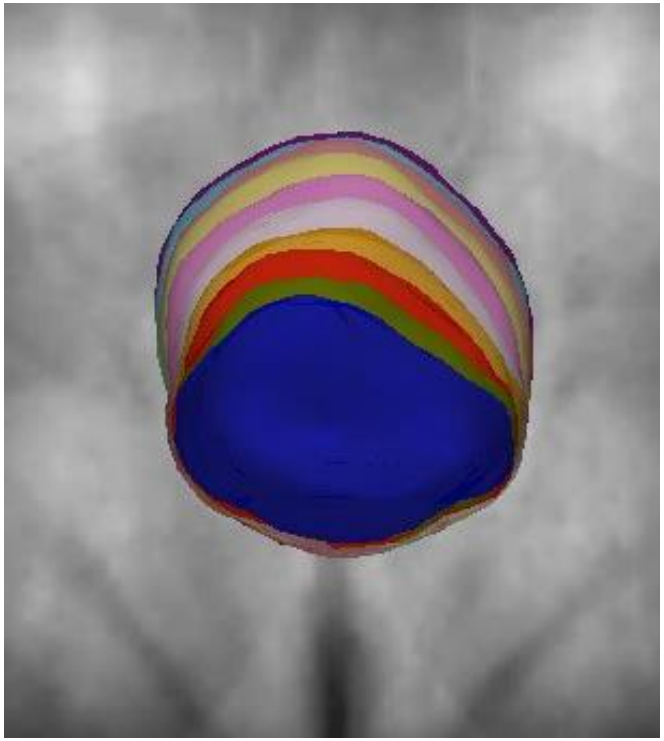
Adaptive workflow - ideal

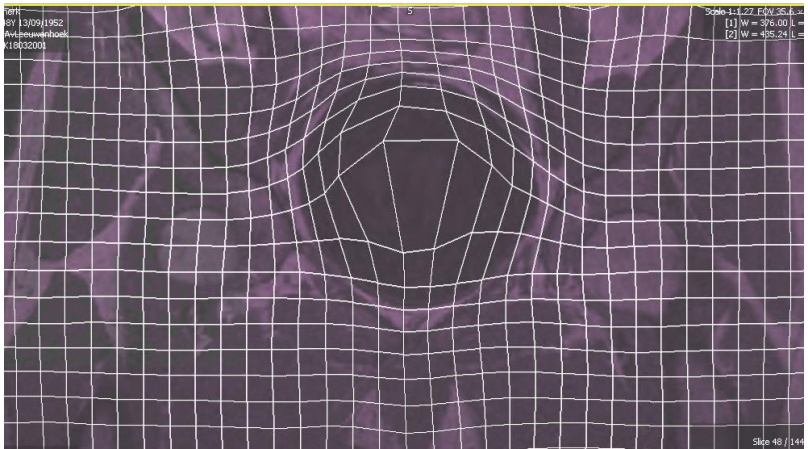


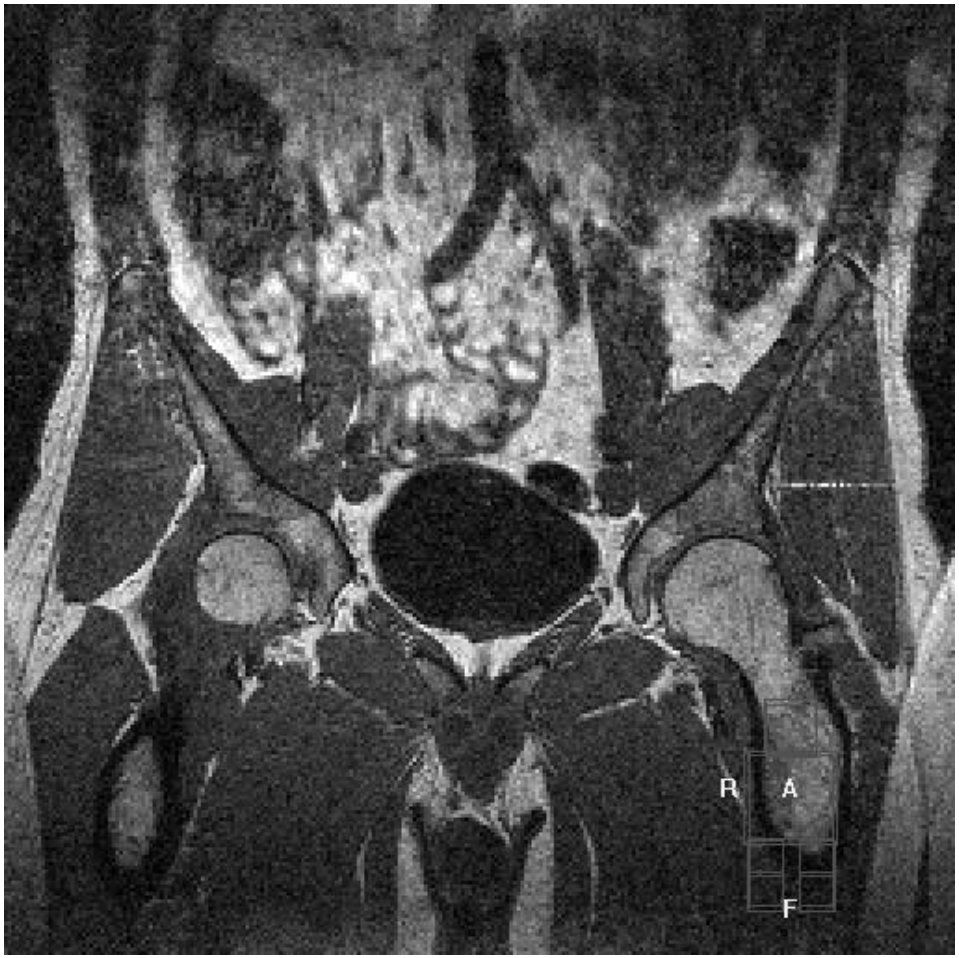
Dosimetric adaptive radiotherapy

- Accumulate dose
- Detect or predict when dose contraints will be exceeded
- Then replan
  - Independently
  - Using bias/background dose
- Evaluate

Easy deformable registration of the bladder?







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

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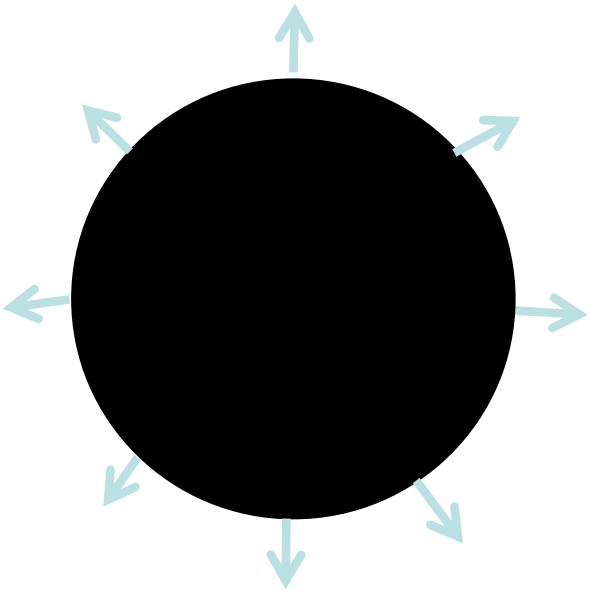
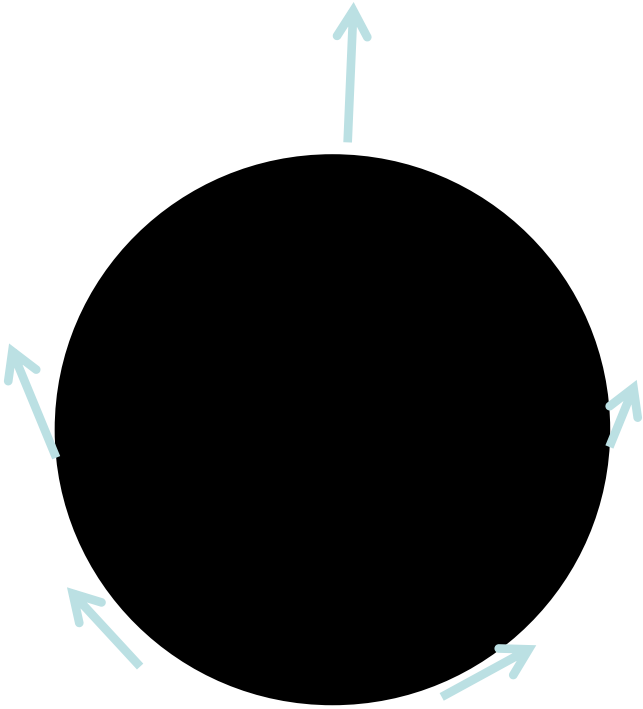
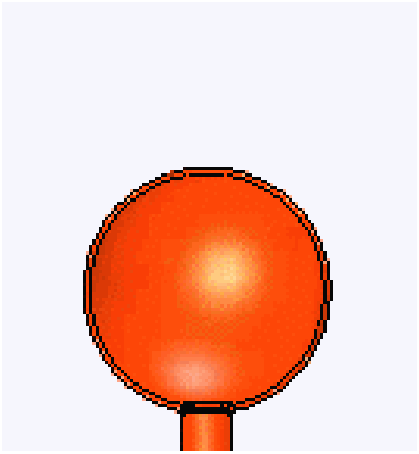
NHS Foundation Trust

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

Is adaptation clinically important?

- Image-guided radiotherapy (IGRT) is commonly utilised to aid patient positioning
- Most evidence relies on surrogate outcomes

Aims

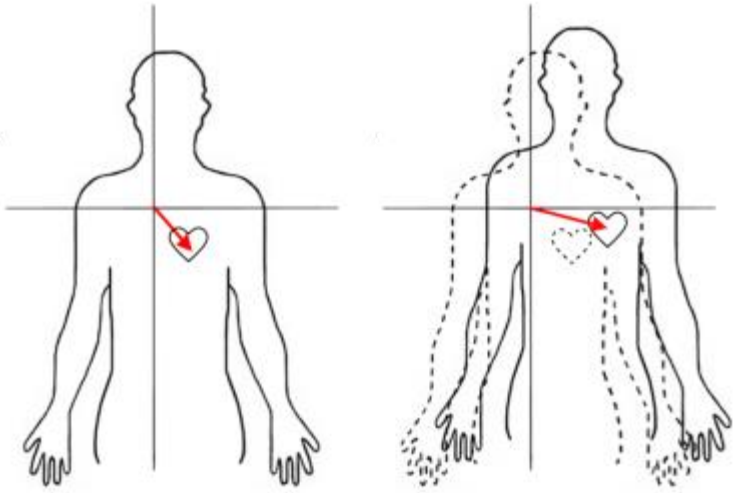
- To assess whether the magnitude of **residual** bony setup errors following IGRT relate to patient survival
- Test effect directionality of the errors to get information about the underlying cause

- → Can we relate a small change in dose with outcome?

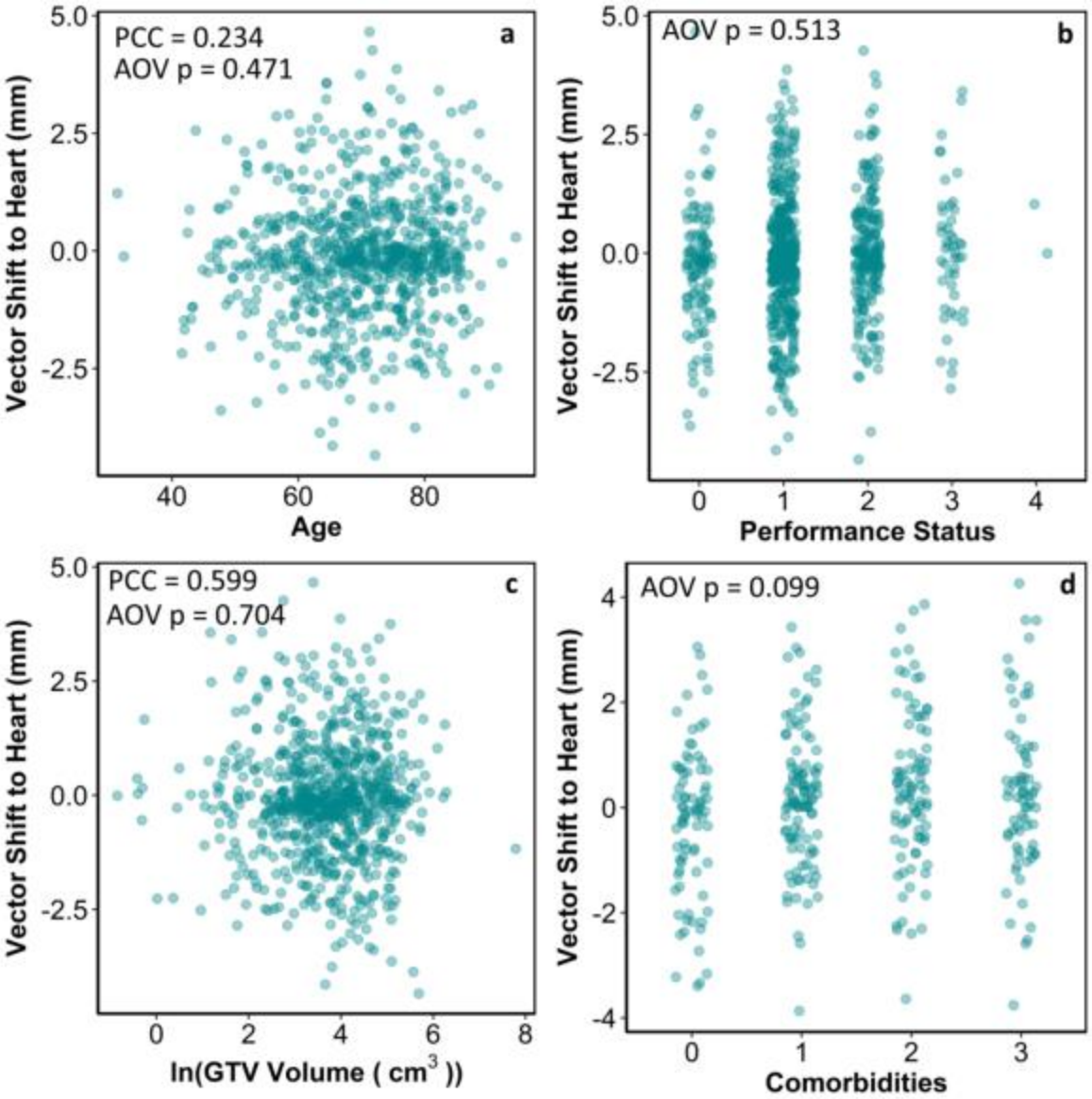
Methods

- 780 Non-small cell lung cancer patients
- IGRT protocol on bony anatomy
  - Imaging on days 1-3 then weekly
  - 5mm action threshold applied

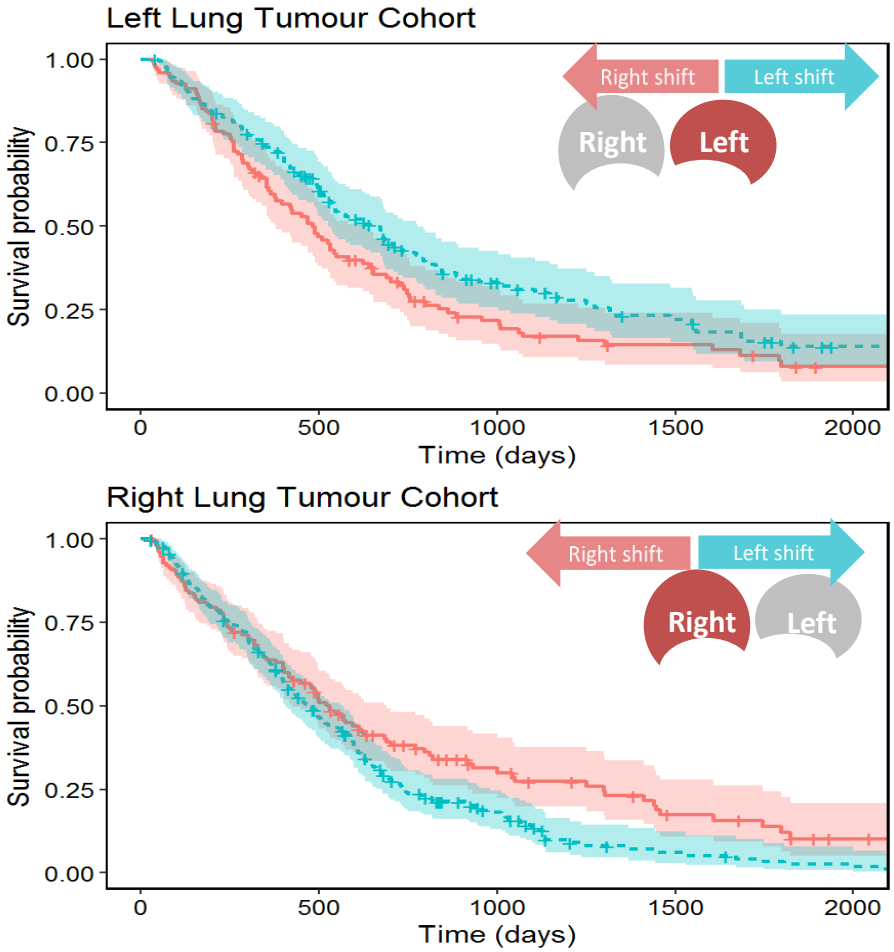
Weighted Residual Shifts			
X (mm)	Y (mm)	Z (mm)	Fraction
0	0	0	1
2.6	1.5	-2.8	2
1.3	3.4	-3.3	3
1.3	3.4	-3.3	4
1.3	3.4	-3.3	5
-0.5	1.1	1.5	6
-0.5	1.1	1.5	7
-0.5	1.1	1.5	8
-0.5	1.1	1.5	9
-0.5	1.1	1.5	10
⋮	⋮	⋮	⋮



- Estimate **residual** shifts
  - summarised as 9 parameters
- Variable selection
- Cox regression to assess significance



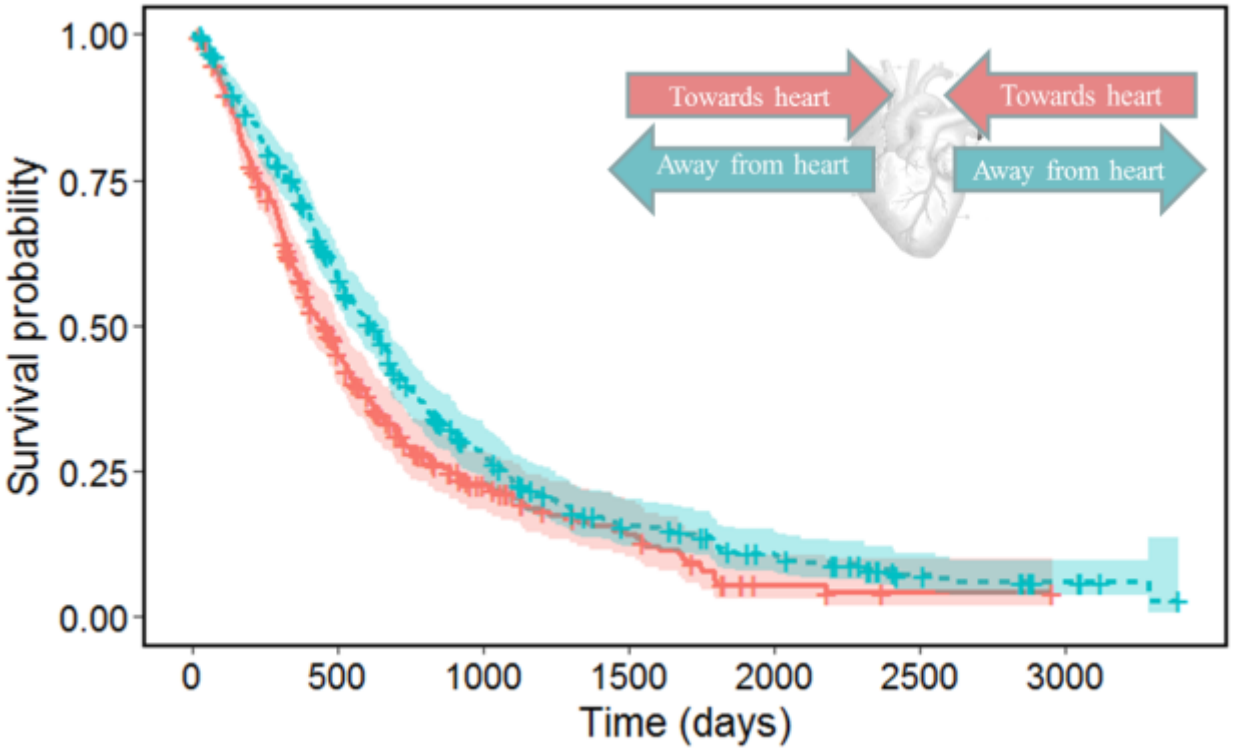
Residual shifts are small and truly random



Cohort	N	Variable	p-value	HR (right shift)
Left Tumours	261	Mean lateral shift	**0.025**	**0.723**
		ECOG-PS	0.032	1.224
		Age	0.430	1.007
		Fractionation	0.044	0.966
		Ln(GTV)	0.002	1.263
Right Tumours	367	Mean lateral shift	**0.007**	**1.401**
		ECOG-PS	0.094	1.132
		Age	0.340	1.006
		Fractionation	<0.001	0.943
		Ln(GTV)	<0.001	1.457

Effects are opposite for left and right tumours

Vector shift to the heart



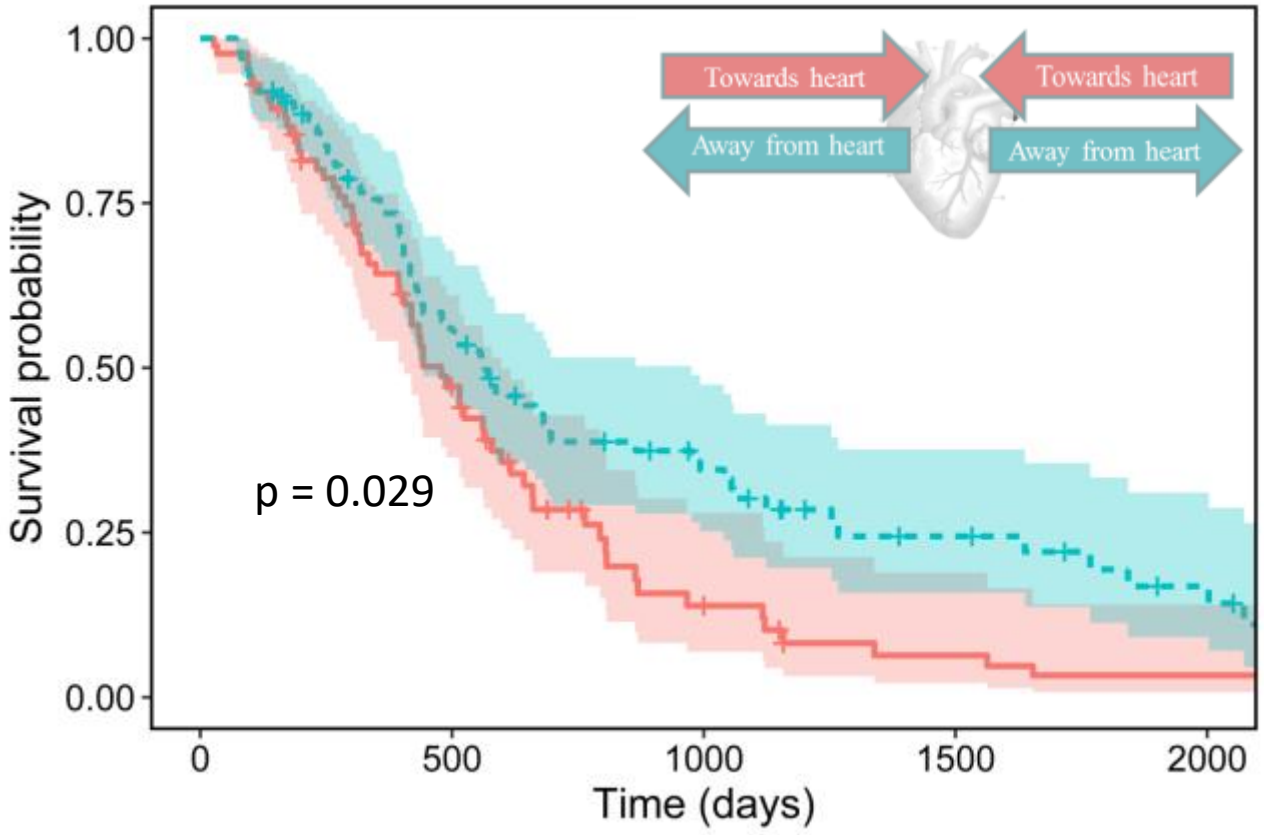
Variable	p-value	HR (shifts away)
Mean lateral shift	<0.001	0.757
ECOG-PS	0.009	1.148
Age	0.214	1.006
Fractionation	<0.001	0.955
Ln(GTV)	<0.001	1.405

As a continuous variable:
(positive shifts = shifts towards heart)

HR = 1.091 per mm (p = 0.007)

Increased risk with increasing shifts towards the heart

Oesophageal cancer cohort for validation (n = 177)



Continuous:	HR = 1.164 per mm (p = 0.041)

Summary

- Very small residual shifts towards the heart after IGRT can significantly affect overall survival
- Setup errors have no correlation with clinical variables

  ⟶ Most likely due to increased heart dose

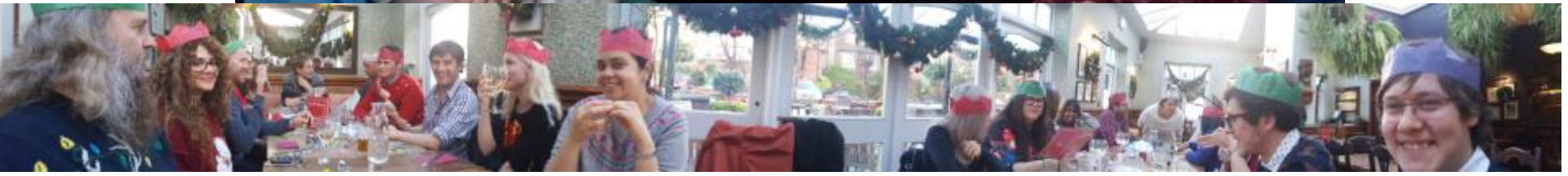
Recommendations

- Strict IGRT protocols should be applied for thoracic cancers
  - Daily imaging with lower action thresholds
- Heart dose planning constraints should be reviewed

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
- Do ***not*** trust dose accumulation

- Greetings from Manchester !



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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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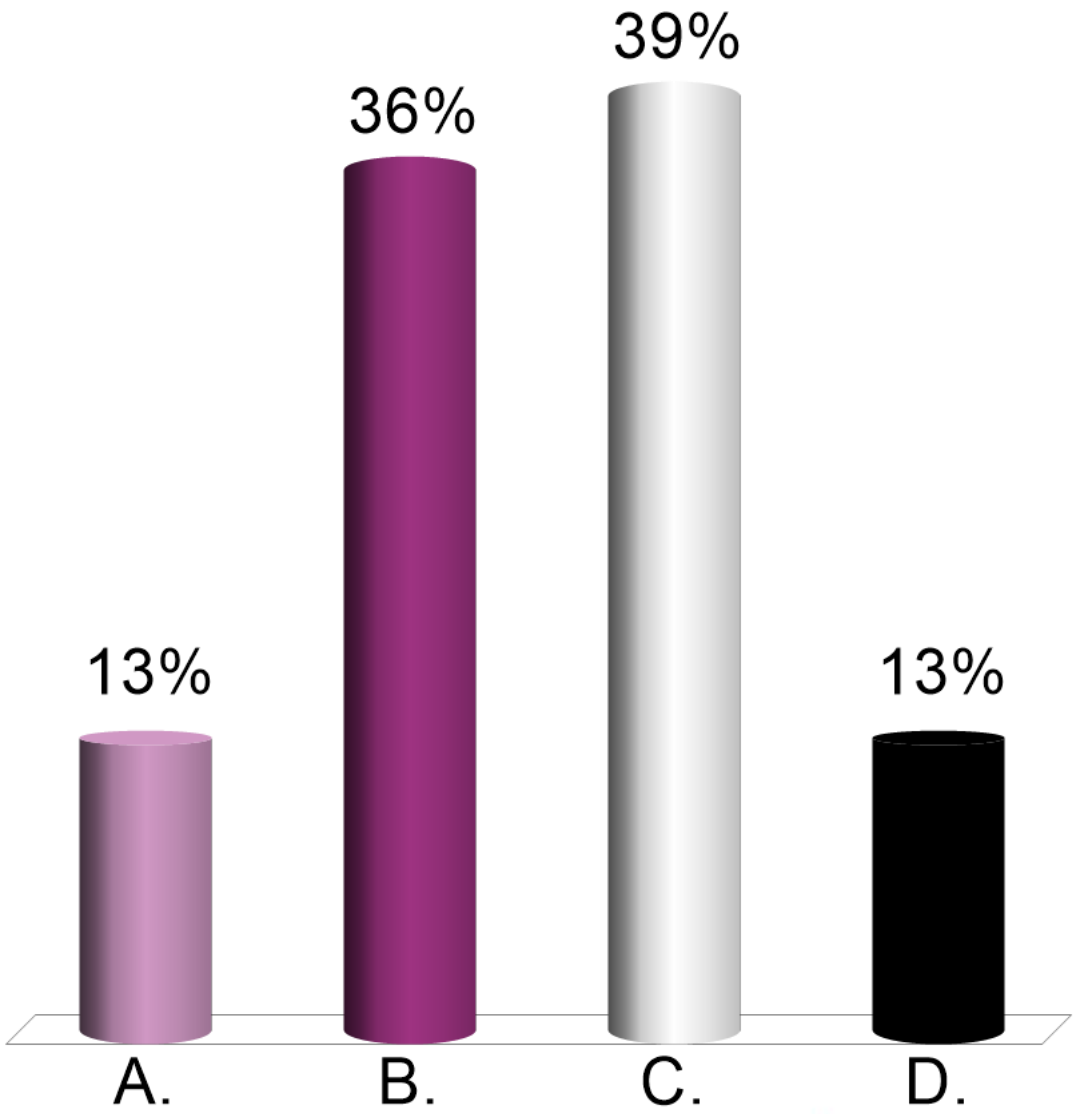
Introduction:
MRI – why, where, when?

- **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

Your experience in MRI planning

A. None
B. Basic (registration)
C. Conventional sequences (T1, T2)
D. Advanced sequences (ADC, DWI, SMR, PWI)



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Introduction:
MRI – why, where, when?

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

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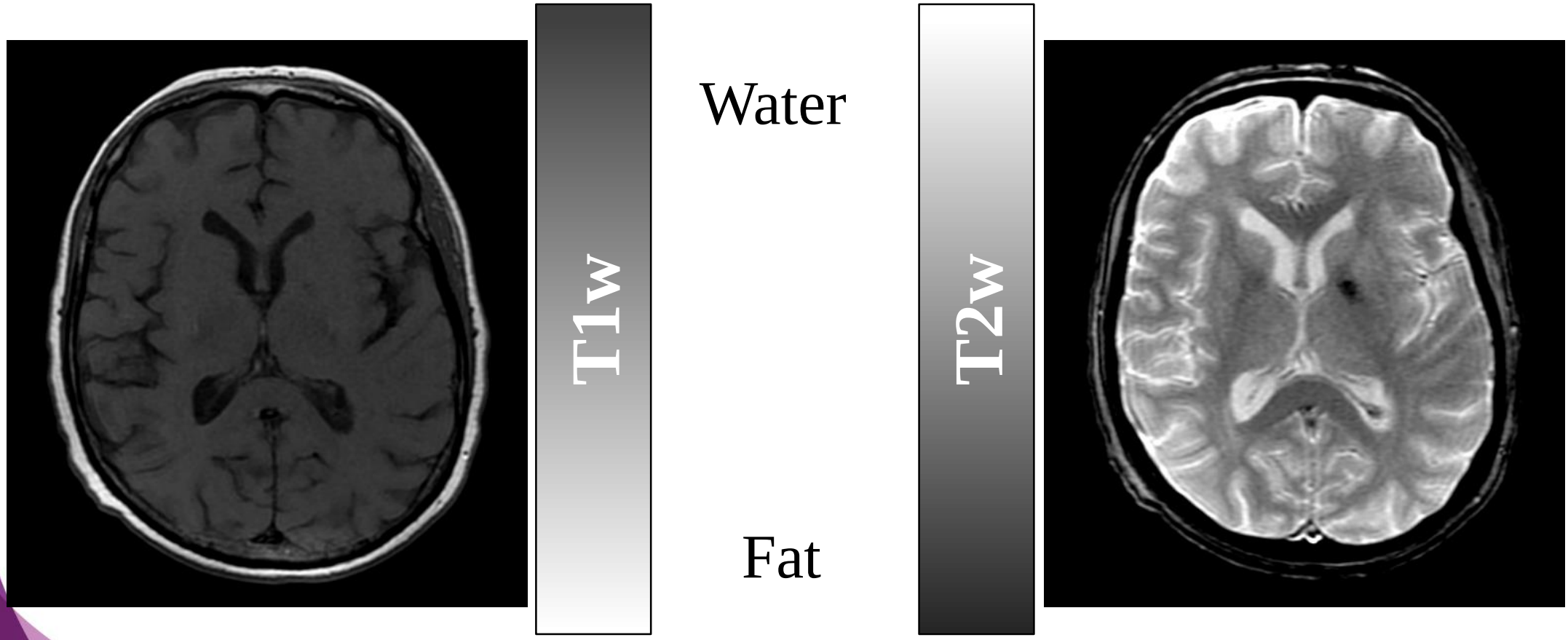
Introduction:
MRI – why, where, when?

- MRI T1w T2w images:



No signal: air, cortical bone

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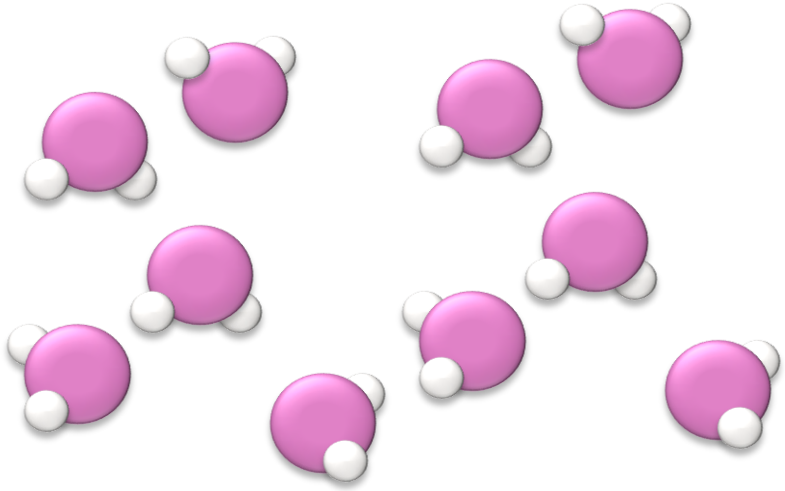
Functional imaging modalities in MRI

- Functional MRI: imaging modalities that focus on physiological/chemical features of tissues and vascularization, rather than morphology
  - Diffusion weighted MRI **DWI**
  - Diffusion tensor imaging **DTI**
  - Perfusion MRI **PWI**
  - Spectroscopy MRI **SMR**

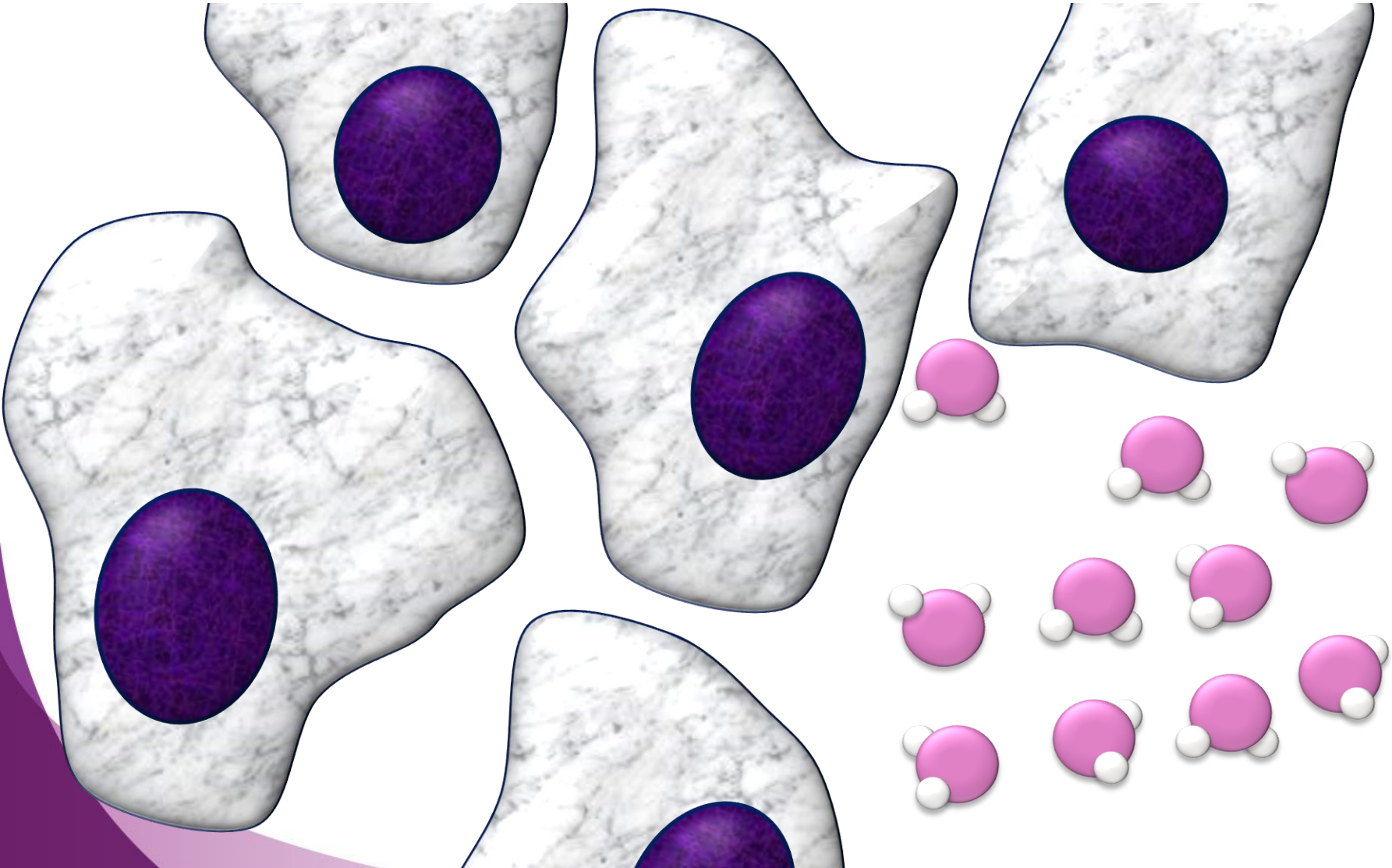
DWI images

- Rationale
  - In biological tissues H2O molecules produce random micro-movements due to the thermal energy (Brownian movements)
  - In DWI images can be obtained by analyzing this kind of movements
  - The micro-diffusion of water molecules gives informations about the normal and pathologic tissues structure



DWI images – ADC maps

- High cellularity – Lower Apparent Diffusion Coefficient (ADC)



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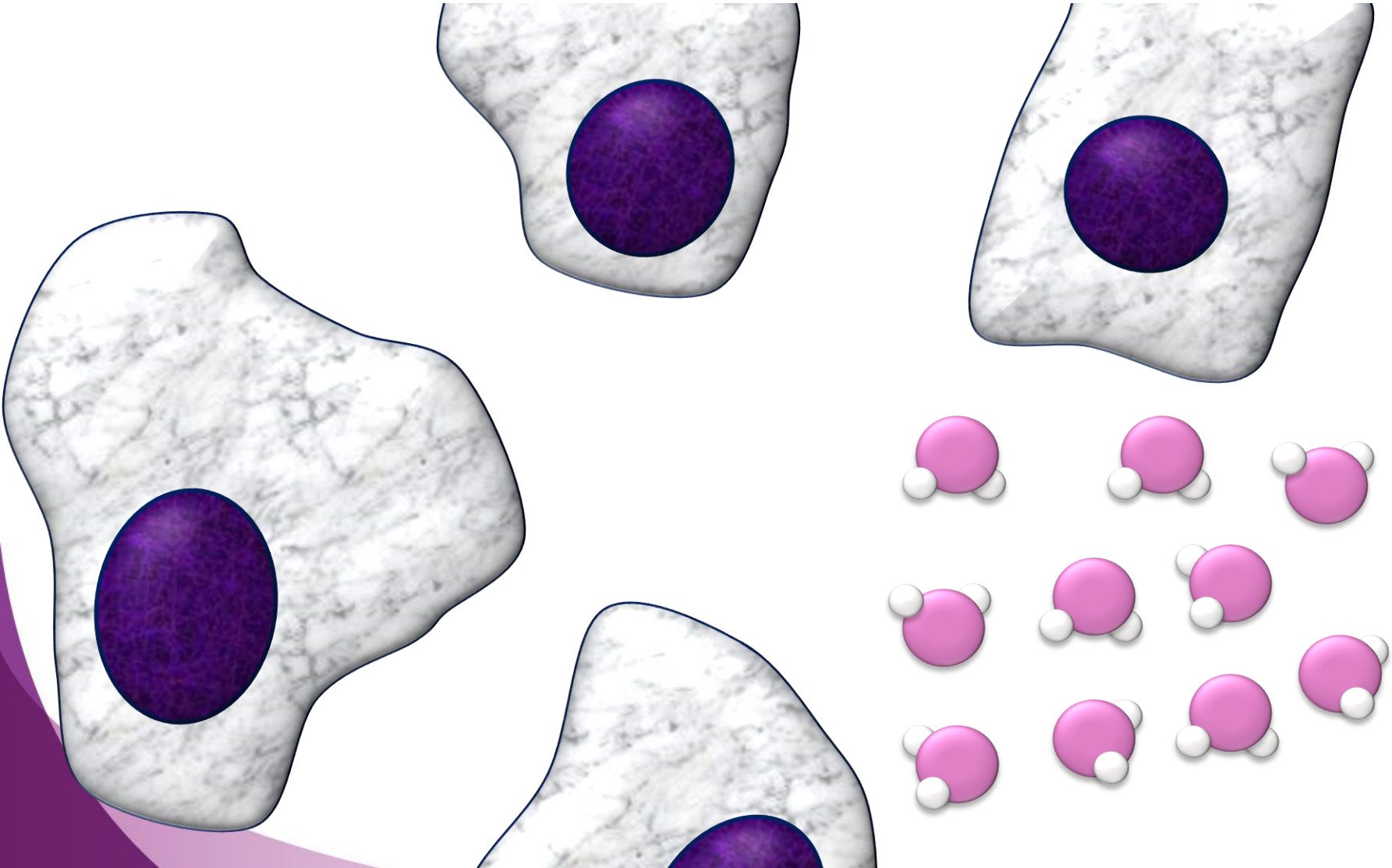
DWI images – ADC maps

- Low cellularity – Higher Apparent Diffusion Coefficient (ADC)



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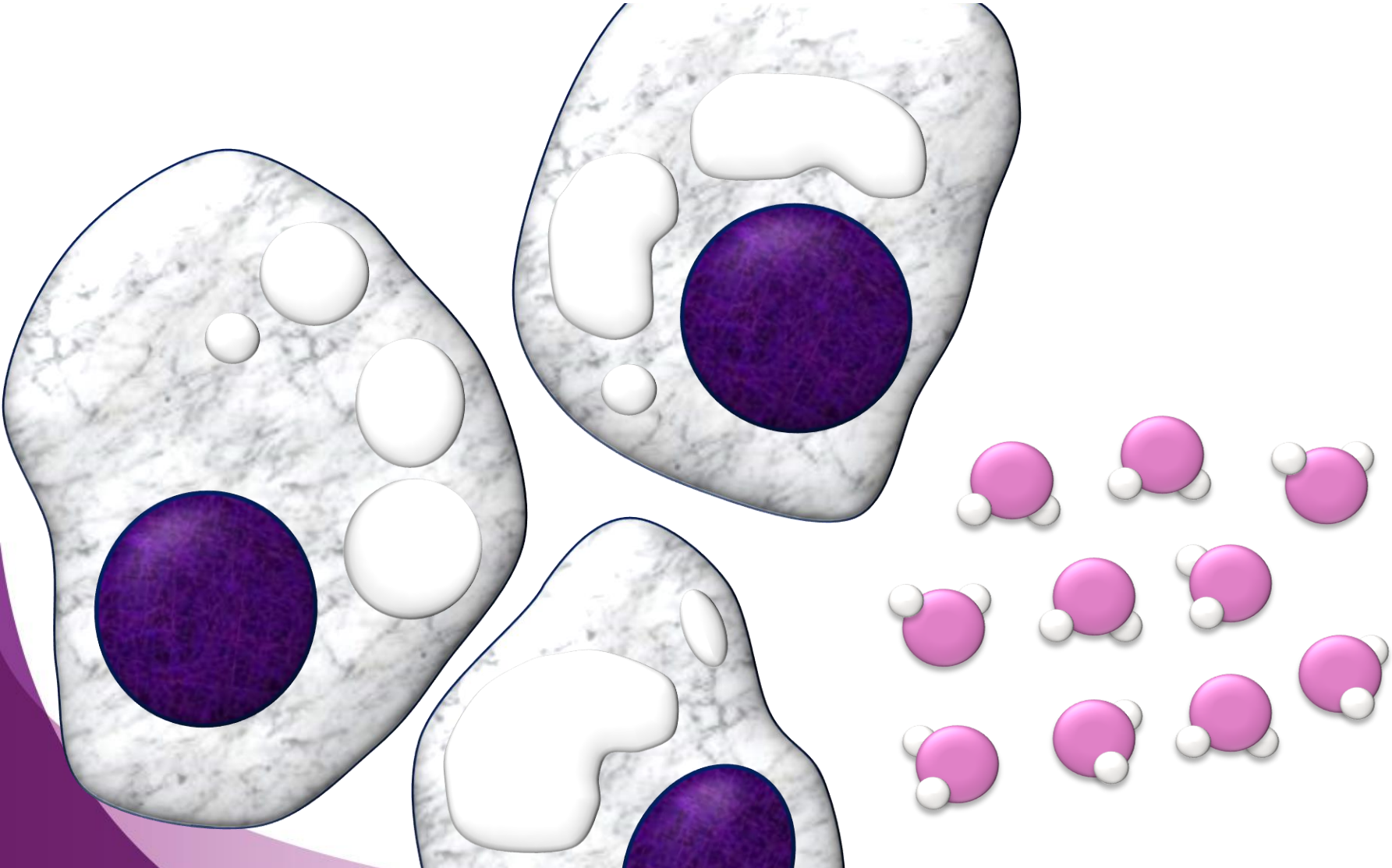
DWI images – ADC maps

- Intracellular edema – Lower Apparent Diffusion Coefficient (ADC)



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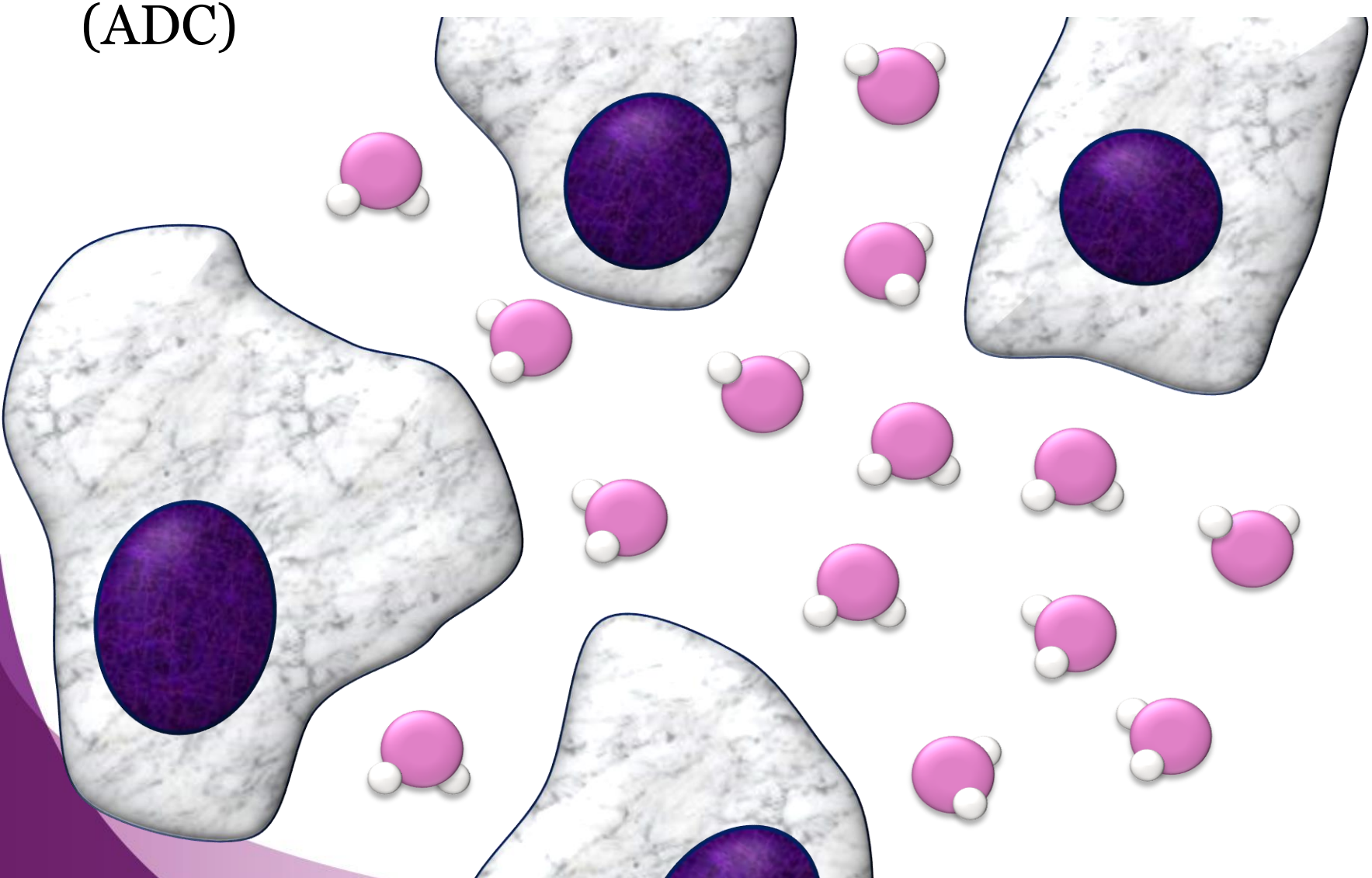
DWI images – ADC maps

- Extracellular edema – Higher Apparent Diffusion Coefficient (ADC)



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DWI images – ADC maps

- ADC mapping allows to obtain more informations on the biological "nature" of the tissues
  - Acute lesion (ischemic) ➡ oedema ➡ ▼ ADC
  - Chronic lesion (post-ischemic) ➡ relaxing tissues ➡ ▲ ADC
  - Neoplastic lesions ➡ high cellularity ➡ ▼ ADC
  - Neoplastic lesions ➡ necrosis ➡ ▲ ADC

I Berry. Imagerie par résonance magnétique. 2004; Masson Editeur, Paris.

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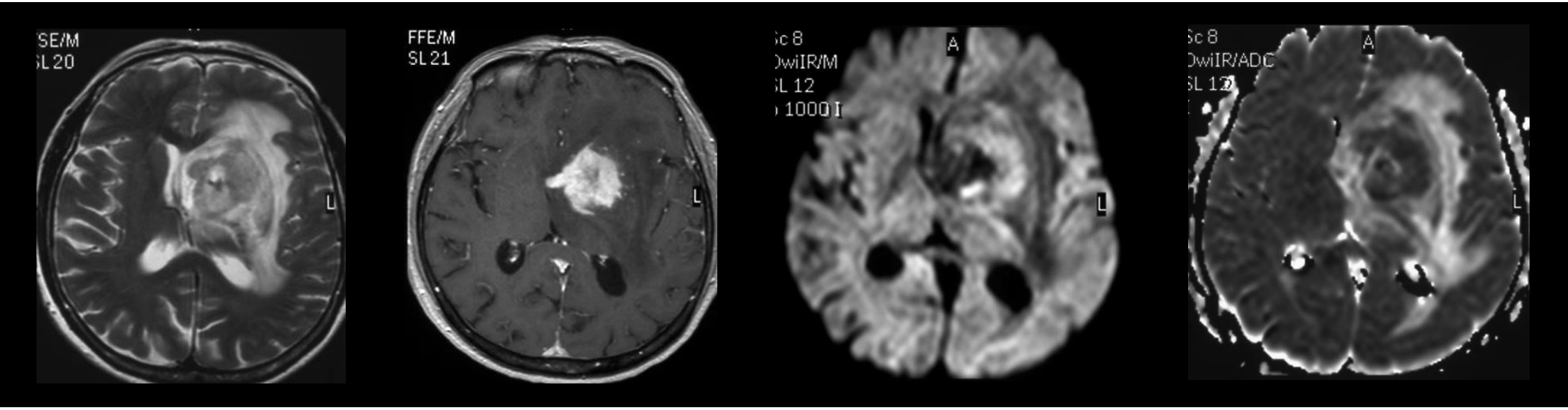
DWI images – ADC maps

T2 low signal CE DWI ▼ADC



High cellularity ➡ Primary Brain Lymphoma

Courtesy of C. Colosimo. Inst. of Radiology/Neuroradiology. UCSC - Rome

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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

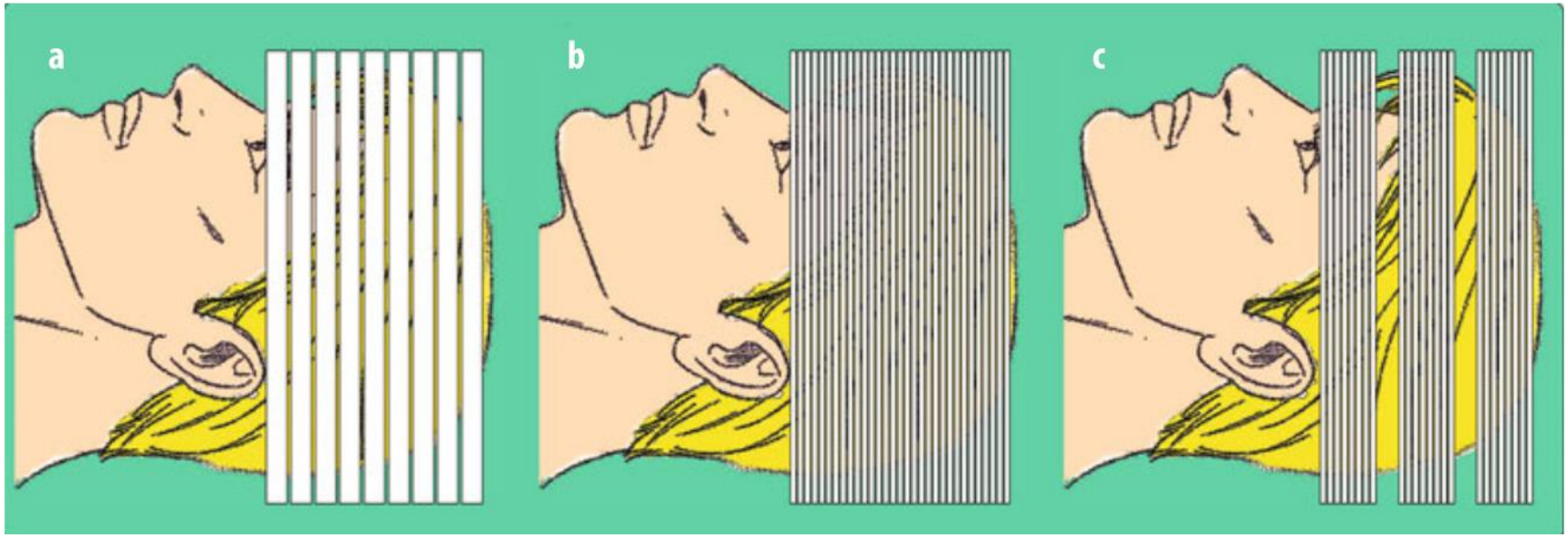
- When using new MRI imaging modalities?
  1. Refining the GTV (**targeting**)

     - 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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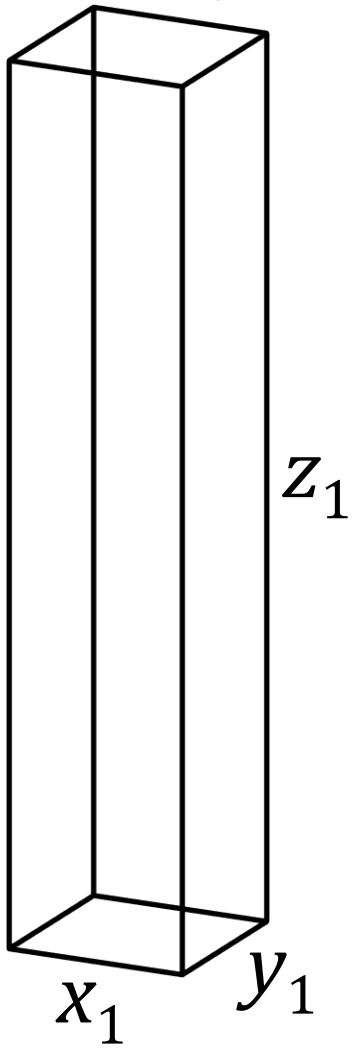
Is there a specific image sequence useful for planning?

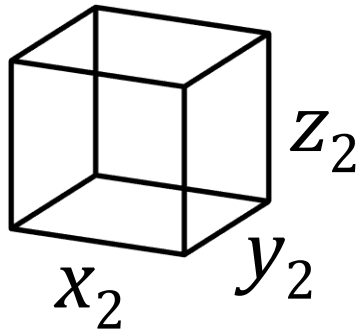
$z_1 \gg x_1, y_1$



2D

$z_2 = x_2, y_2$

$x_1 < x_2$



3D

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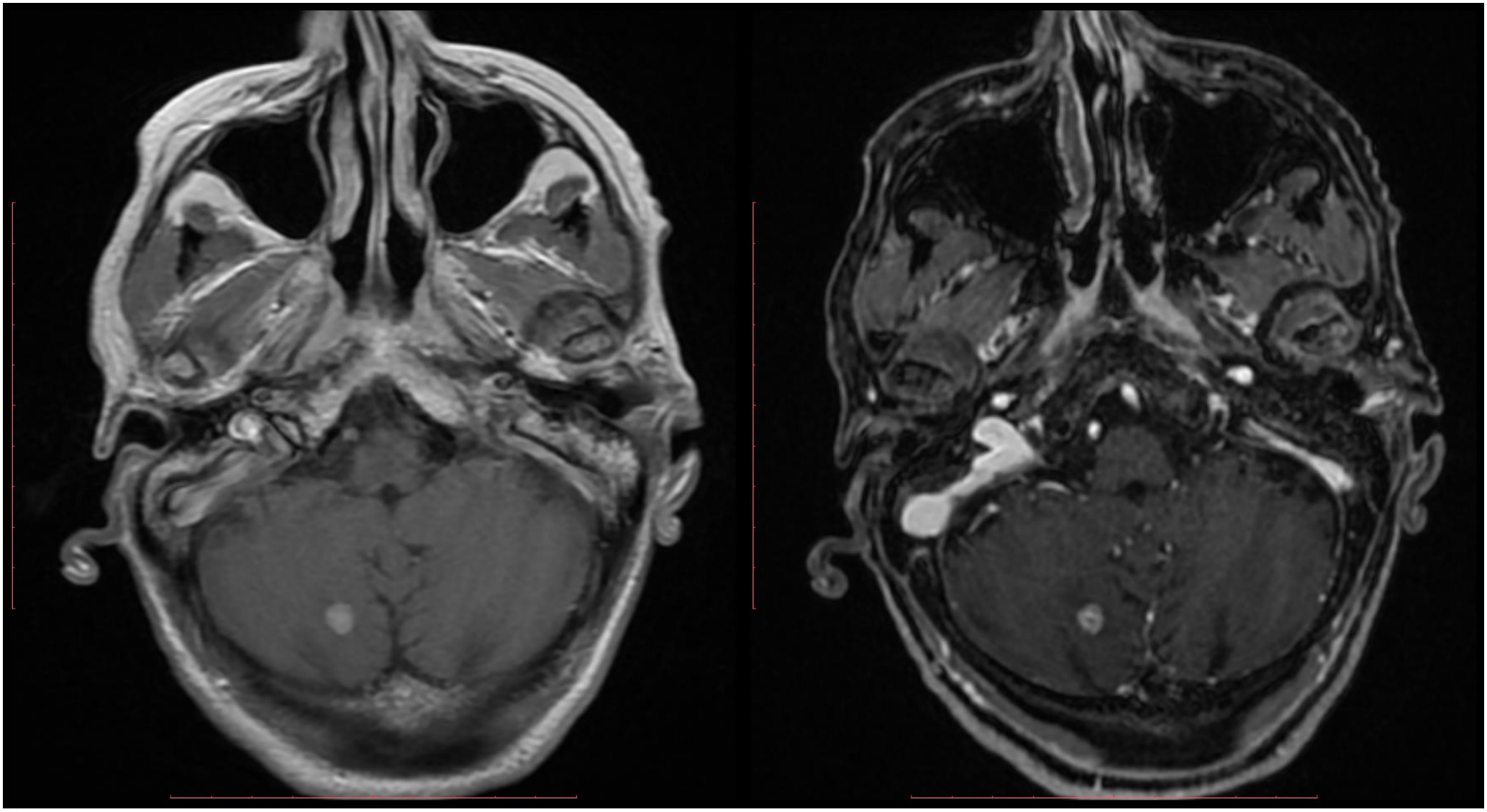
Is there a specific image sequence useful for planning?



2D – T1c

3D – FSPGR
(fast spoiled gradient echo)

Is there a specific image modality useful for planning?

- Switch screen

Partial volume artifact

Z coordinates Signal Intensty

FSPGR z	FSPGR val	T1c val	T1c z
0	10	68	0
0,5	12	68	0
1	15	68	0
1,5	27	68	0
2	28	68	0
2,5	26	68	0
3	168	68	0
3,5	258	68	0
4	285	160,375	4
4,5	284	160,375	4
5	274	160,375	4
5,5	223	160,375	4
6	78	160,375	4
6,5	64	160,375	4
7	52	160,375	4
7,5	23	160,375	4
8	10	22,5	8
8,5	7	22,5	8
9	12	22,5	8
9,5	78	22,5	8
10	15	22,5	8
10,5	33	22,5	8
11	15	22,5	8
11,5	10	22,5	8

Consider a voxel that contains fractional amounts f_A and f_B of two materials, A and B. The MR signal from the entire voxel (SV) will then reflect the **weighted average** of signals S_A and S_B from the two components

$$SV = f_A S_A + f_B S_B$$

Imperfect RF-pulse profiles may also cause to partial volume effects by exciting tissues outside the desired slice. When multiple slices are placed side, this interference is known as ***cross-talk***.

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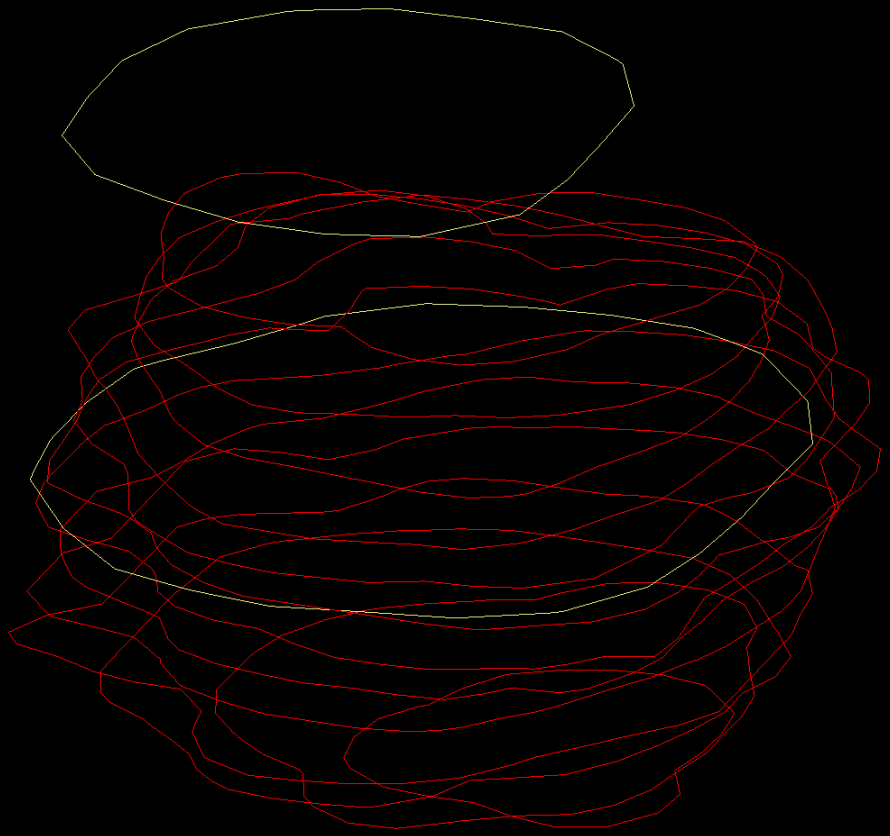


Wires

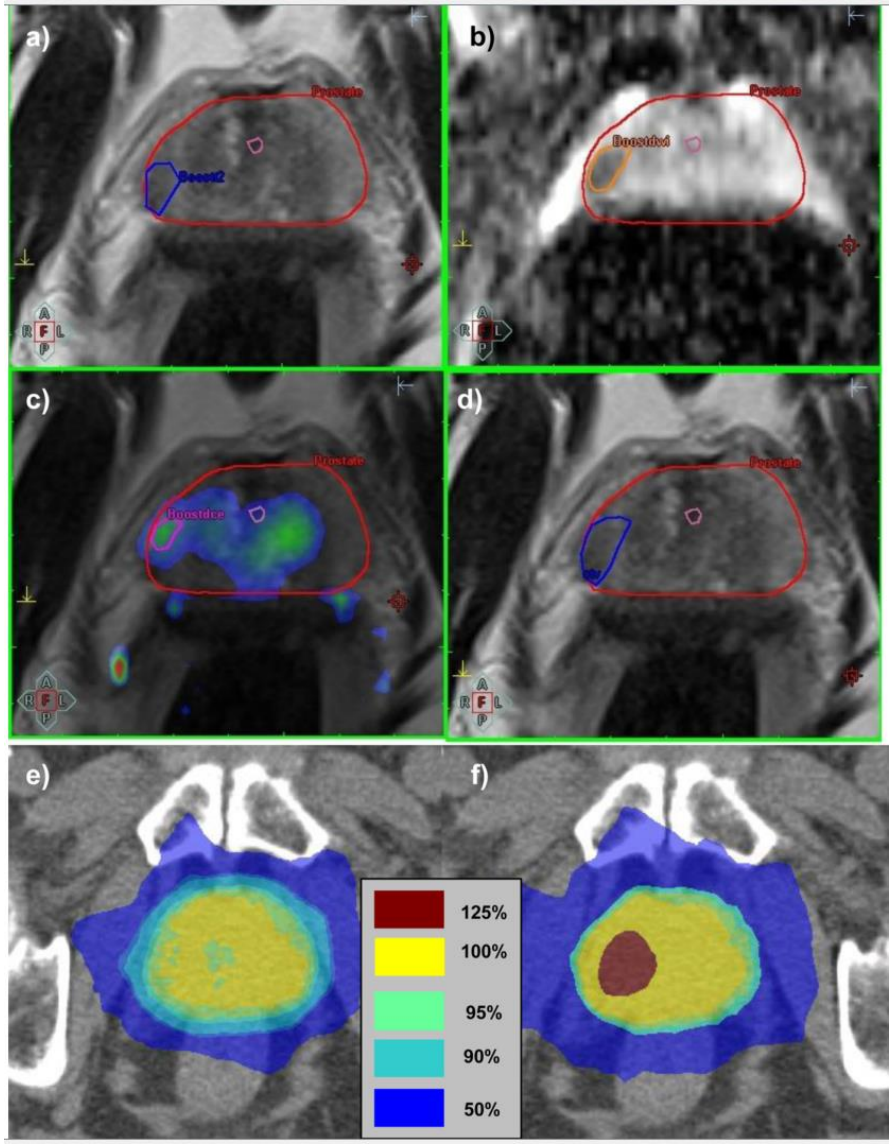
3D model

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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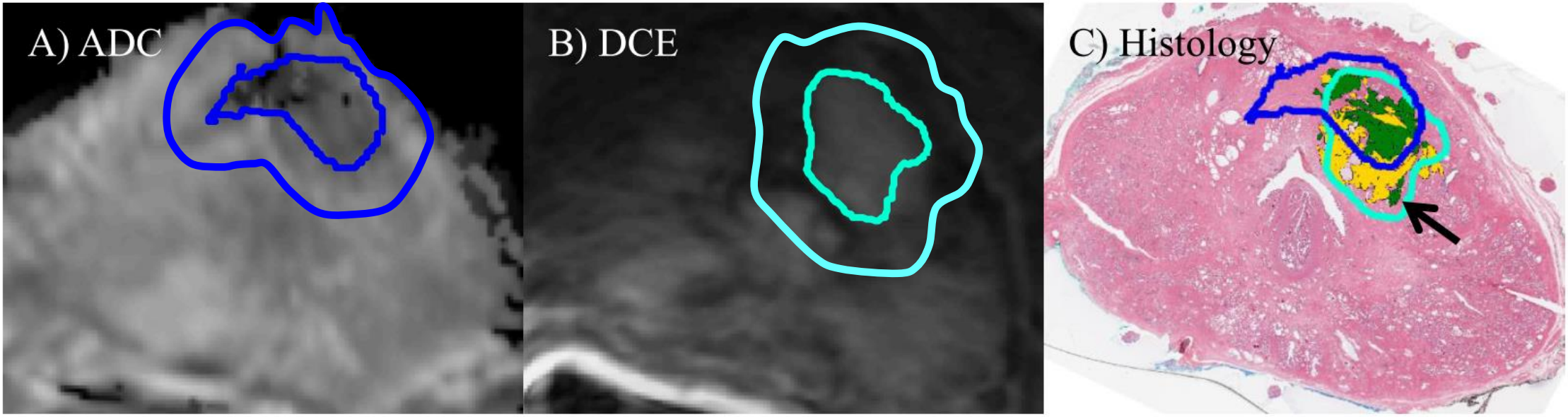
1. MRI for targeting: prostate



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

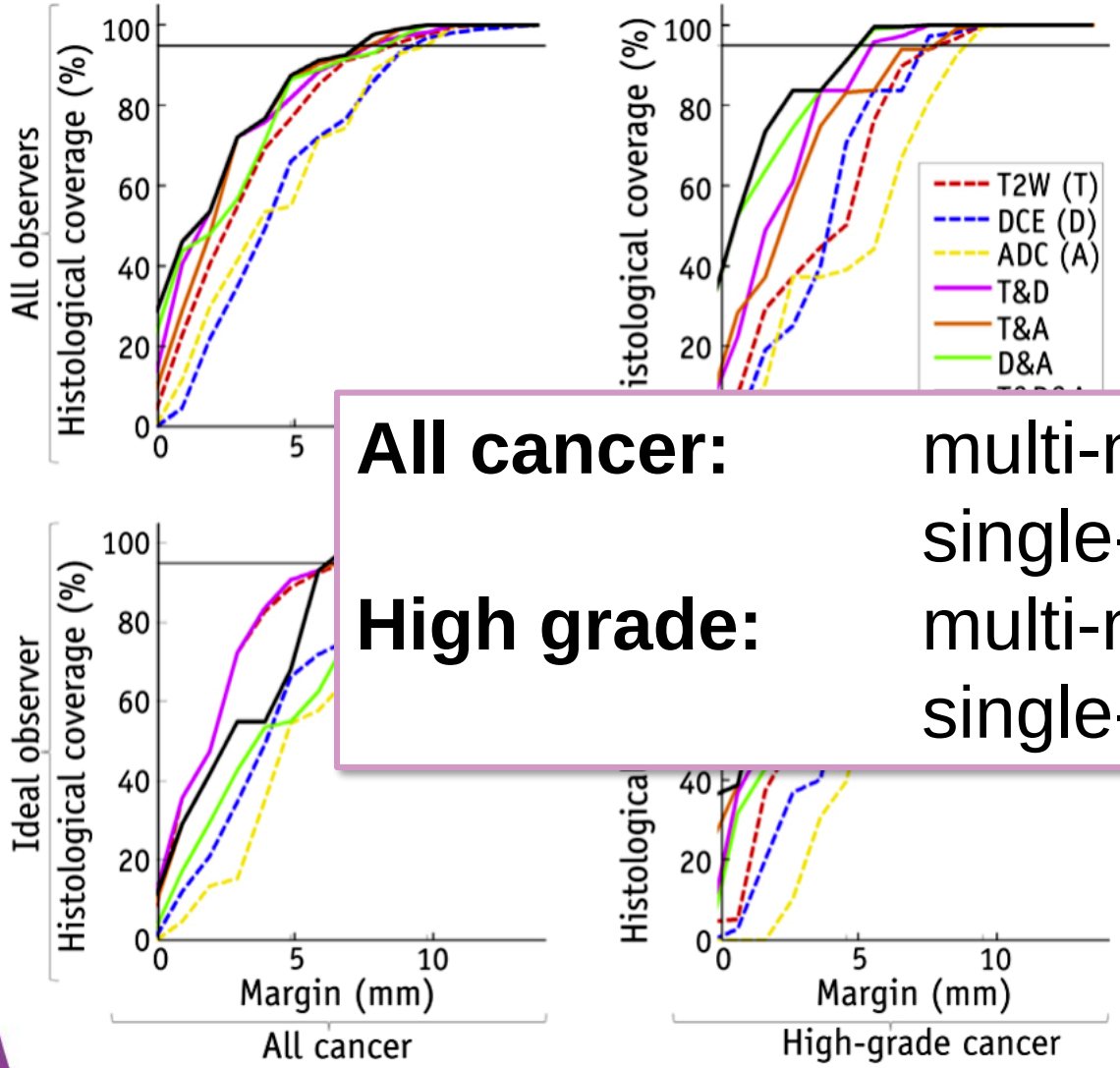

Table 2 Isotropic margins to cover 95% of histologic cancer for prospective case and proportion of prostate tissue spared by CTVs with such margins

	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
				55-68
				71-81
				70-80
				60-71
				53-67
				64-77

t; CTV = clinical
= T2 weighted.

Spared tissue is reported as the range (across observers) of the median proportion of prostate tissue not covered by CTVs. These 95% coverage margins account for interobserver and intertumor variability in the required boundary expansions, as necessary for development of guidelines to be used for future patients in prospective studies. CTV types are denoted by magnetic resonance imaging sequence (combinations of T, A, and D).

All cancer: multi-modality **8 mm**
single-modality **9-10 mm**

High grade: multi-modality **6-9 mm**
single-modality **9-10 mm**

Gibson E, Bauman GS, Romagnoli C, et al. Toward Prostate Cancer Contouring Guidelines on Magnetic Resonance Imaging: Dominant Lesion Gross and Clinical Target Volume Coverage Via Accurate Histology Fusion. Int J Radiat Oncol. 2016;96:188–196.

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New MRI imaging modalities and radiotherapy planning

- When using new MRI imaging modalities?
  1. Refining the GTV (**targeting**)

     - Dose escalation protocols

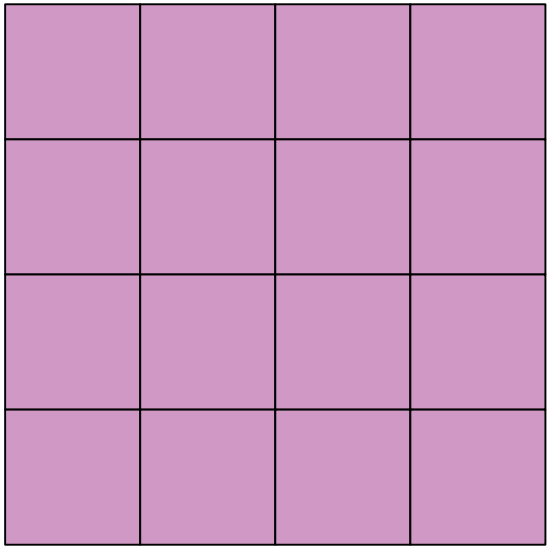
     - Dose distribution-imaging adaptation for simultaneous or sequential boost treatments
  2. Direct **planning** on MRI images
  3. Hybrid machines

2. Direct planning on MRI images

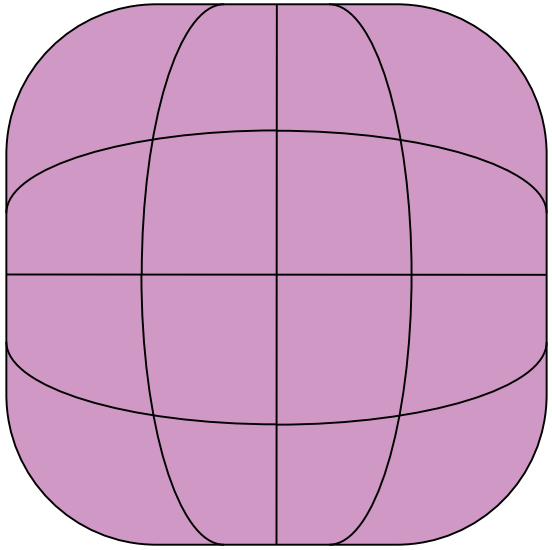
- Problems in using only MRI for planning
  1. Image **distortion**
  2. Dose calculation (lacking informations needed to recontruct **electron density maps**)

2. Direct planning on MRI images

- Strategies for reduce geometry artifact due MRI images acquisition process



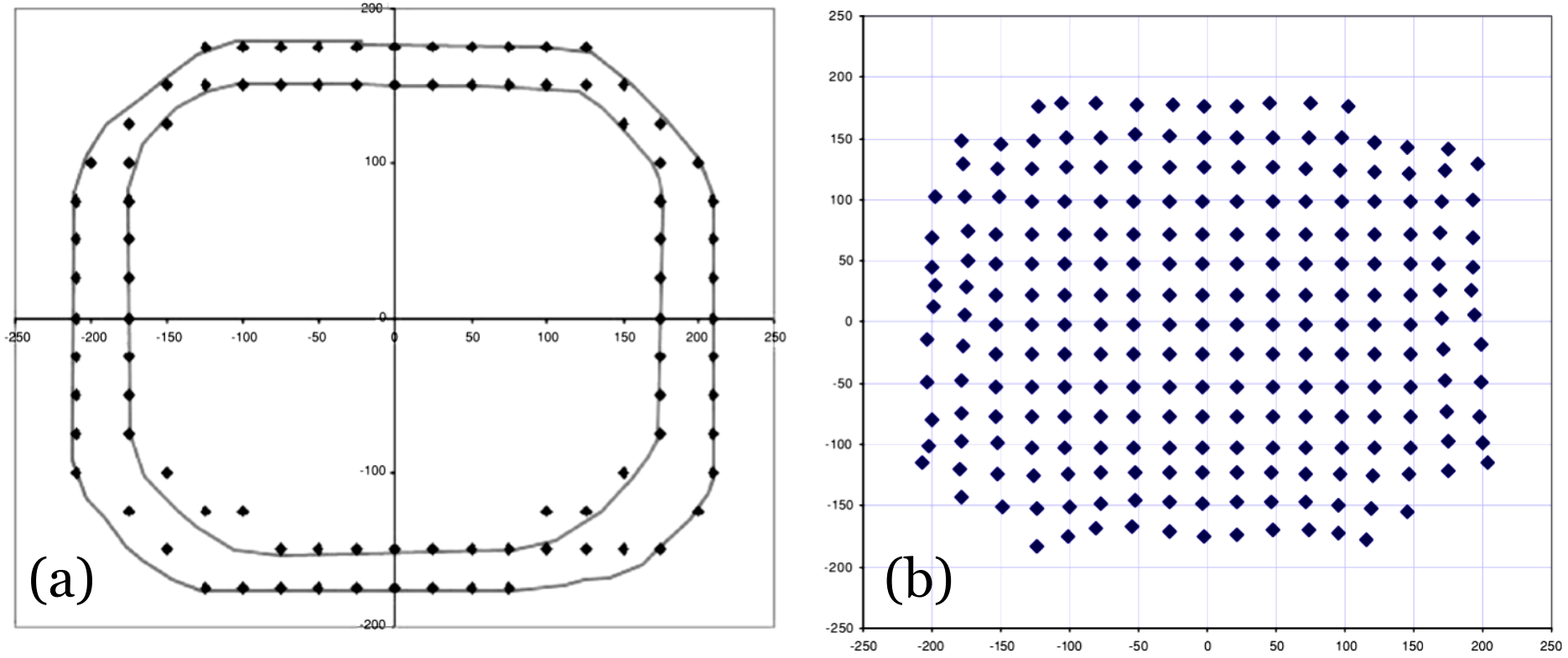
CT



MRI

2. Direct planning on MRI images

- Definition of viewable area of the scanner (a) and creation of a distortion map (b)



Z Chen et al. Investigation ofMR image distortion for radiotherapy treatment planning of prostate cancer. Phys.Med. Biol. 51 (2006) 1393–1403

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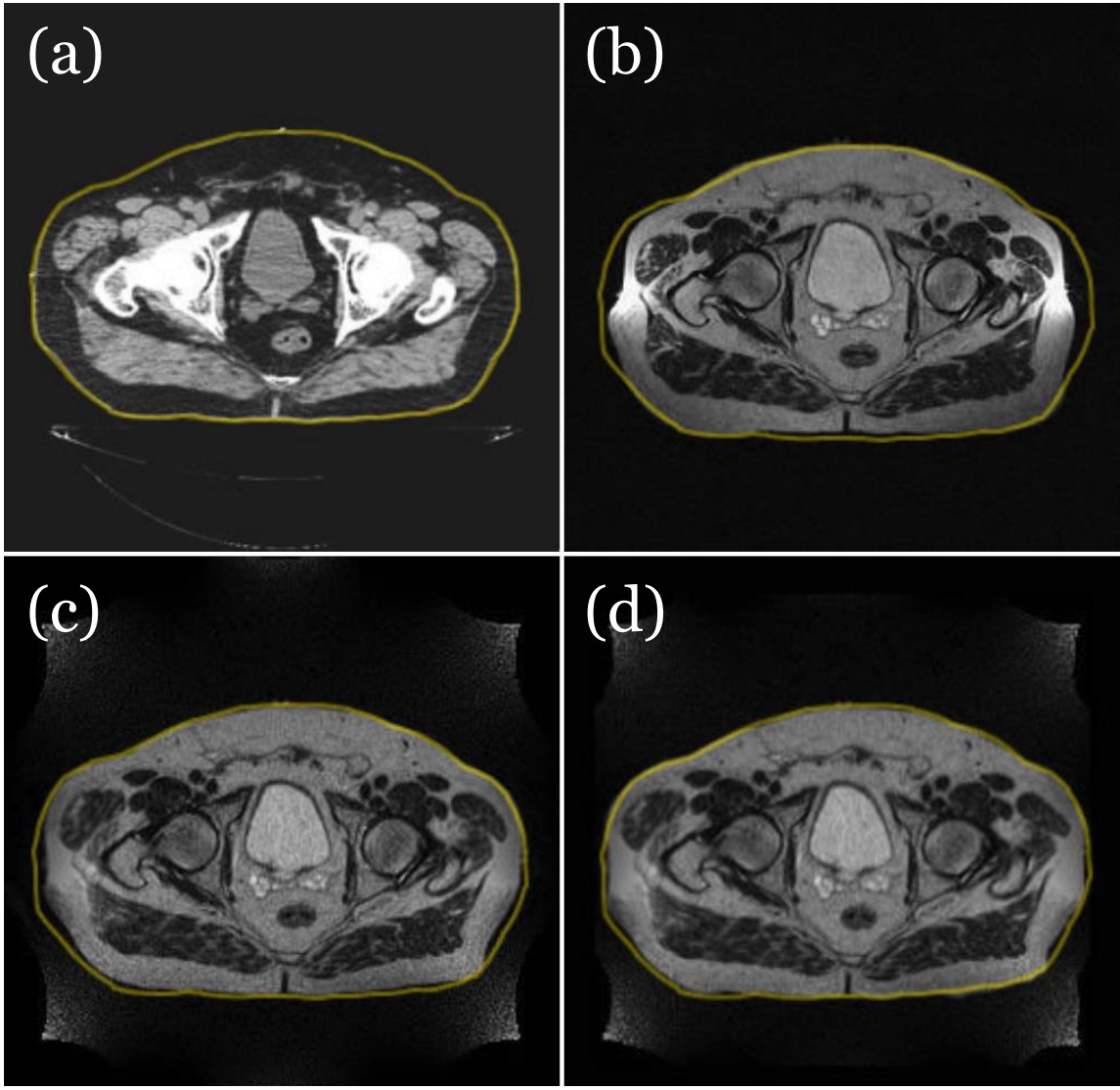
2. Direct planning on MRI images

- Use of scanner software and correction map for image correction
  a) CT scan
  b) MRI uncorrected
  c) On-scanner correction
  d) Distortion map correction



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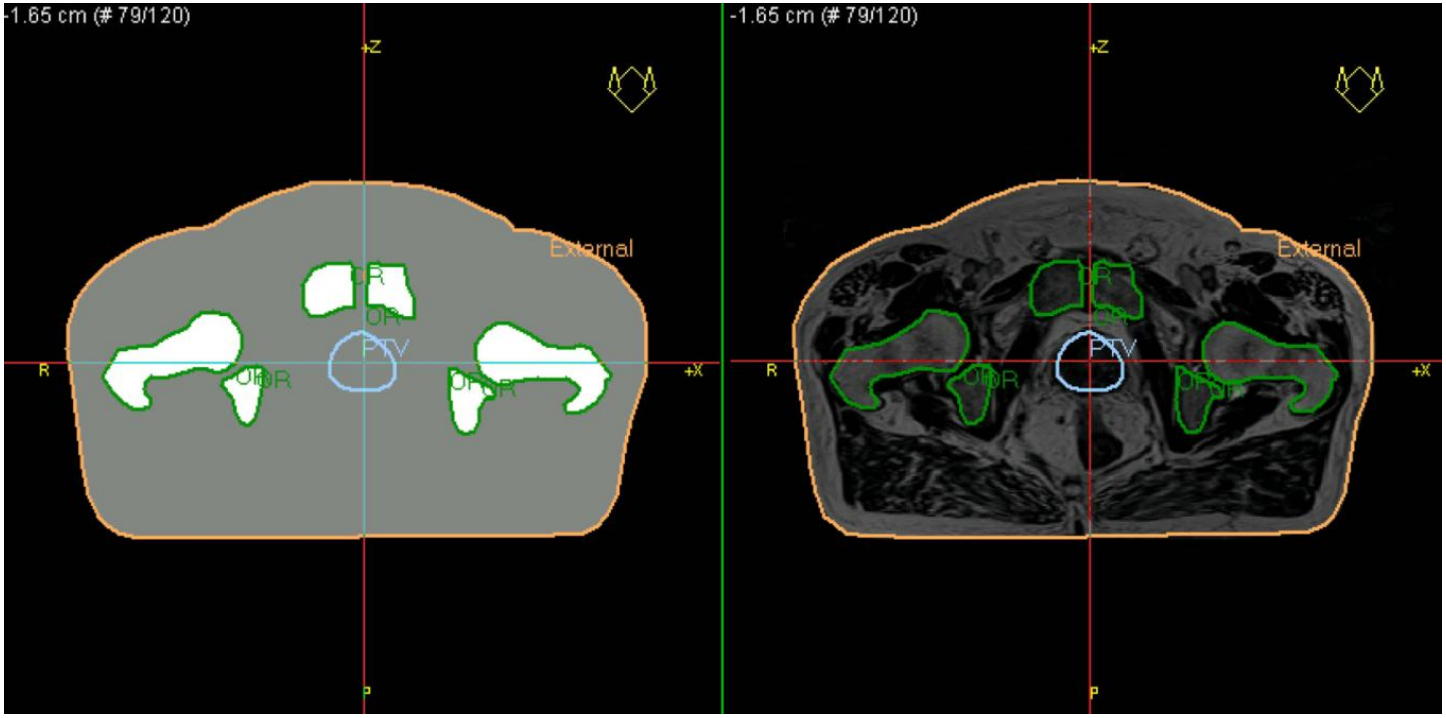
2. Direct planning on MRI images

- Strategies for adding informations to allow calculation of dose distribution
  - Image registration
  - Creation of **bulk-density CT images**
  - Creation of **simulated CT-images** (**s-CT**)

2. Direct planning on MRI images

- **Bulk-density images** are synthetic CT images where the HU are simulated in a simplified way, using the anatomy in MRI to create regions to be assigned with a specific HU value



JH Jonsson et al. Treatment planning using MRI data: an analysis of the dose calculation accuracy for different treatment regions. Radiation Oncology 2010, 5:62

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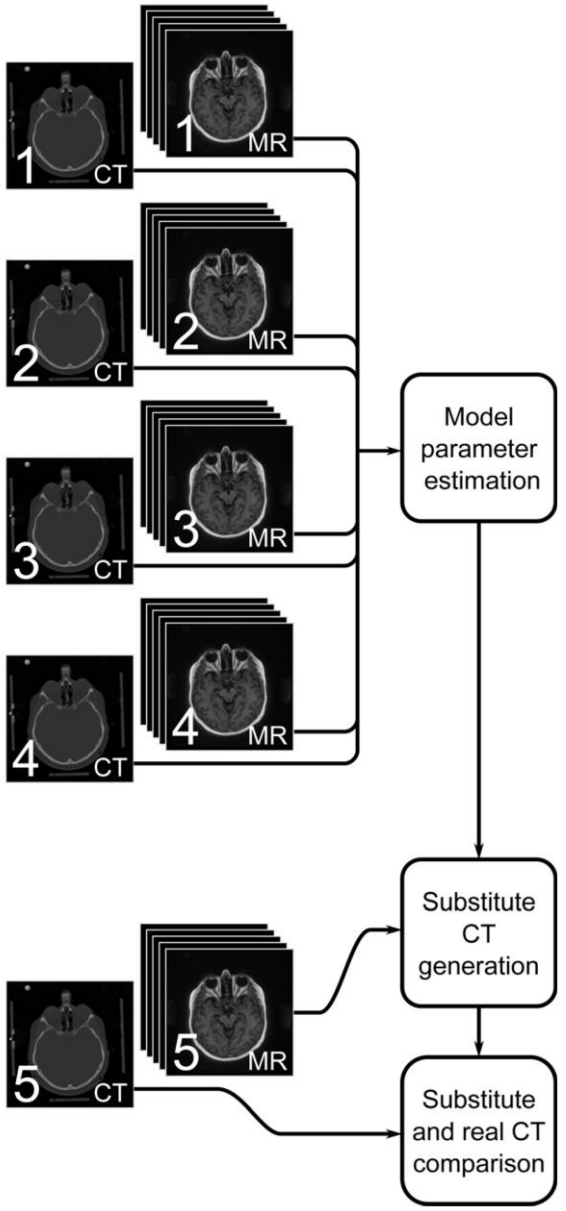
2. Direct planning on MRI images

Model definition for creating simulated CT images: Gaussian mixture regression (**GMR**) model

Model optimization and parameters estimation

s-CT generation and model results verification



A Johansson et al. CT substitute derived from MRI sequences with ultrashort echo time. Med. Phys. 38 (5), 2011

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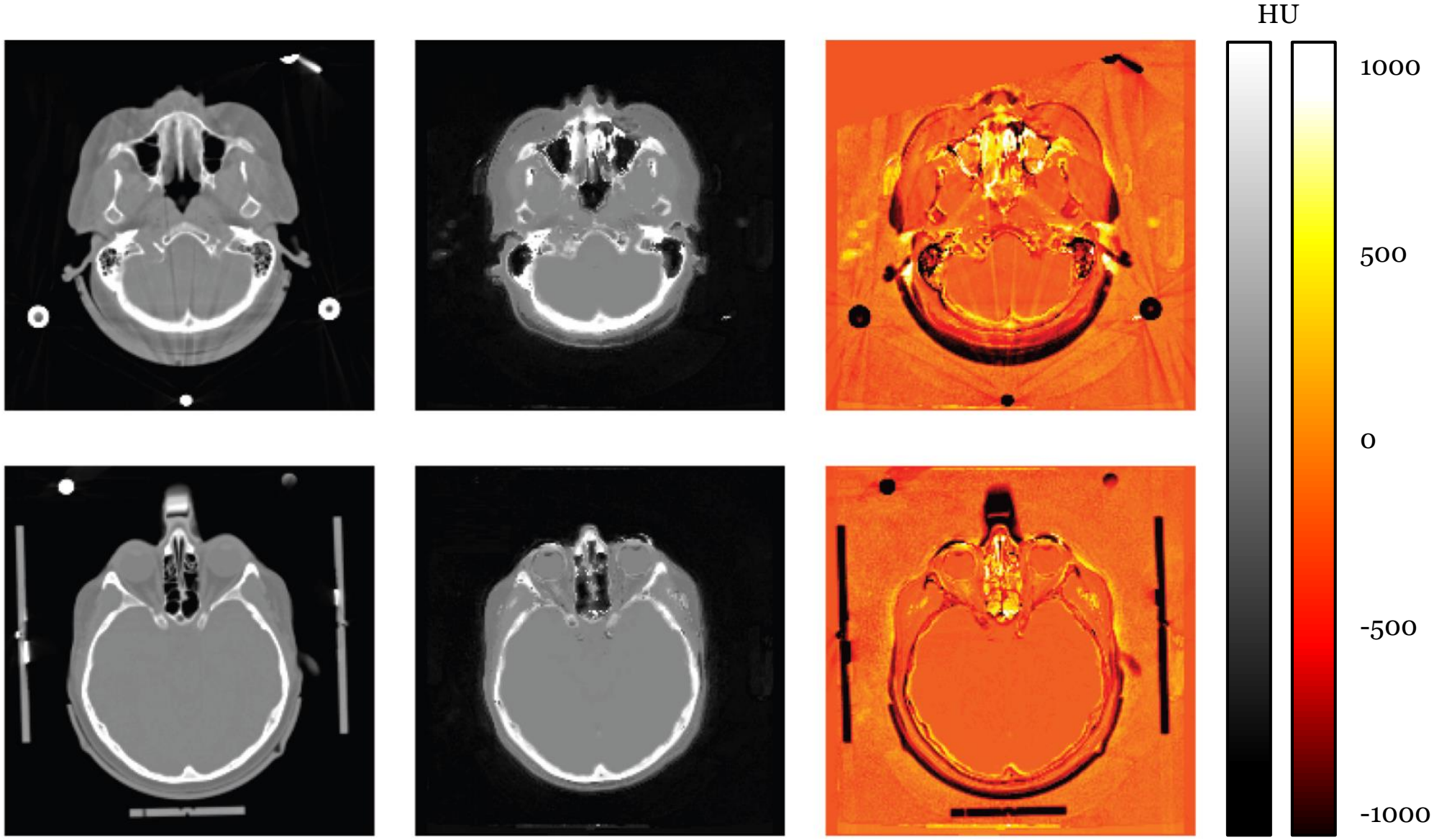
2. Direct planning on MRI images



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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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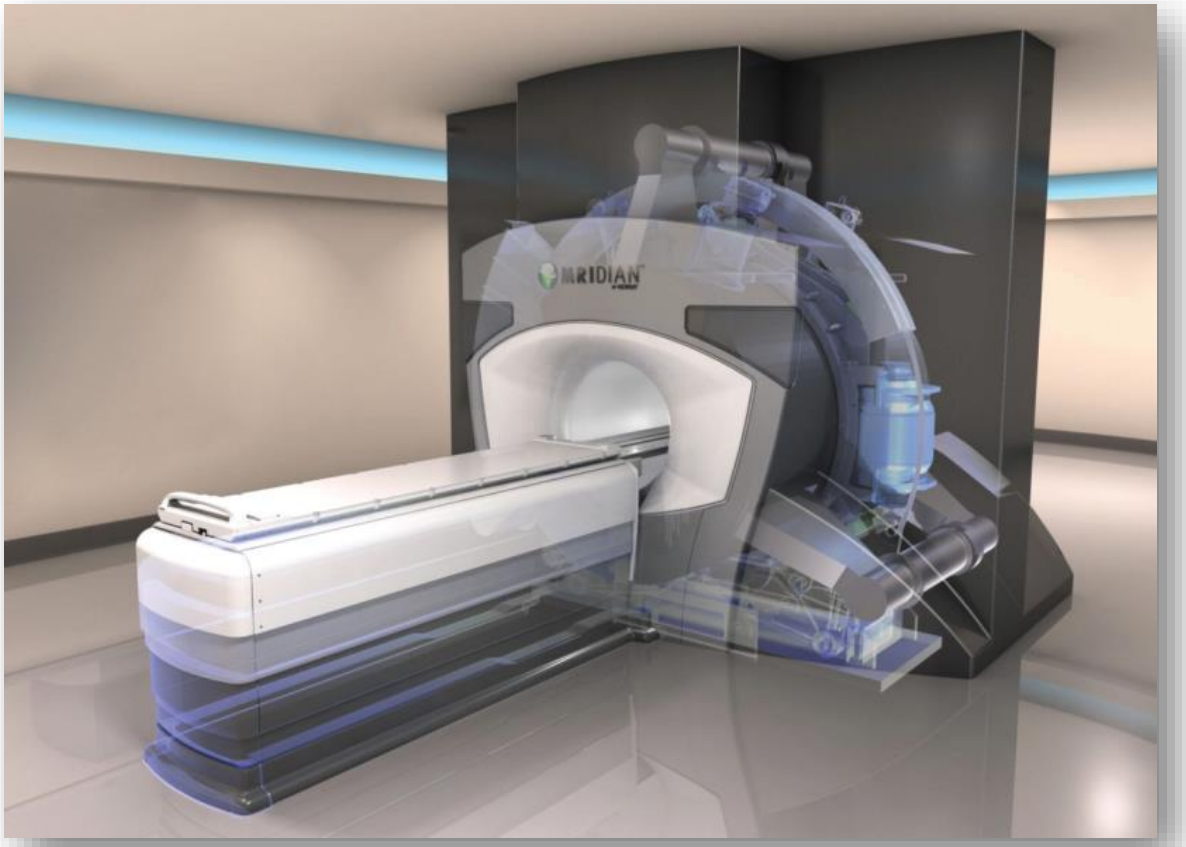
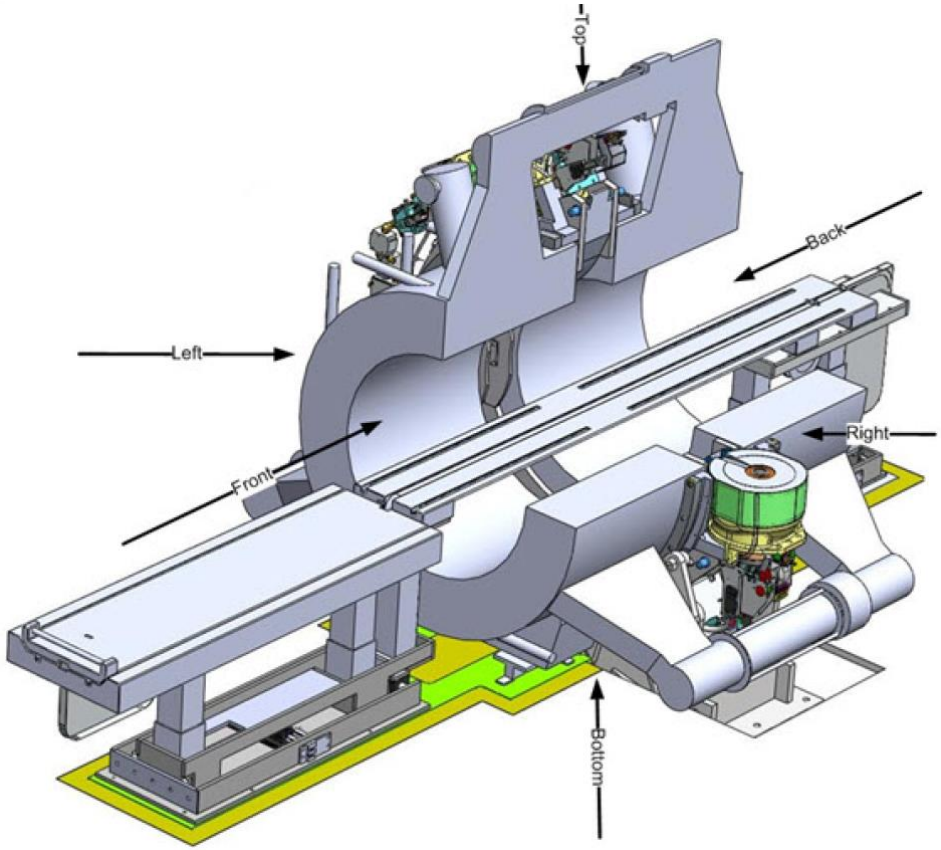
Low Tesla MR-^{60}Co





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

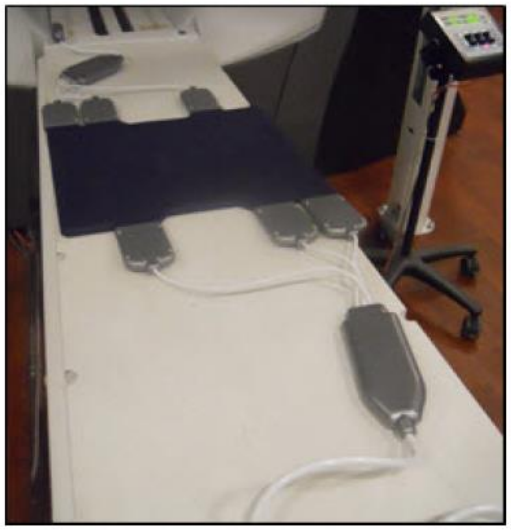
6 MV Linac
(FFF; Drate = 600 cGy/min)

+

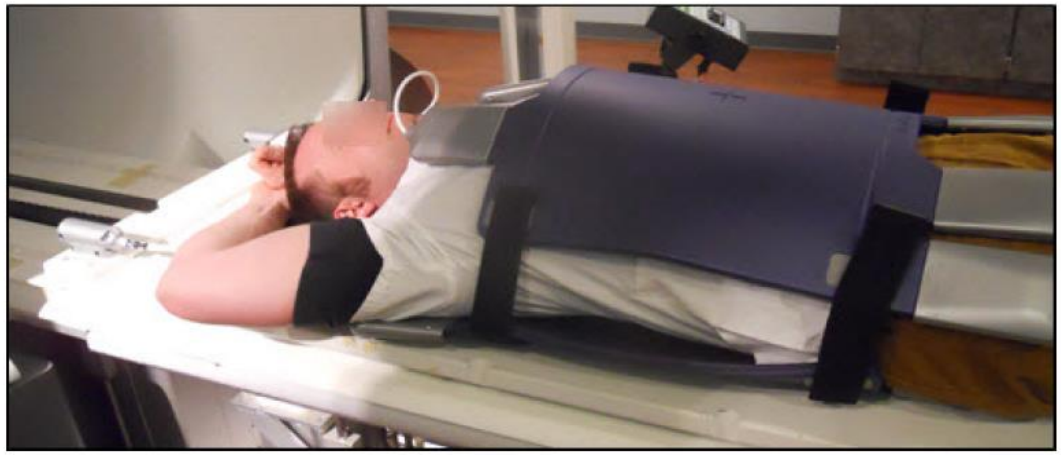
MR Siemens @ 0,35 T

MRI – ^{60}Co: imaging features

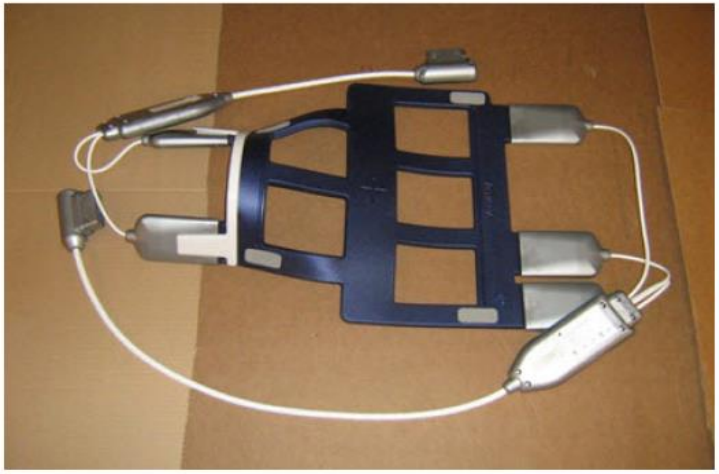
Torso Coil half



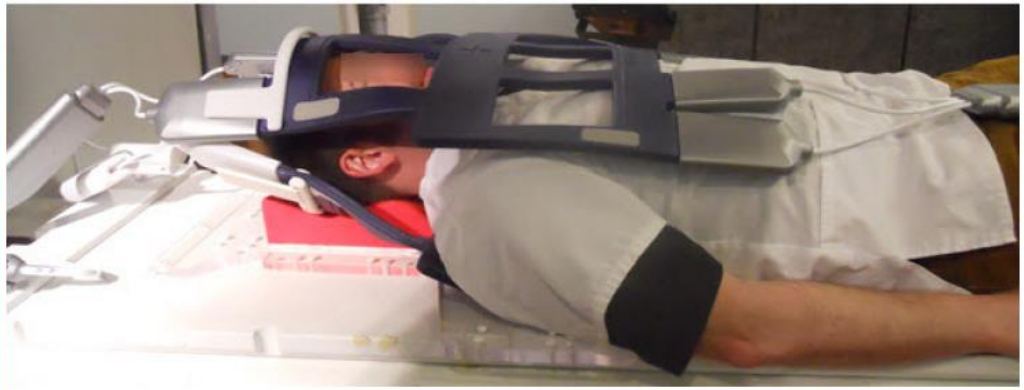
Torso Coils in place



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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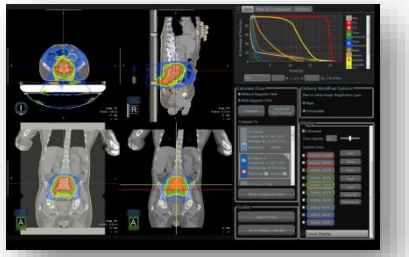
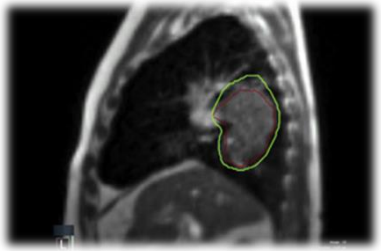
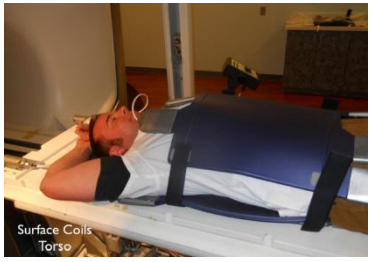
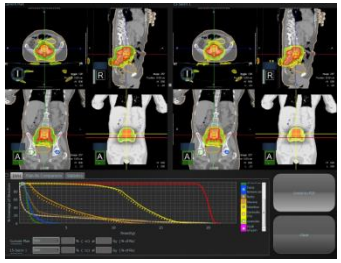
ViewRay workflow





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*





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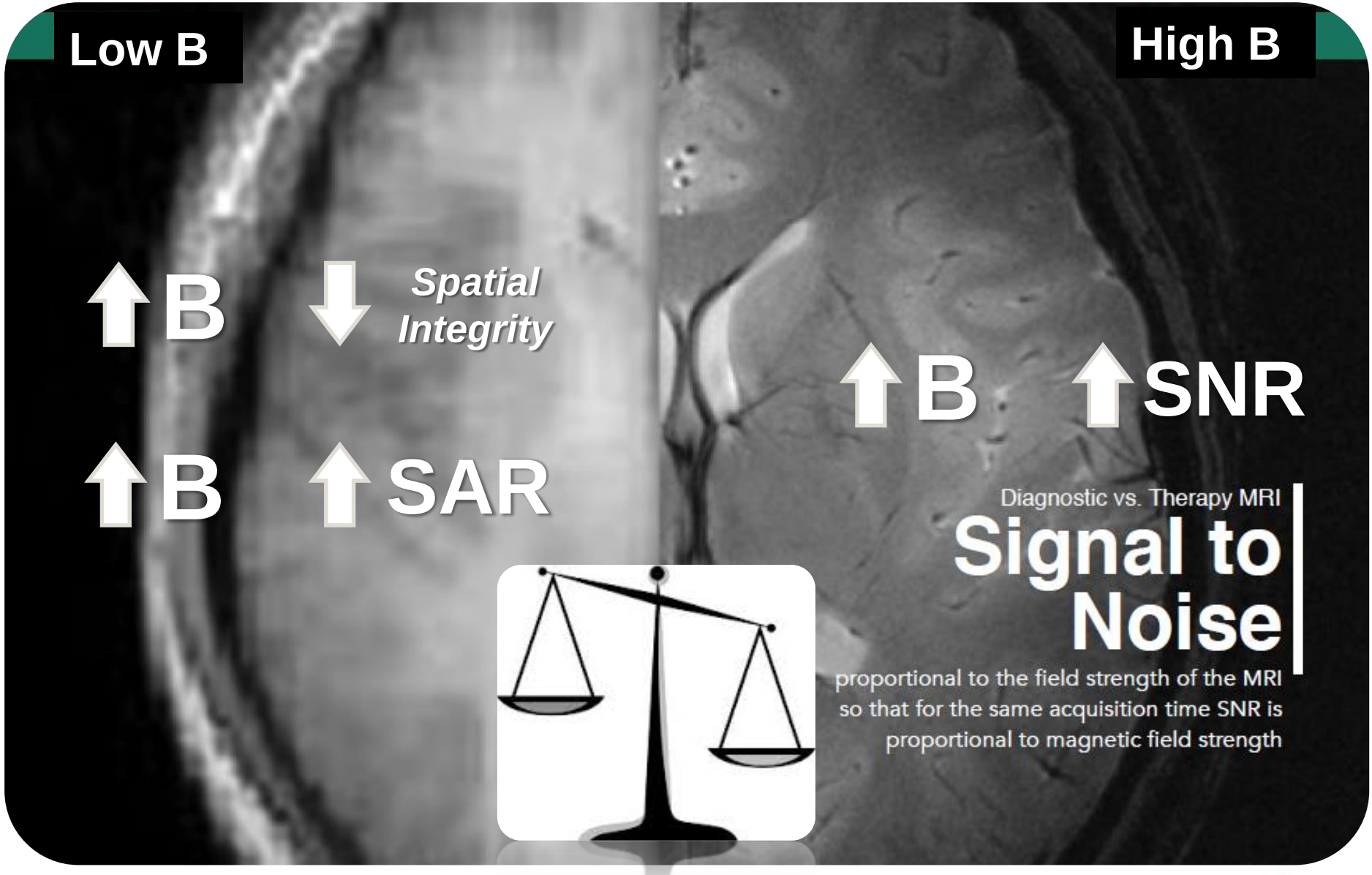
MR for planning



ESTRO School

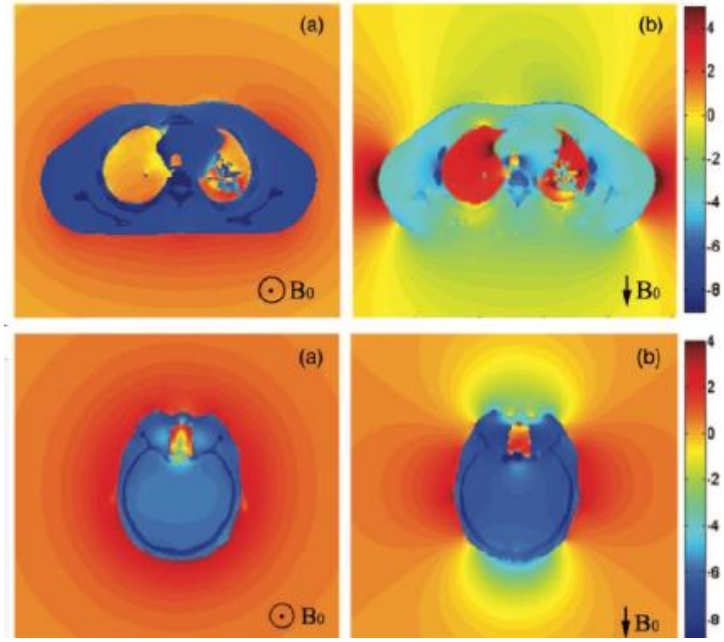
Spatial integrity

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

ESTRO School

Spatial integrity

Chemical Shift

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

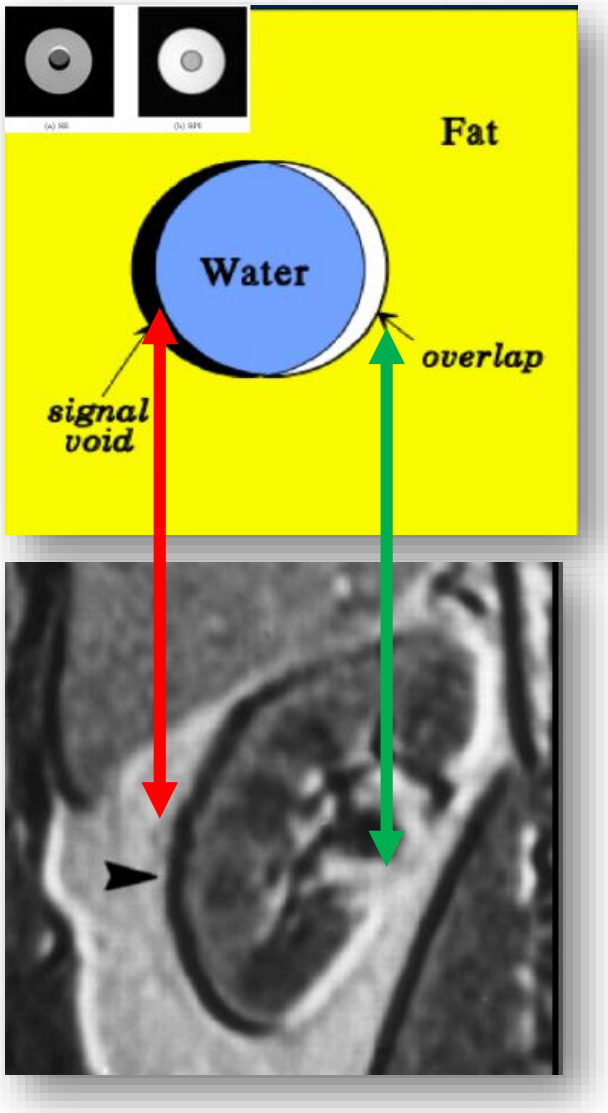
This effect depends from B

~ mm → ***224 Hz @ 1,5 T***

51 Hz @ 0,35 T

↑

< 1 mm



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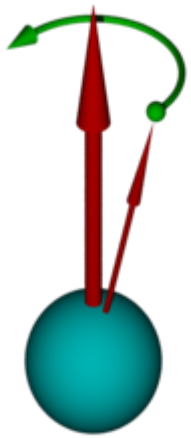
SAR

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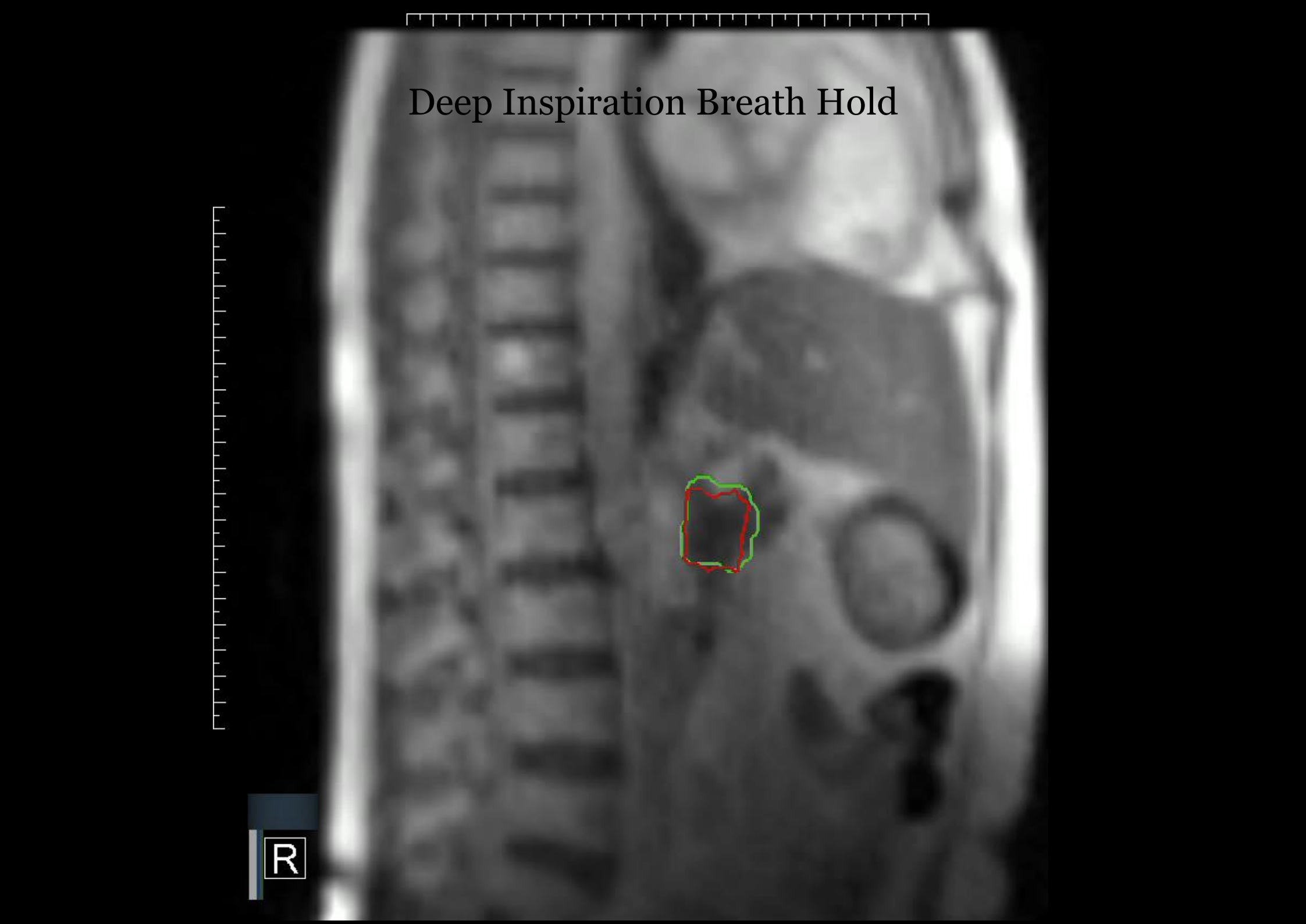
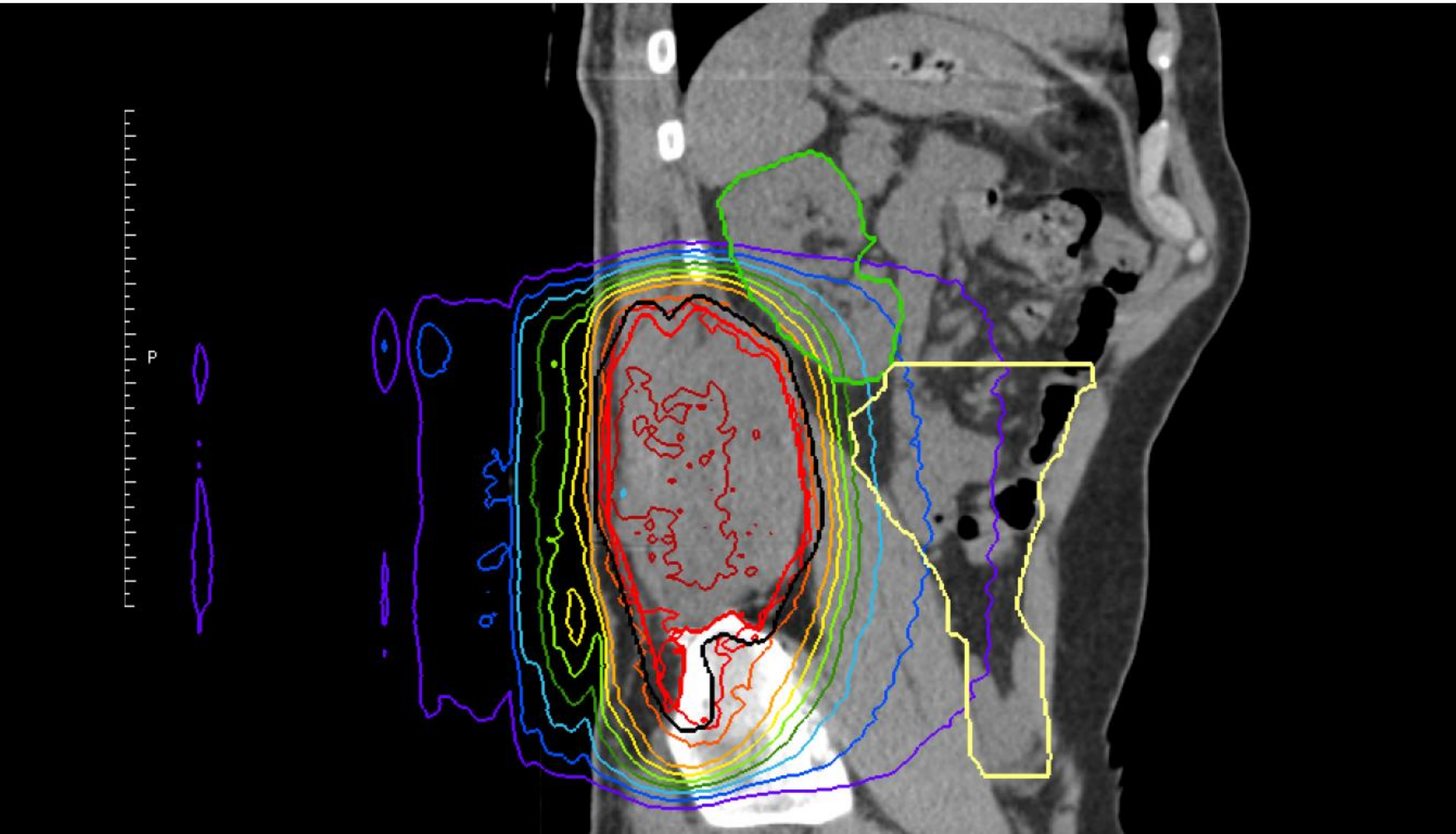
Gating treatment for target movements or target volume shape changes (air)


Deep Inspiration Breath Hold
R

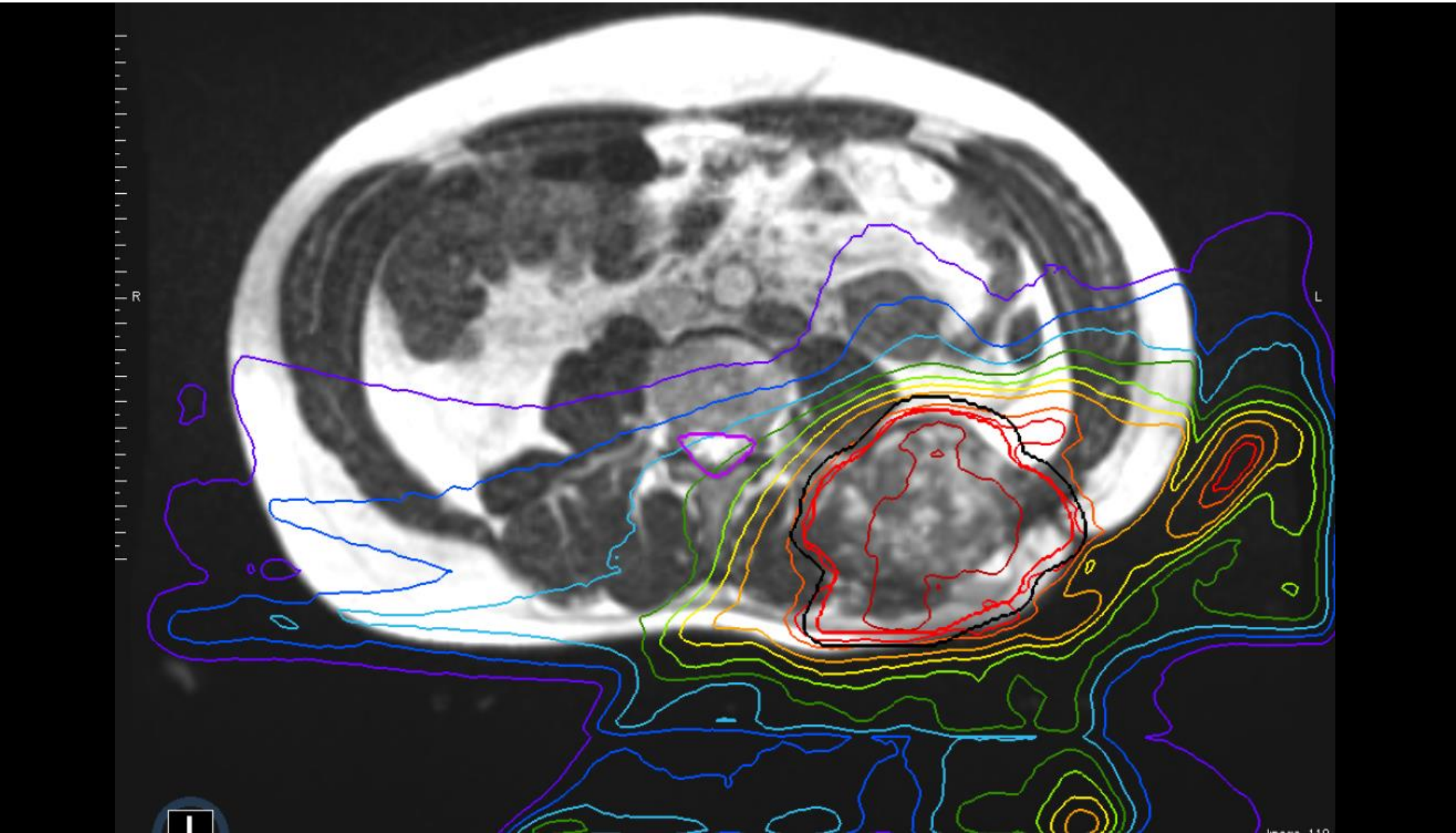
Gating treatment for OAR movements or for PRV boundaries definition

Rhabdomyosarcoma of the back recurrence, near the left kidney

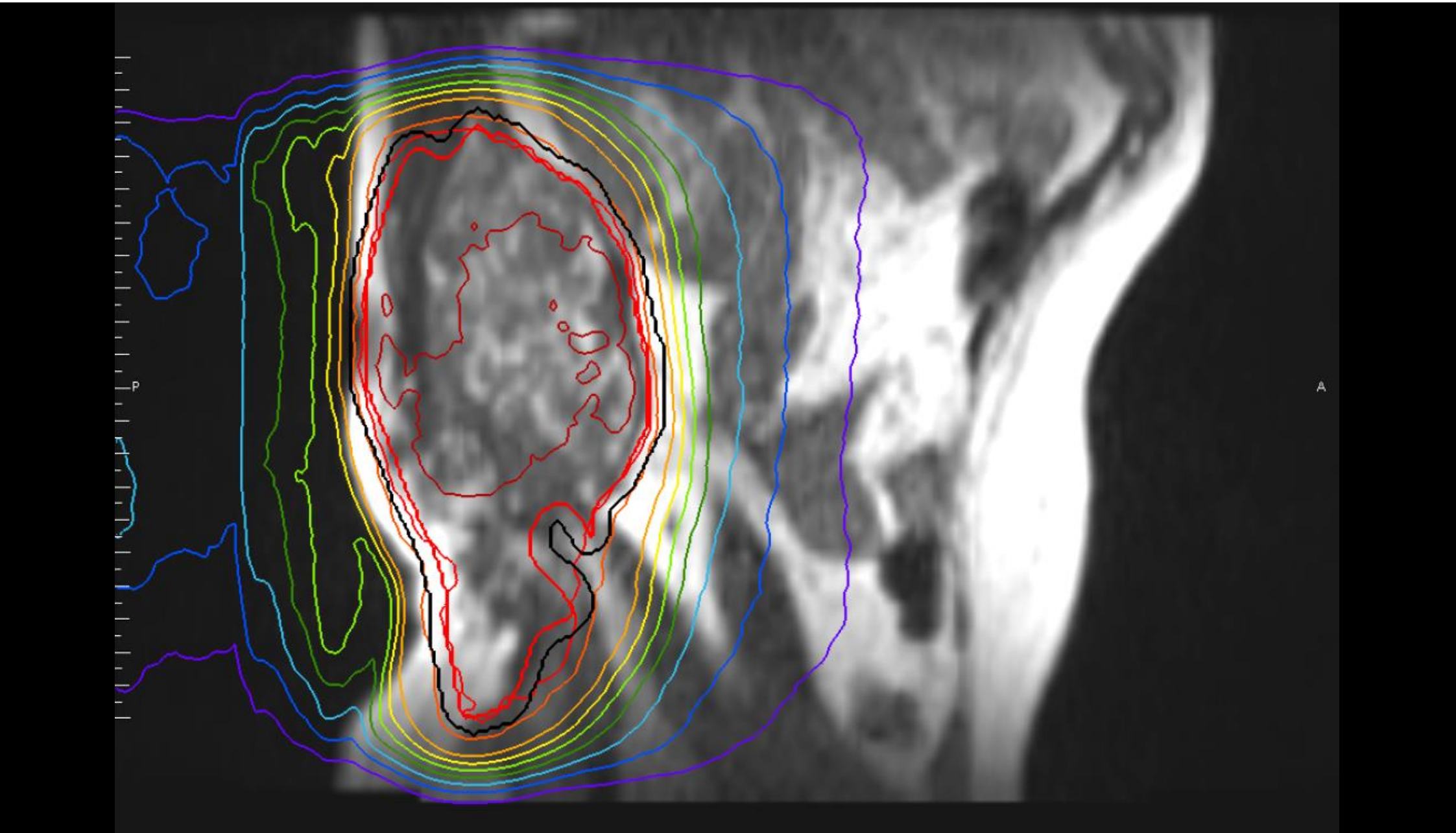
Gating treatment for OAR movements or for PRV boundaries definition



Gating treatment for OAR movements or for PRV boundaries definition



Gating treatment for OAR movements or for PRV boundaries definition

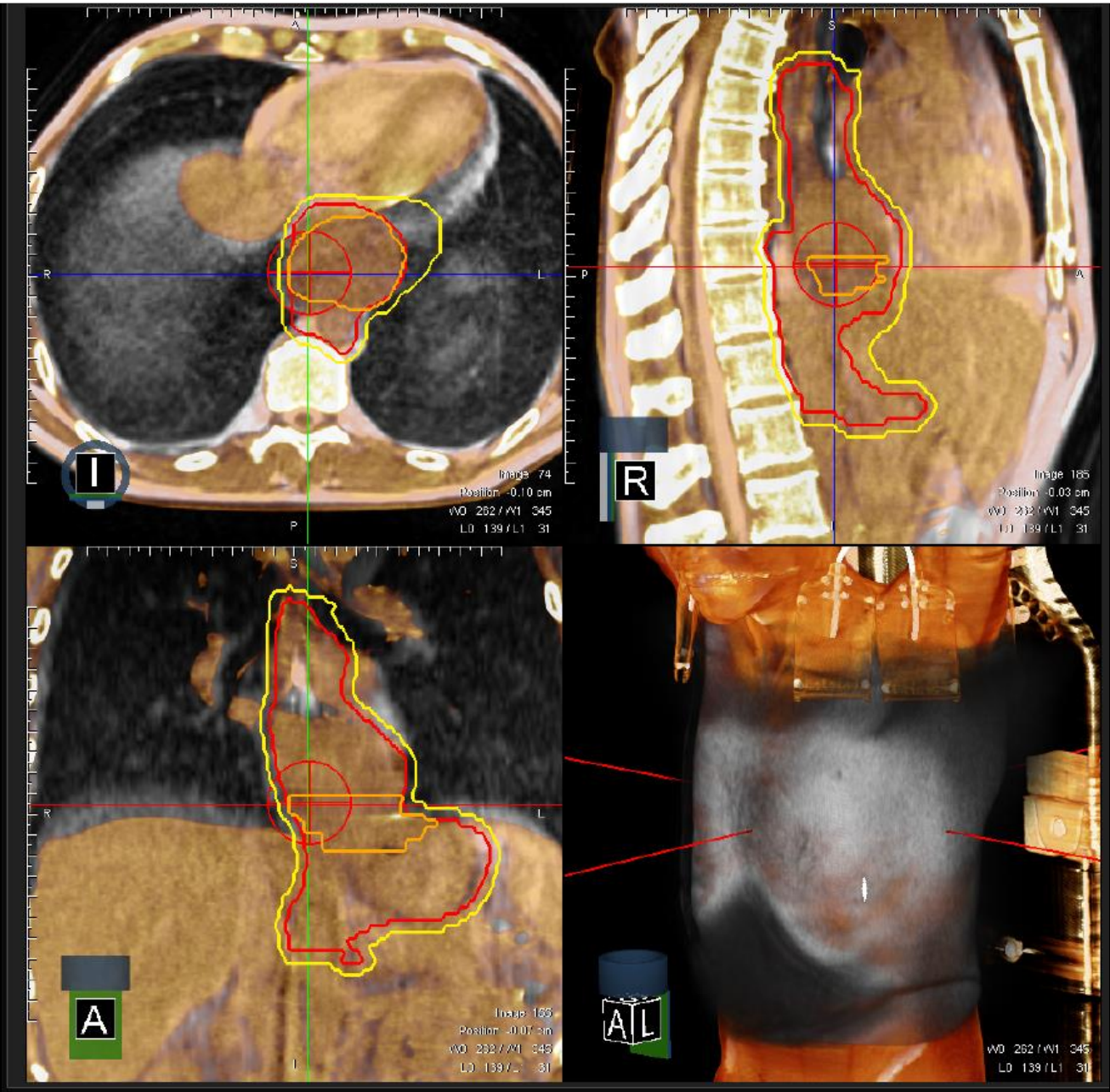


MR for Replanning treatment

Esophageal cancer after 17 fractions

MR for Replanning treatment

Day 1



Day 1

Day 17

Thank you!

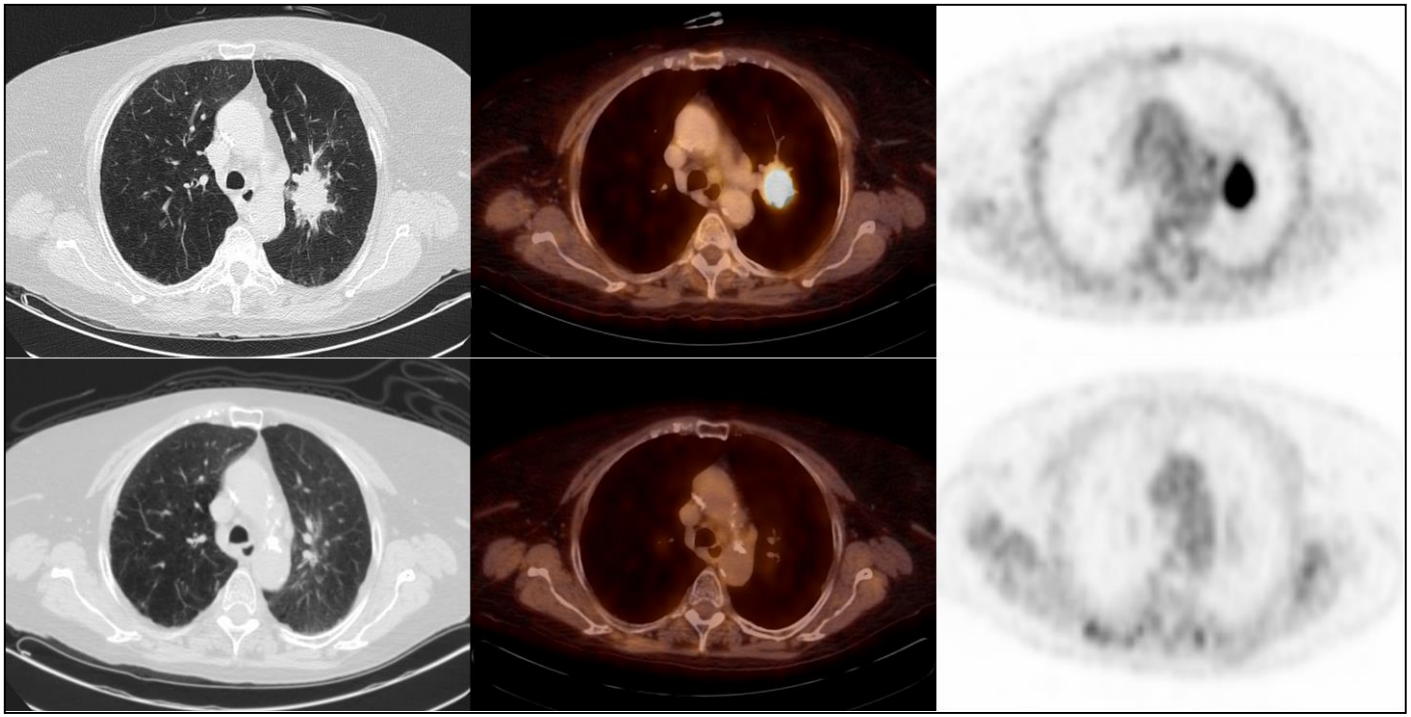
Grazie!

ESTRO School

ESTRO School

Kliniken Maria Hilf
Mönchengladbach

UNIVERSITÄTS KLINIKUM FREIBURG



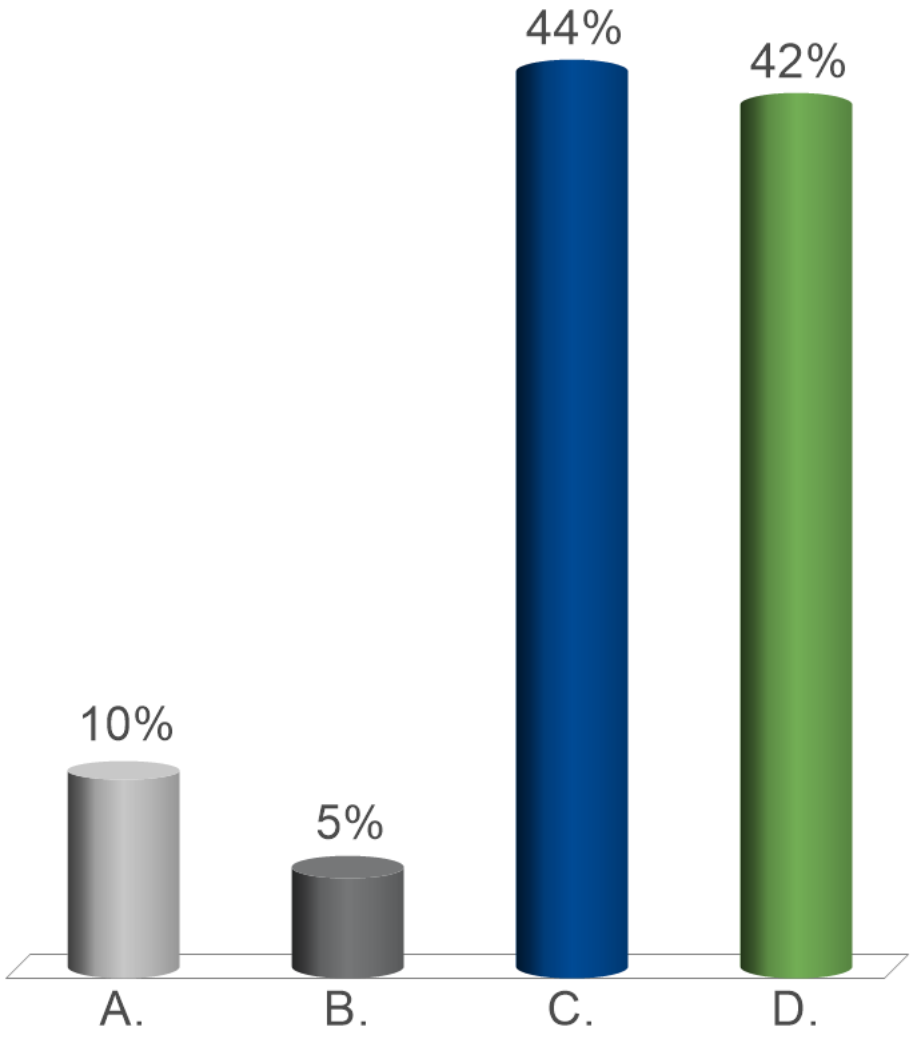
Advanced planning strategies for lung cancer

Example: SBRT for lung tumors

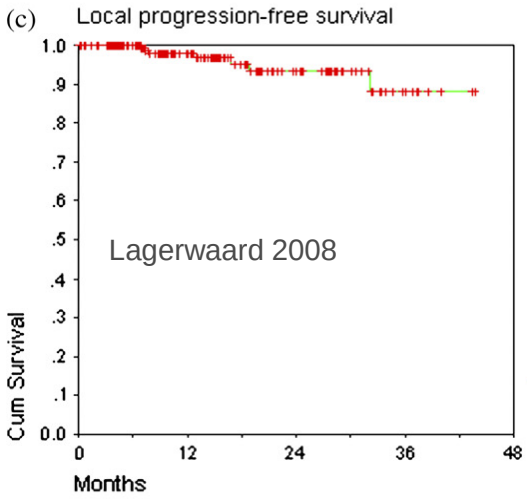
Prof. Ursula Nestle

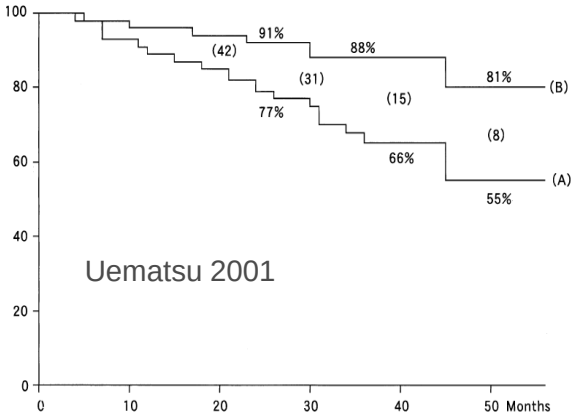
Q1: Do you routinely apply SBRT?

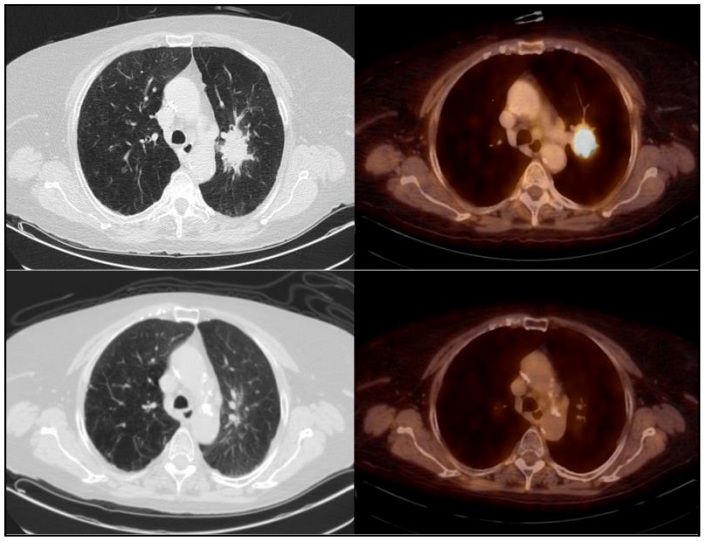
A. Yes, lung tumors
B. Yes, in lung and liver tumors
C. Yes, in lung, liver and other sites
D. no

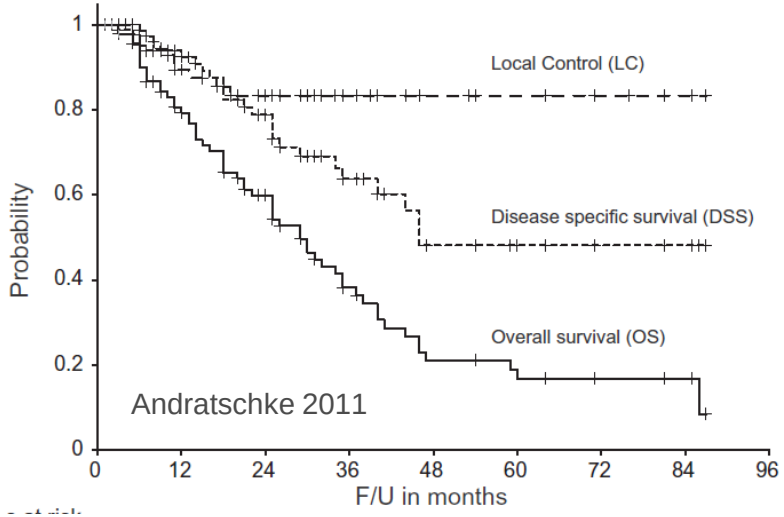


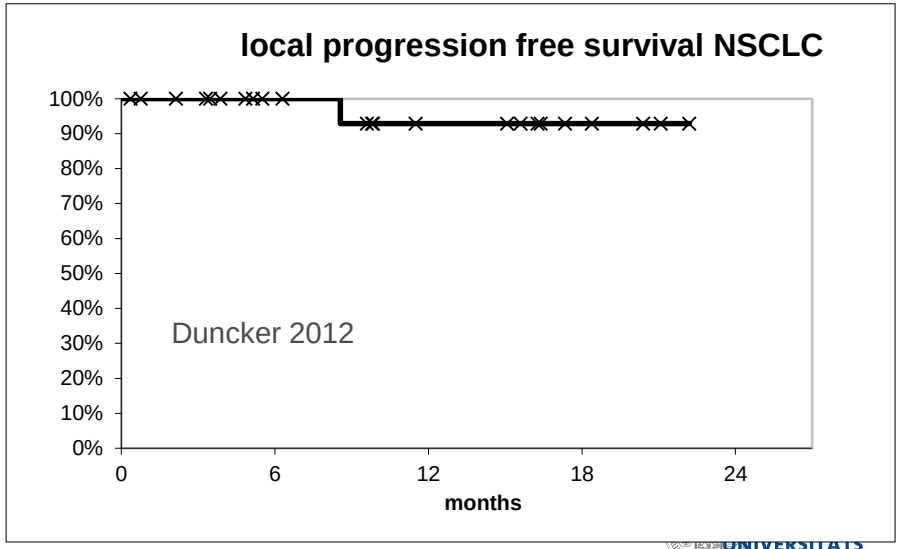
SBRT: success story





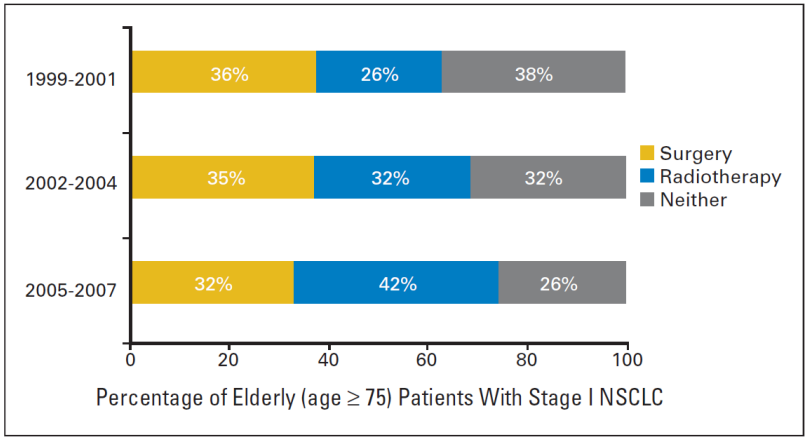




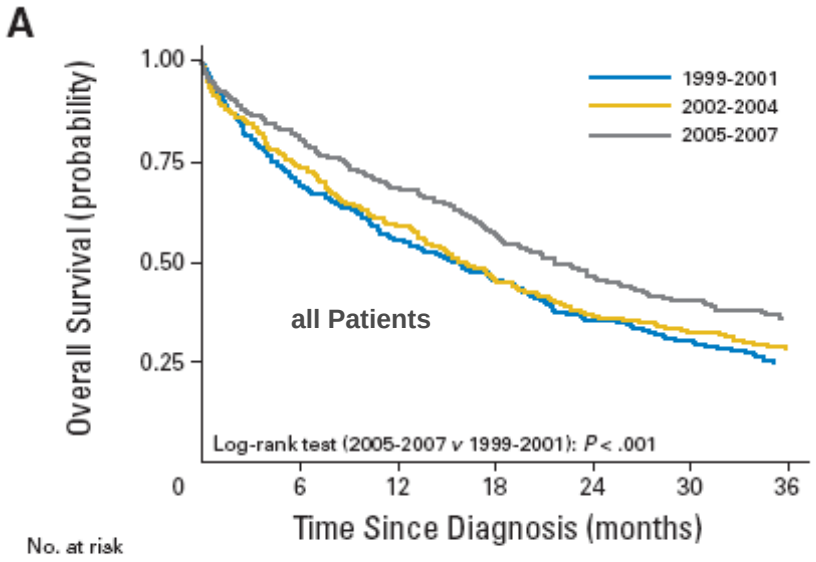


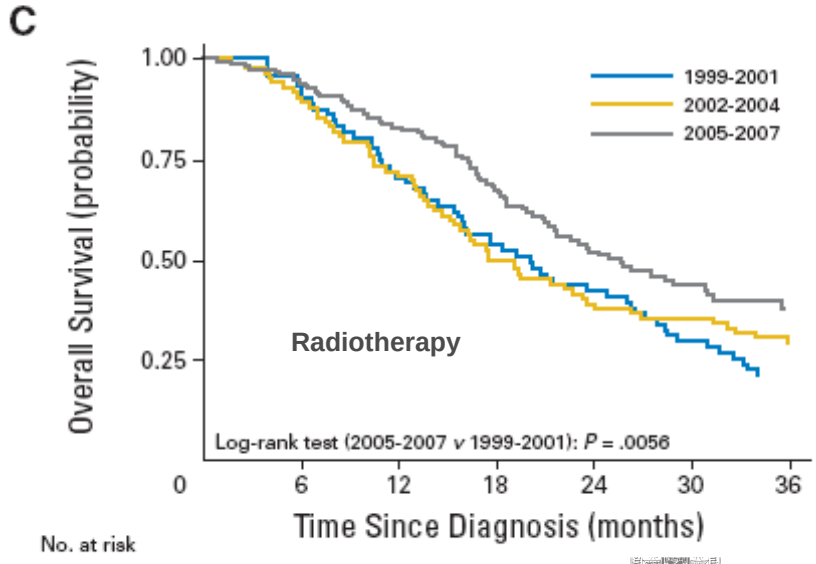
SBRT: improving outcomes stage I LC

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?

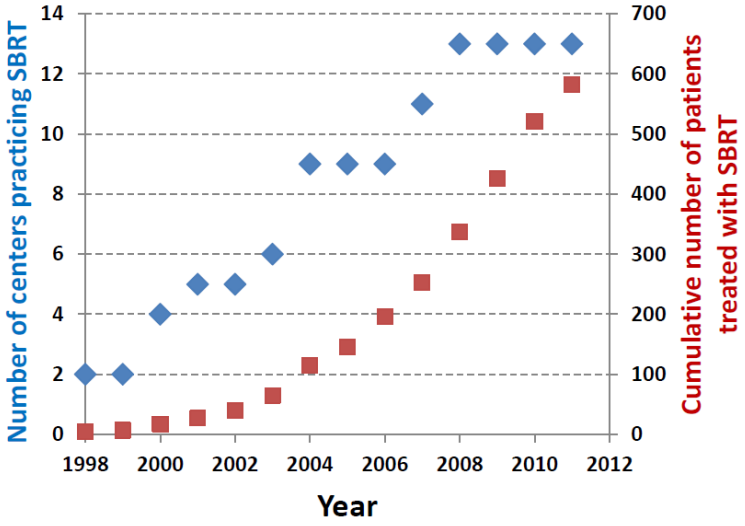
Author	fractionation	dose prescription on % isodose	dose encompassing the PTV	BED for tumor (prescribed dose)	BED on 100%
van Baardwijk [22]	10 x 6 Gy	100%	60 Gy	96 Gy	
Haasbeek [45]	8 x 7.5 Gy	100%	60 Gy	105 Gy	
Mc Garry [16]	3 x 8 Gy	80%	24 Gy	43 Gy	
Mc Garry [16]	3 x 20 Gy	80%	60 Gy		262 Gy
Mc Garry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

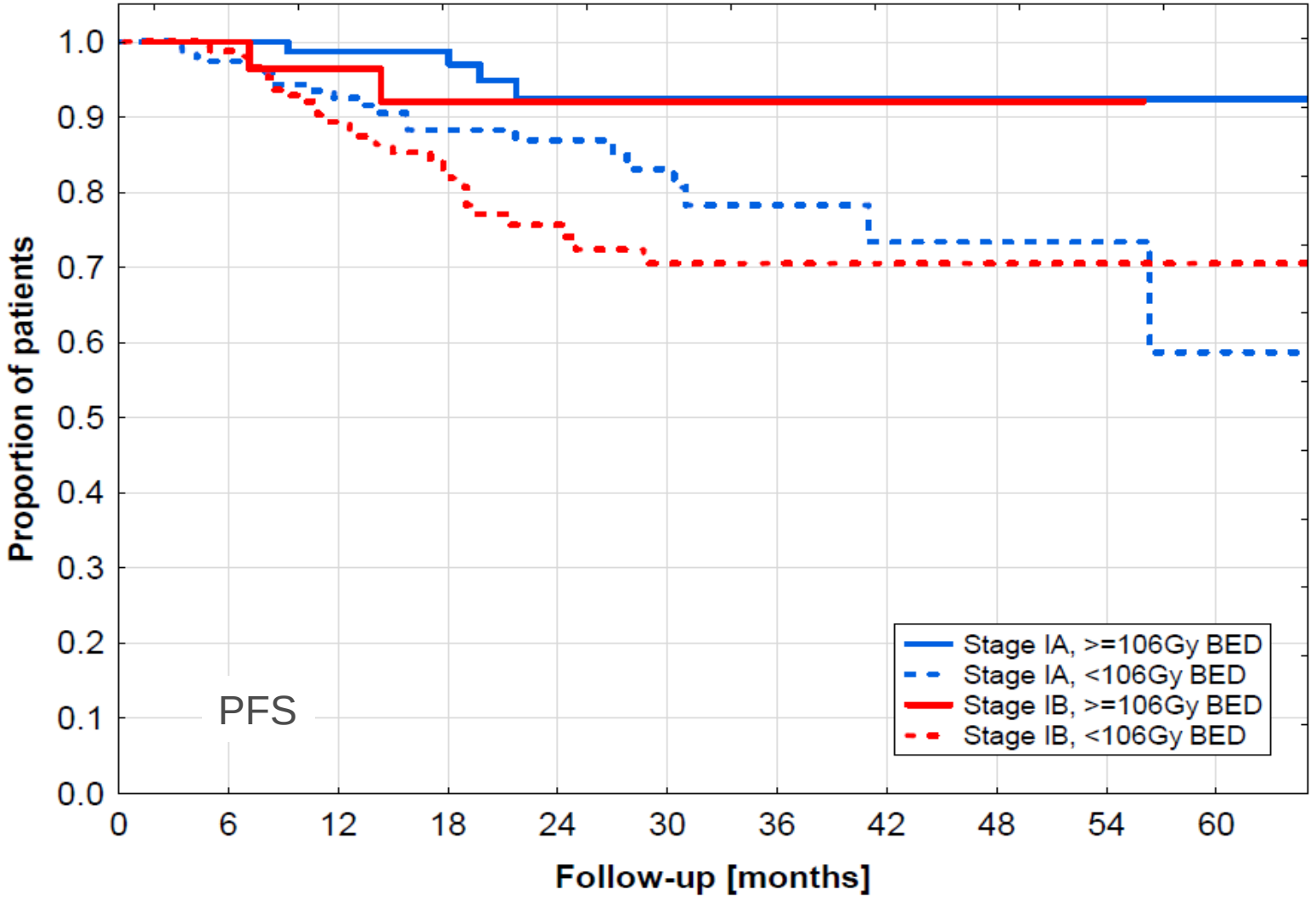
SBRT: wide use, high heterogeneity

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

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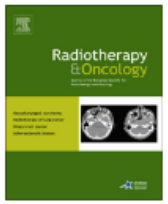
journal homepage: www.thegreenjournal.com



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

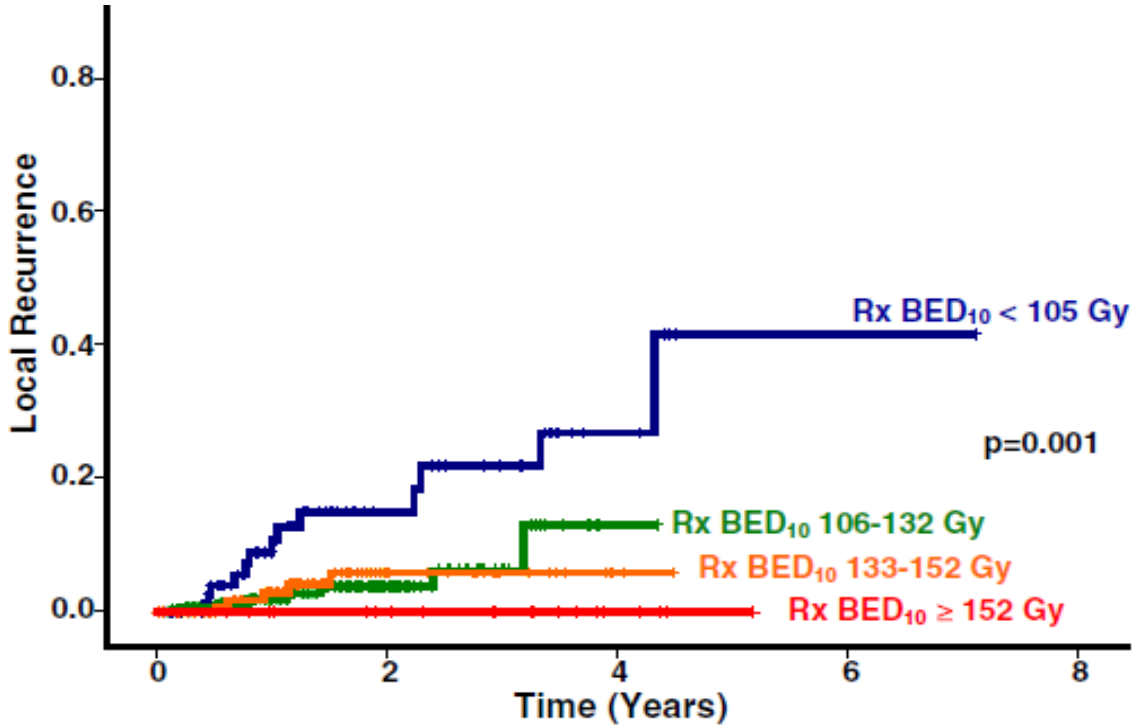
prescriptions (median: 54 Gy/3 fx):

- 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

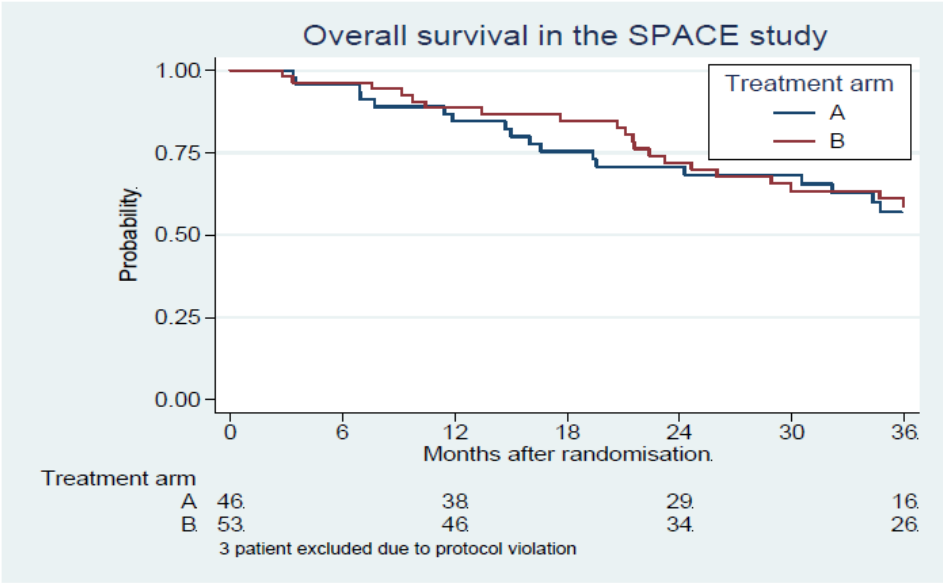
102 patients,
- (T1-2N0M0) NSCLC,
- significant comorbidity

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

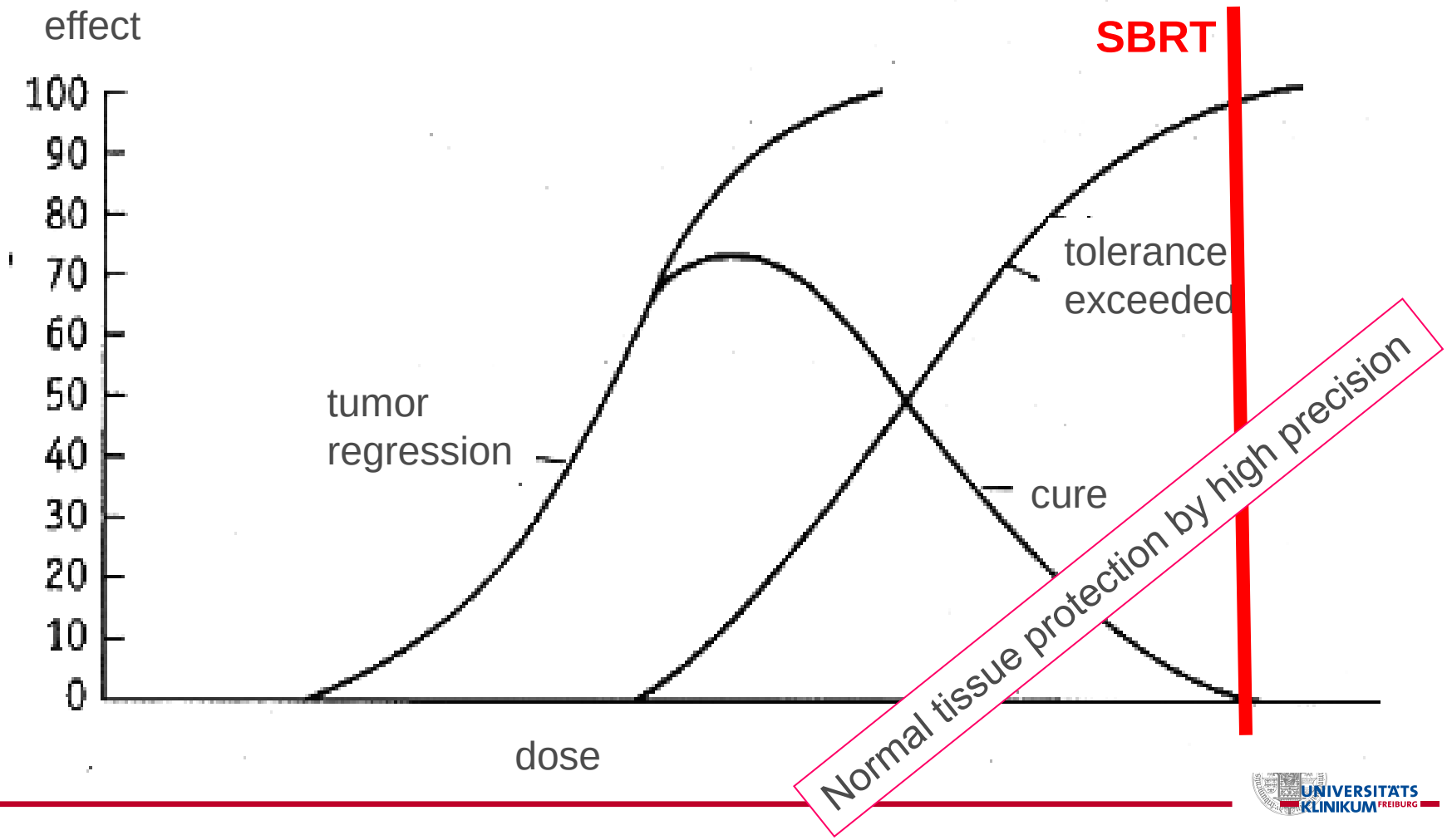
1. In this randomized phase II trial stage I patients treated with SBRT had the same PFS and OS as the 3DCRT patients despite an imbalance in prognostic factors (T2 tumors and male gender)
2. There was a tendency to improved disease control rate at the end of study in the SBRT patients
3. SBRT patients 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

Abstract 923: The SPACE study: A. Hallqvist

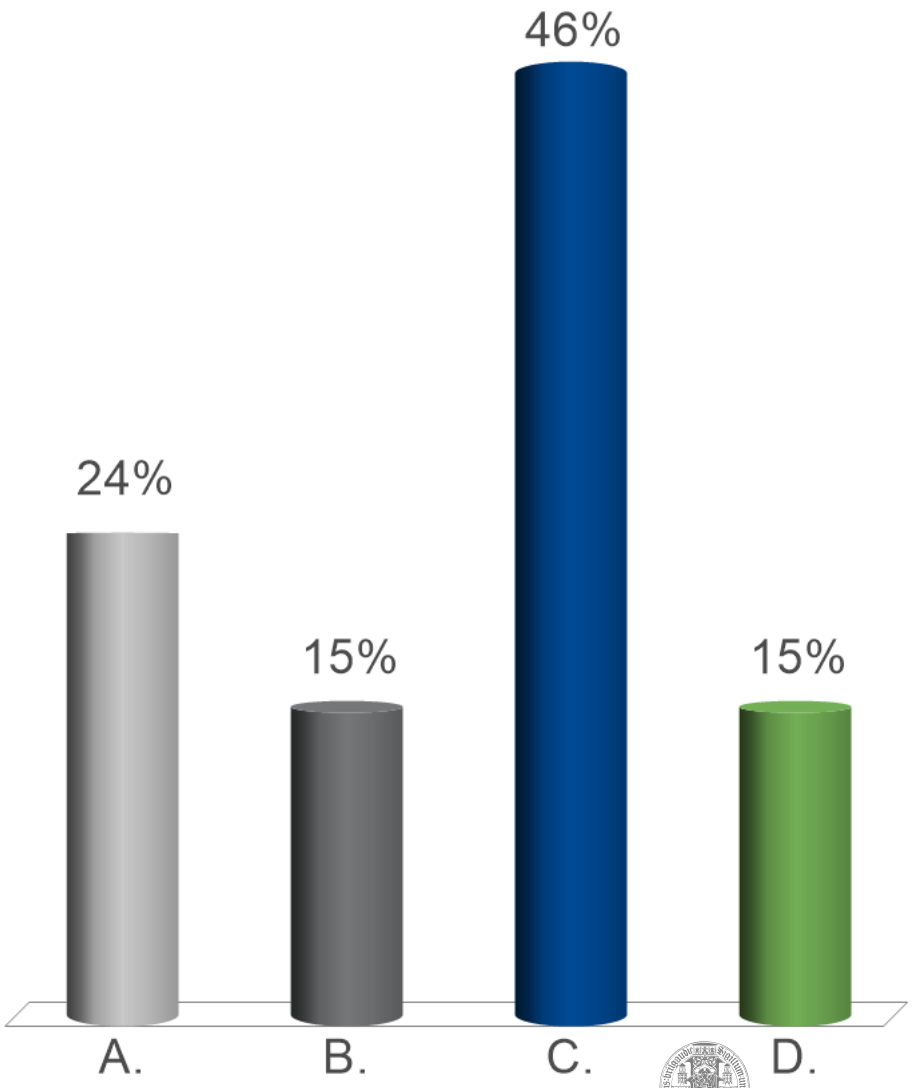
IASLC 40 YEARS

Radiobiology and high-precision RT…



Q2: in SBRT for central lung tumors, what are your limits?

A. We do not treat central lung tumors because of possible toxicity
B. We treat all but ultra-central tumors (trachea, main bronchi)
C. We treat central tumors but with reduced dose and/or fractionation
D. We do not treat tumors invading the main bronchi or large vessels



Central tumors: outcome from expert treatment

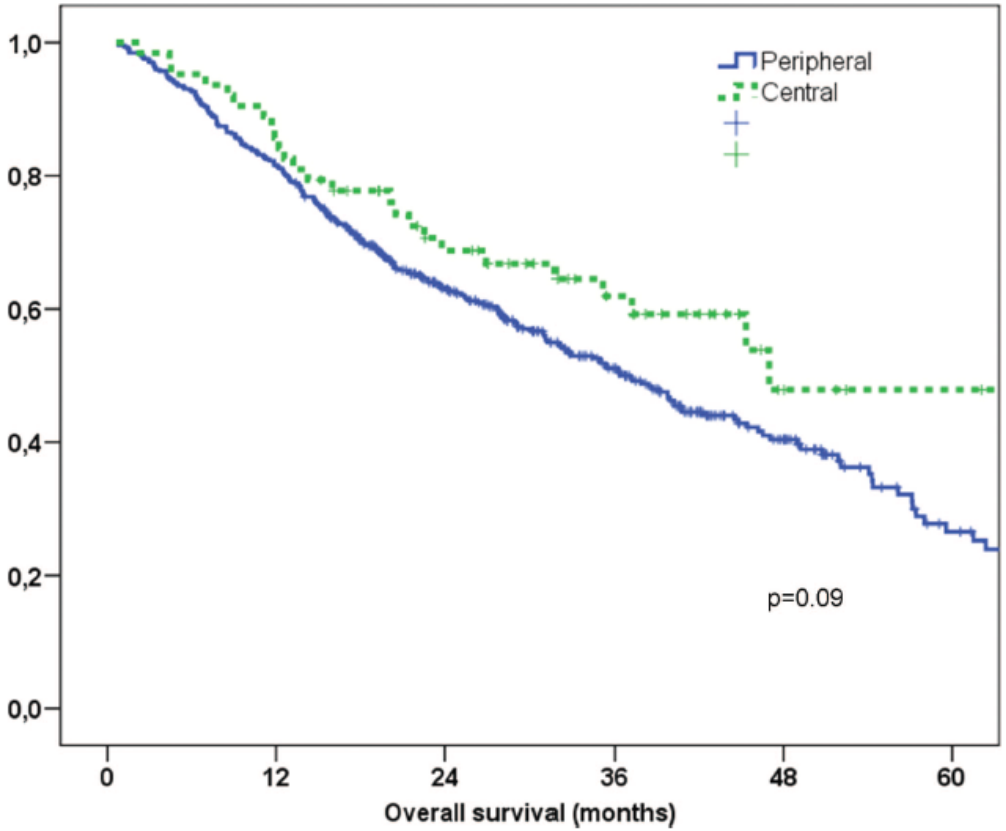
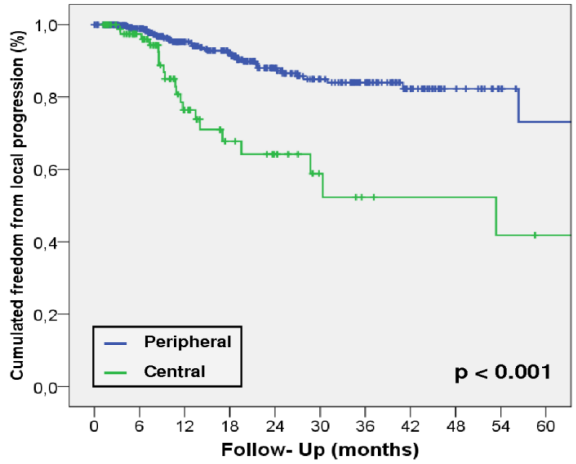


FIGURE 3. Overall survival for central and peripheral early-stage lung tumors after stereotactic ablative radiotherapy (SABR).

Haasbeek JTO 2011, BED_{10}=105 Gy

Central tumors, multicenter database

A



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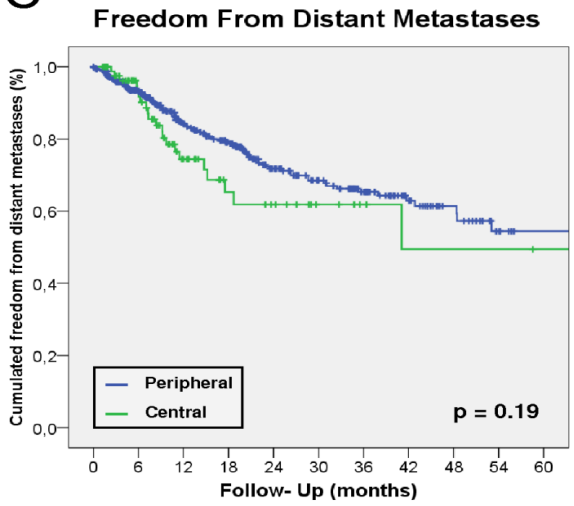
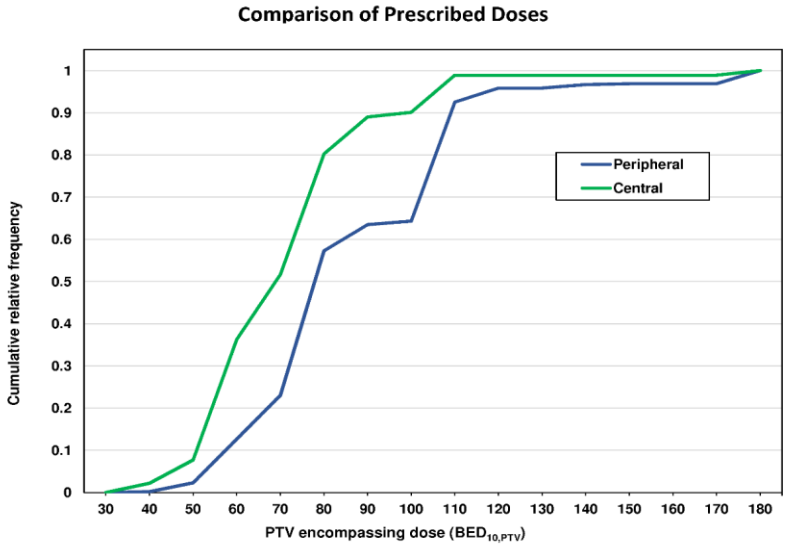




"Local tumor control in patients treated with SBRT for centrally located, early-stage NSCLC was favorable, provided ablative radiation doses were prescribed."

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

Schanne, D. et al. S&O 2013

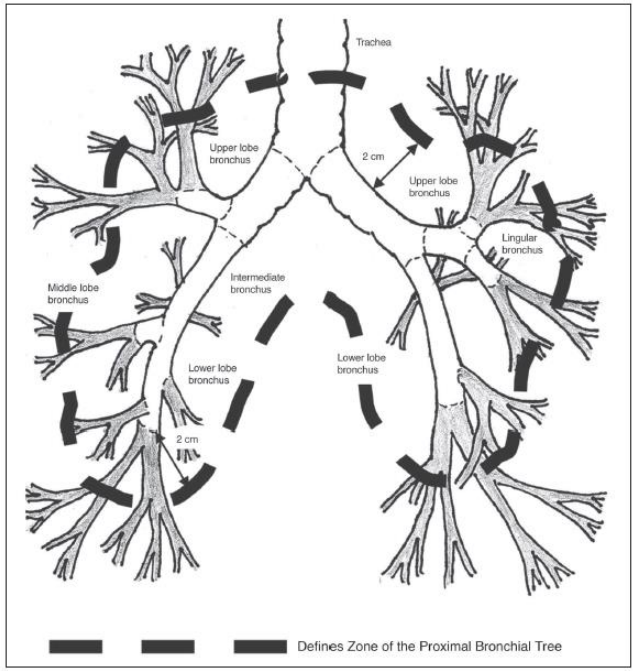
Toxicity!

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

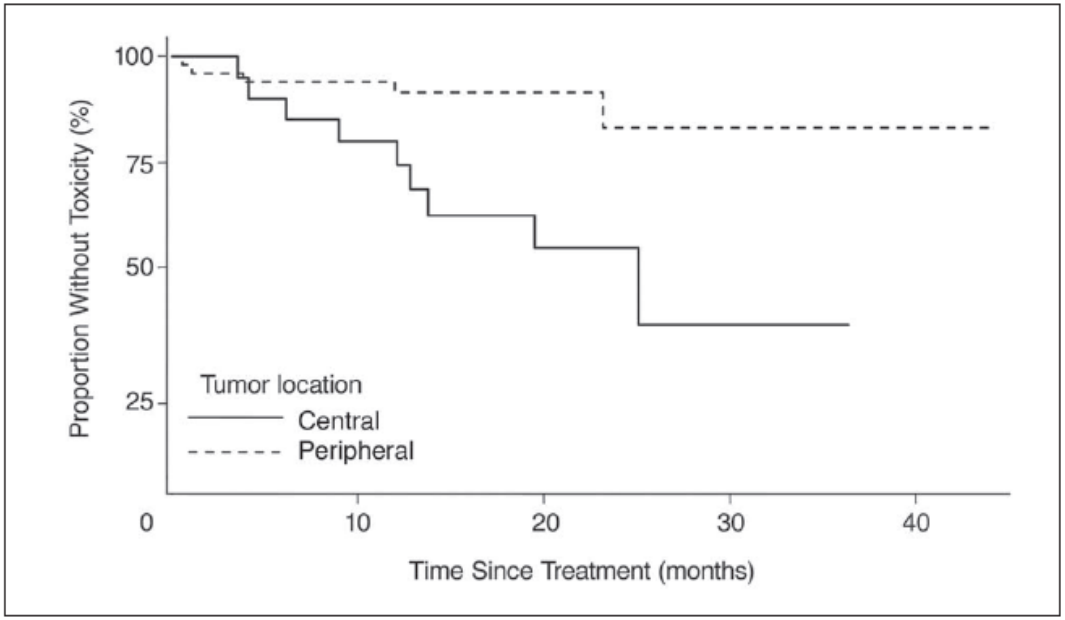
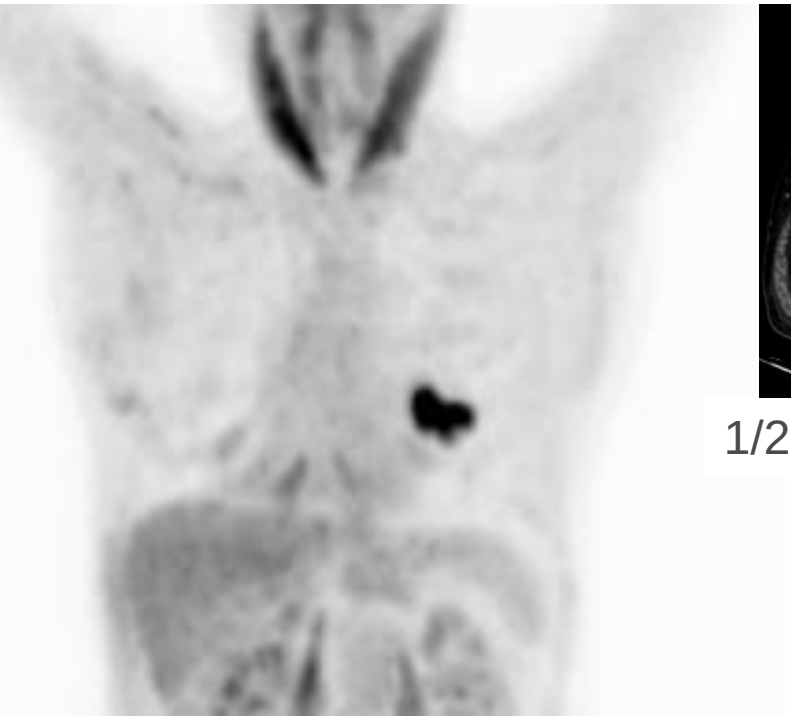
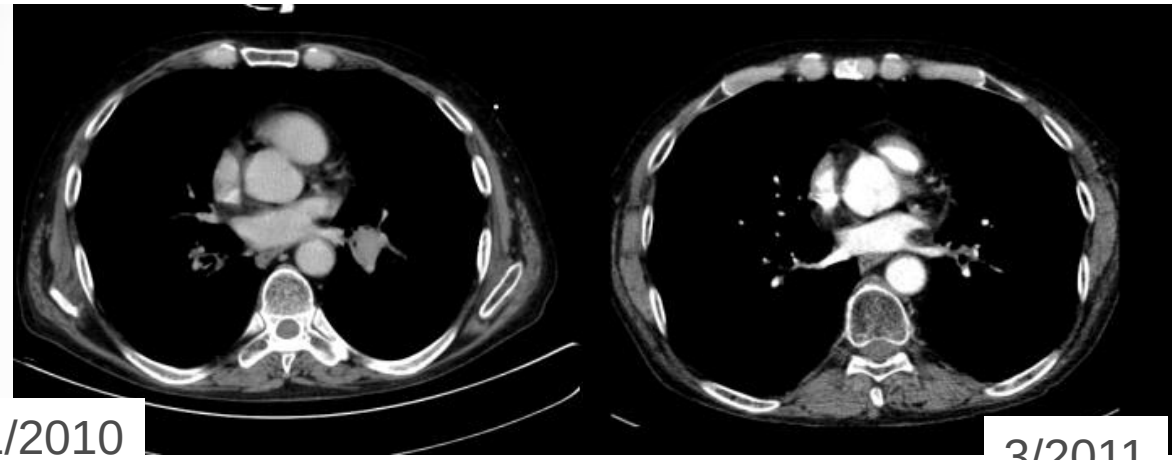


Fig 4. Kaplan-Meier plot of time from treatment until grade 3 to 5 treatment related toxicity comparing patients with tumors in the central (perihilar and central mediastinal) regions from those with more peripheral tumors.

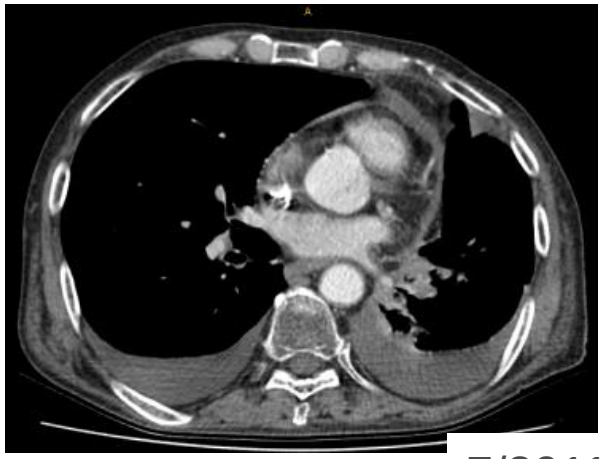
Pat. S.D. *1943, SCC



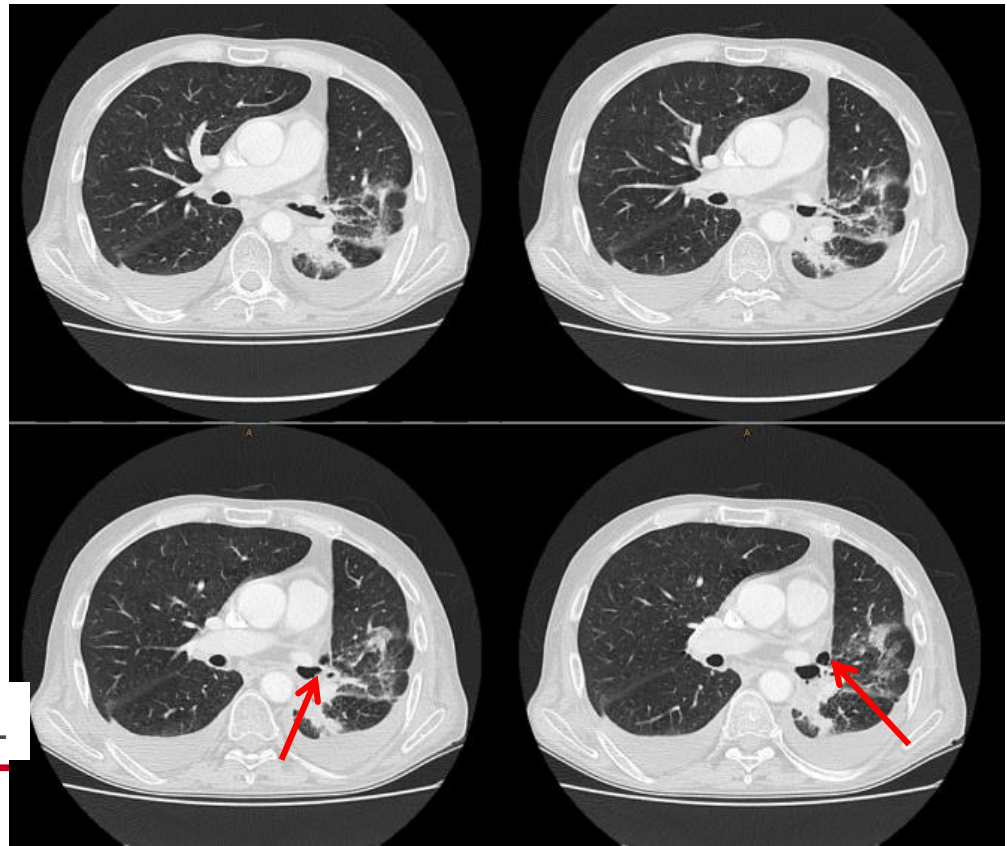


1/2010

3/2011



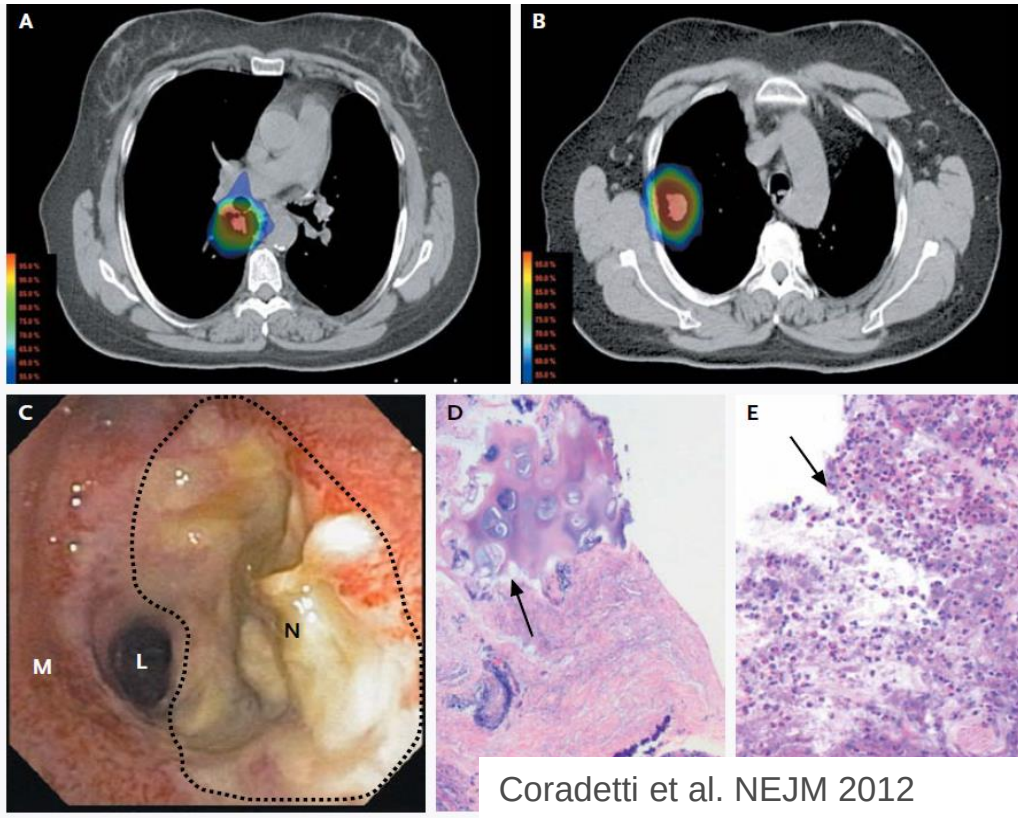
7/2011



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

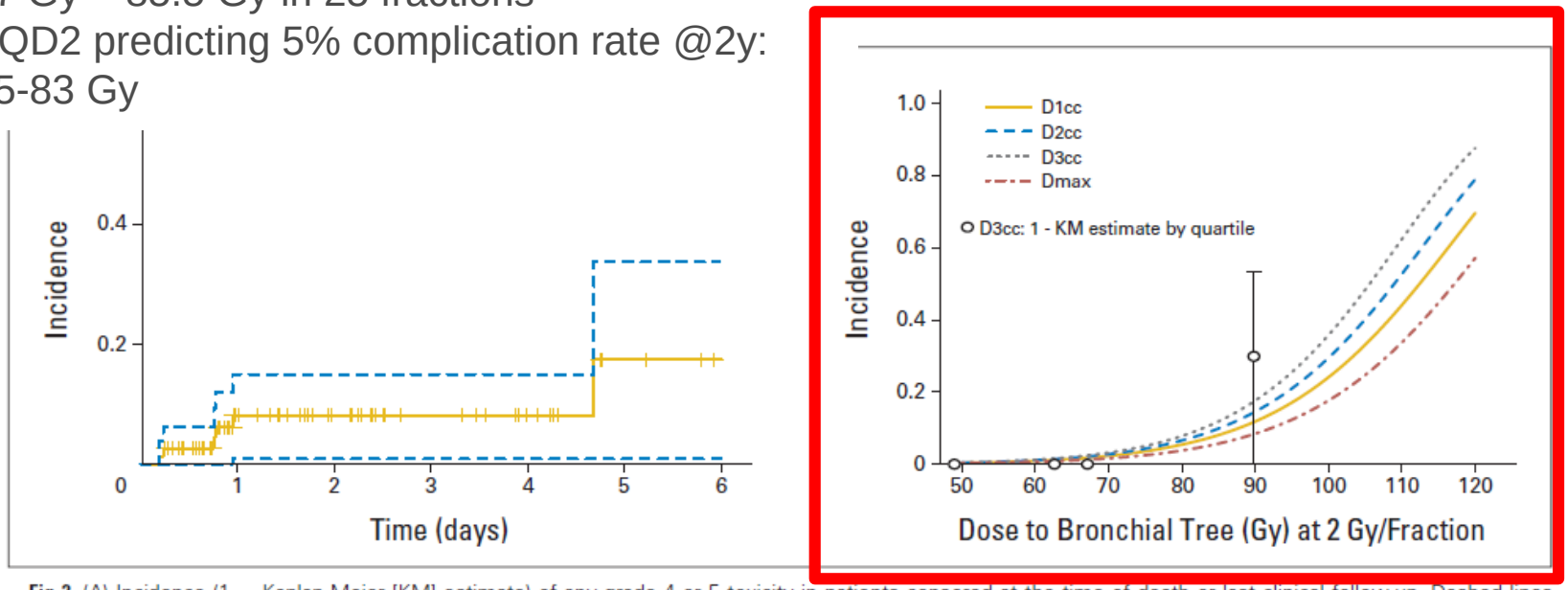
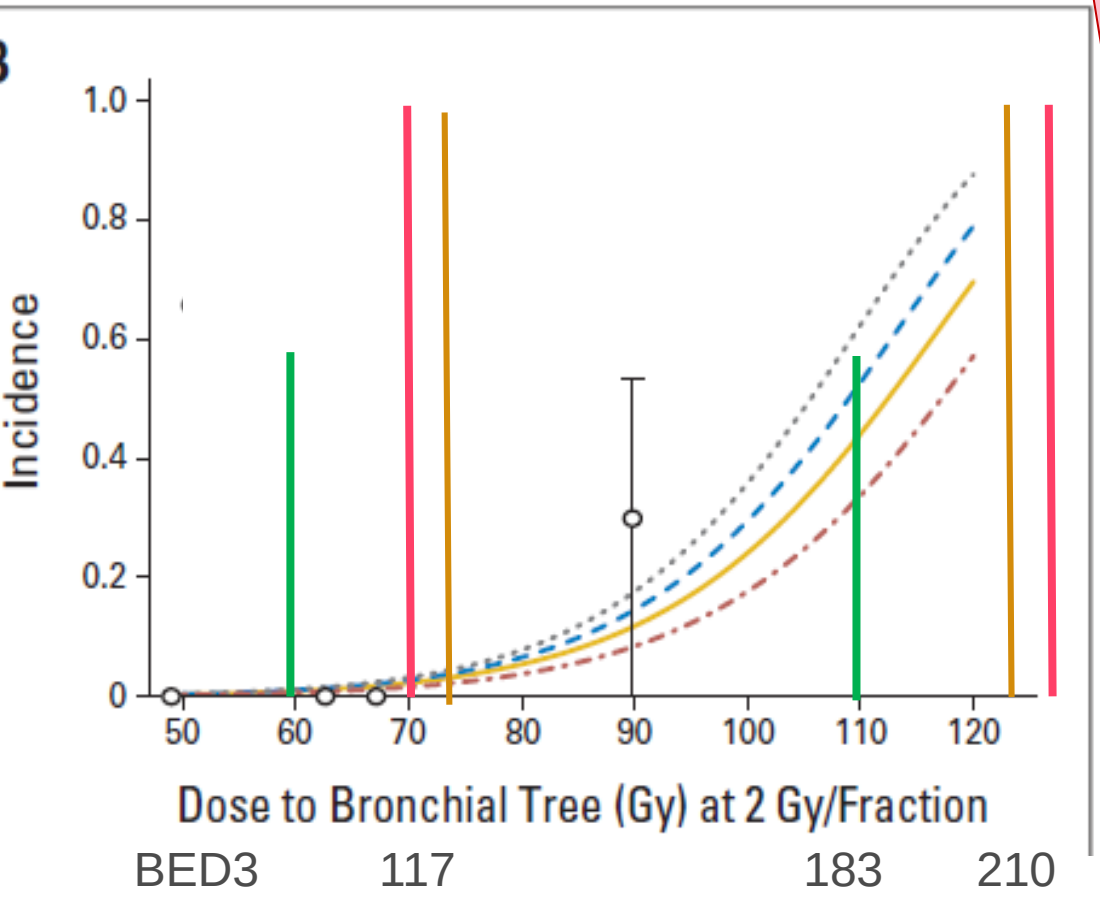


Fig 2. (A) Incidence (1 − Kaplan-Meier [KM] estimate) of any grade 4 or 5 toxicity in patients censored at the time of death or last clinical follow-up. Dashed lines represent the 95% CI. (B) Two-year probabilities of late grade 4 or 5 toxicity according to dose-per-fraction normalized dose (EQD2) to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

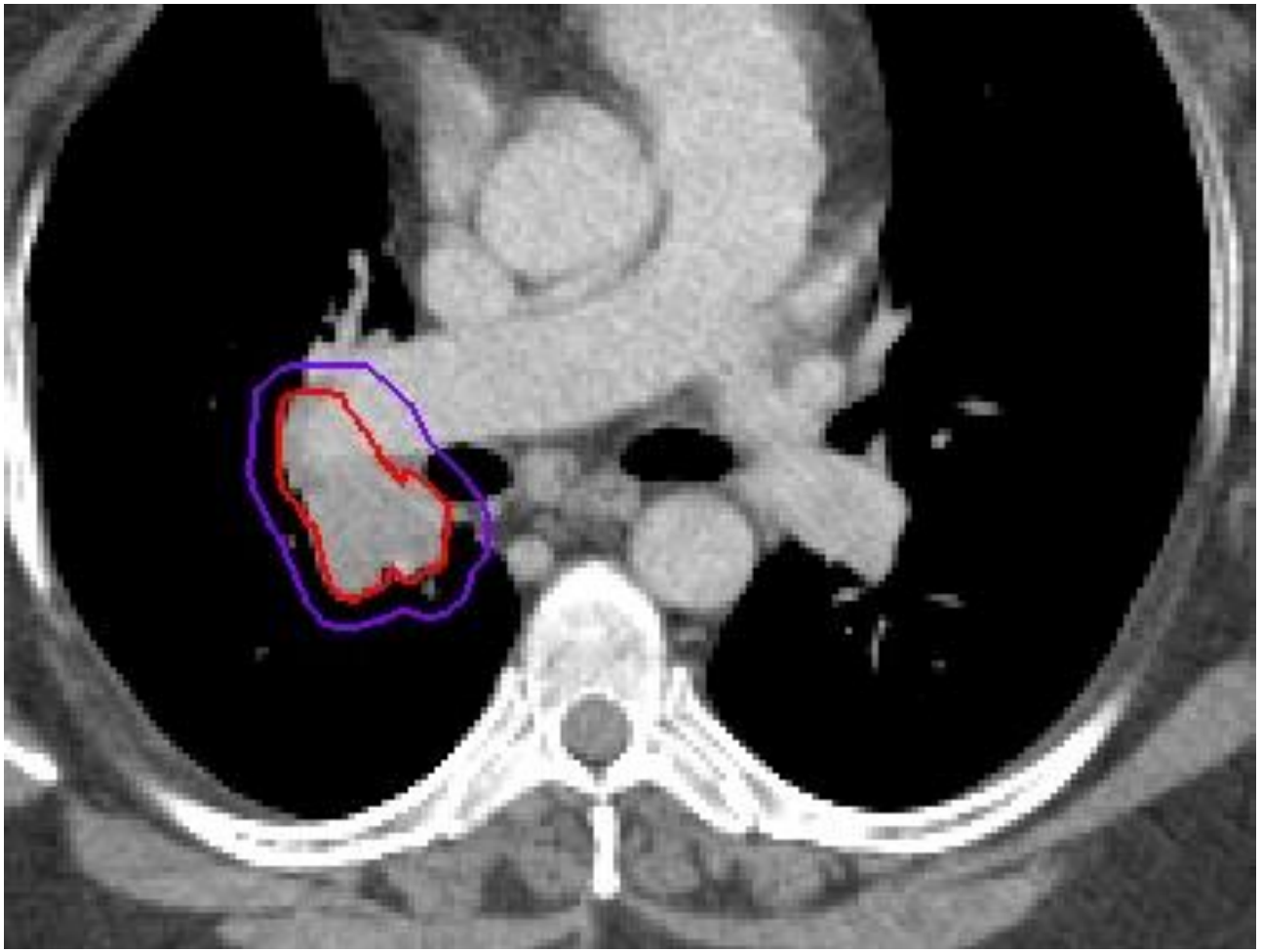
MTD of 83 Gy/ 2Gy
= „magic“ BED_{10} of 100 Gy,
Narrow therapeutic corridor



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

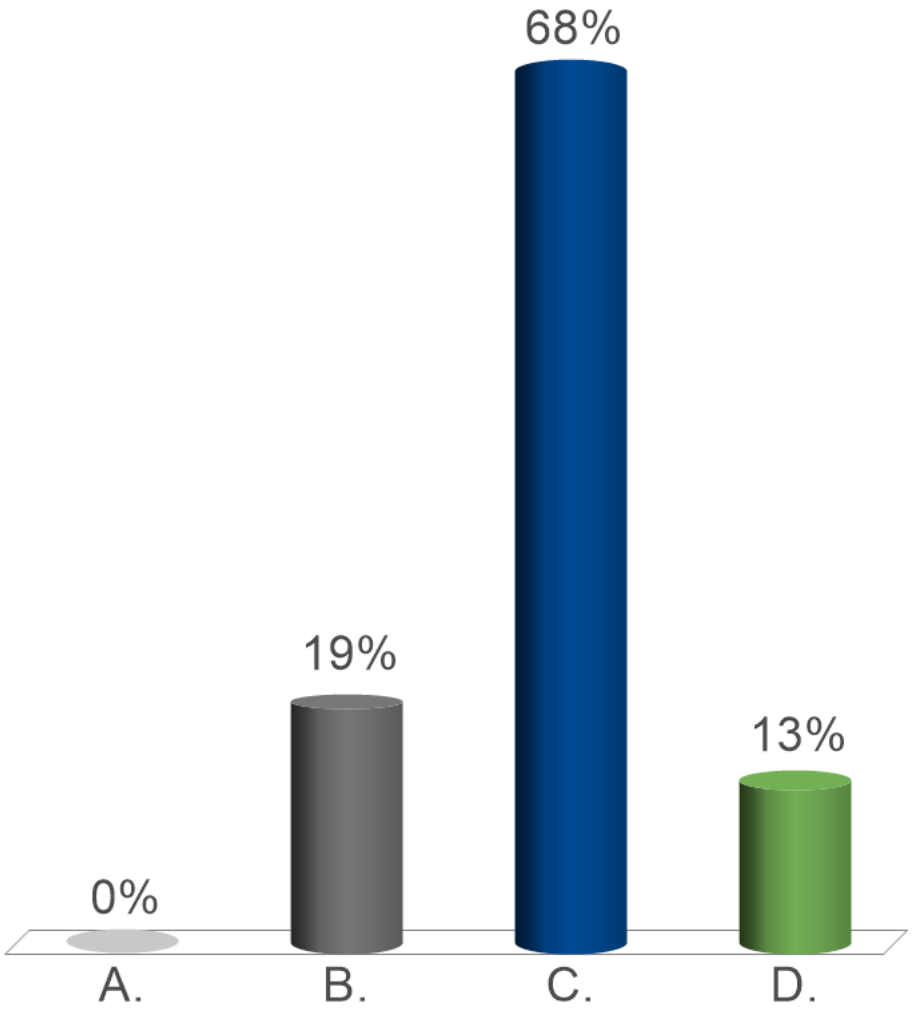
Need for a more detailed view on doses and volumes..

“competing risk”:
Tumor invasion of bronchus and vessel



Q3: Which kind of NT-dose constraints do you use in SBRT?

A. No constraints, just realize prescribed dose
B. Individually prescribed by the treating physician
C. Standardised constraints (table)
D. SOP for planning with stepwise constraints/objectives



DOSE CONSTRAINTS FOR SBRT OF CENTRAL LC

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

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

Critical Review

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

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

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

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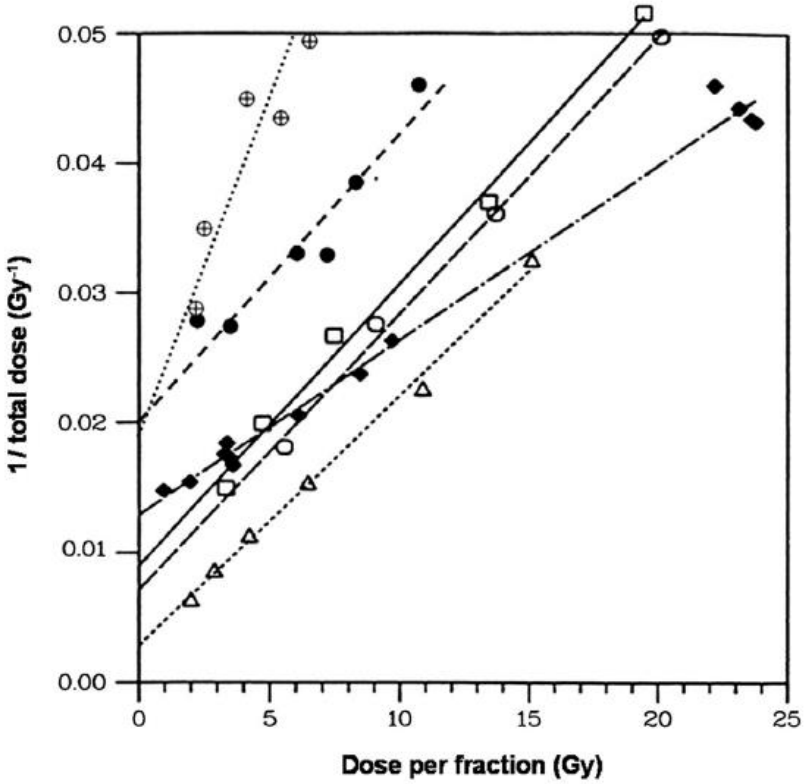


"Thus, we suggest that for most tumors, the standard radiobiology concepts of the 5 Rs are sufficient to explain the clinical data …"

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

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

DOSE CONSTRAINTS: OAR IN MORE „CENTRAL“ SBRT

- bronchial tree
- heart
- large vessels
- esophagus

problem:

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

DOSE CONSTRAINTS: **PROX BRONCHIAL TREE**

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

Reference	*Number of reported patients (treated tumours)*	*Number of centres*	*Pro (p)-/ retro(r)-spective*	*Results (max. point dose or dose/fractionation*
Timmerman (50)	70	1	r	with 19.5
Fakiris (50)				ns),
M				rs
O				
Br				
Ung				
Canc		1	p	CFRT: **EqD2 of 75-83 Gy** predicting a 5% complication rate, 3 x fatal hemoptysis, 85 and 75 Gy, 25 fractions (**EqD2 118 and 90, respectively**), tumors encasing or abutting a mainstem or proximal lobar bronchus and partially local invasion of adjacent normal structures

Recommendations/NT constraints

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

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

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

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

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

Gy)[#]

Gy, **EqD2 not applicable**)

EqD2: 140 Gy)[#]

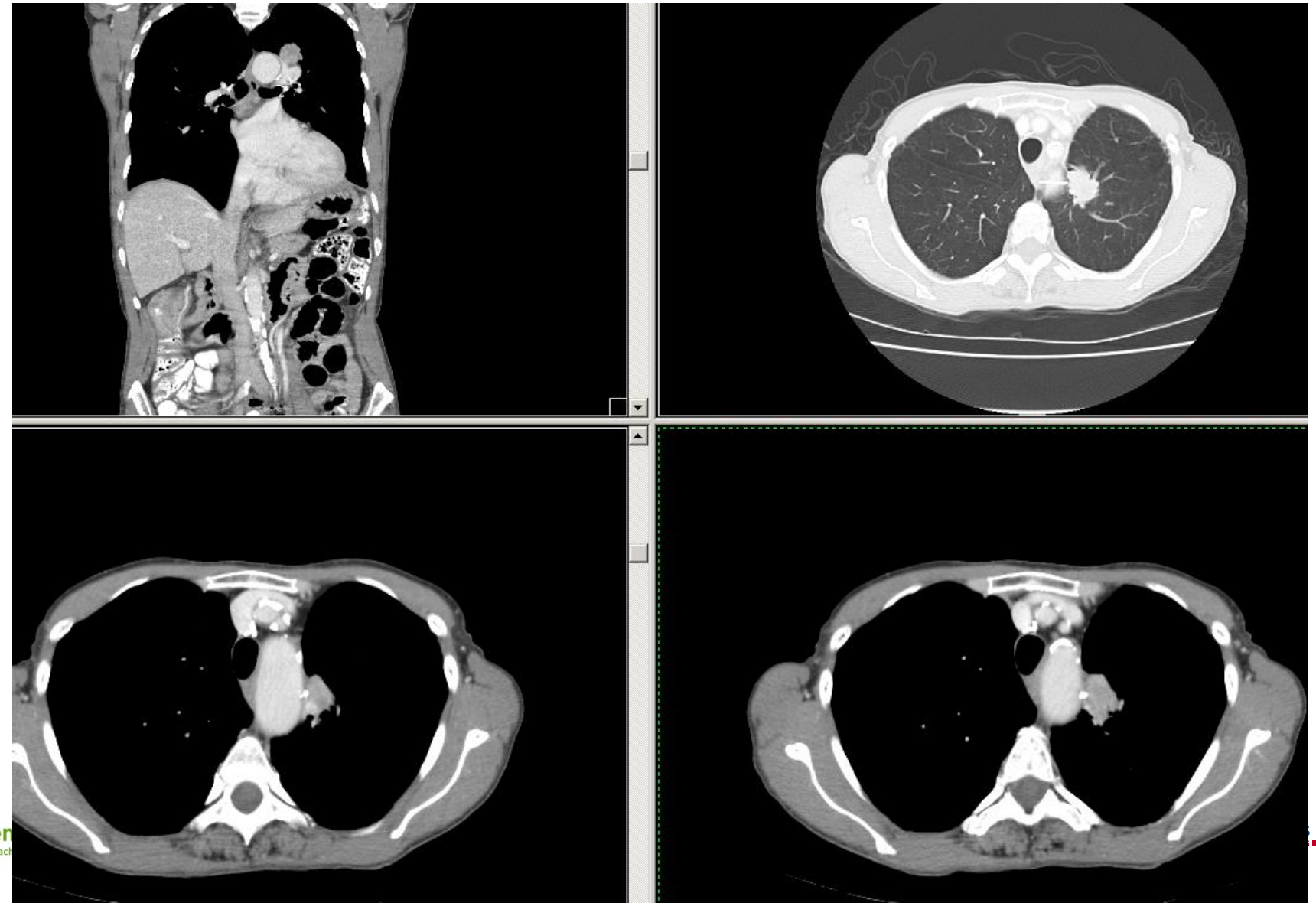
essively fatal hemoptysis after stent insert, 4x15Gy=60Gy (**EqD2:**

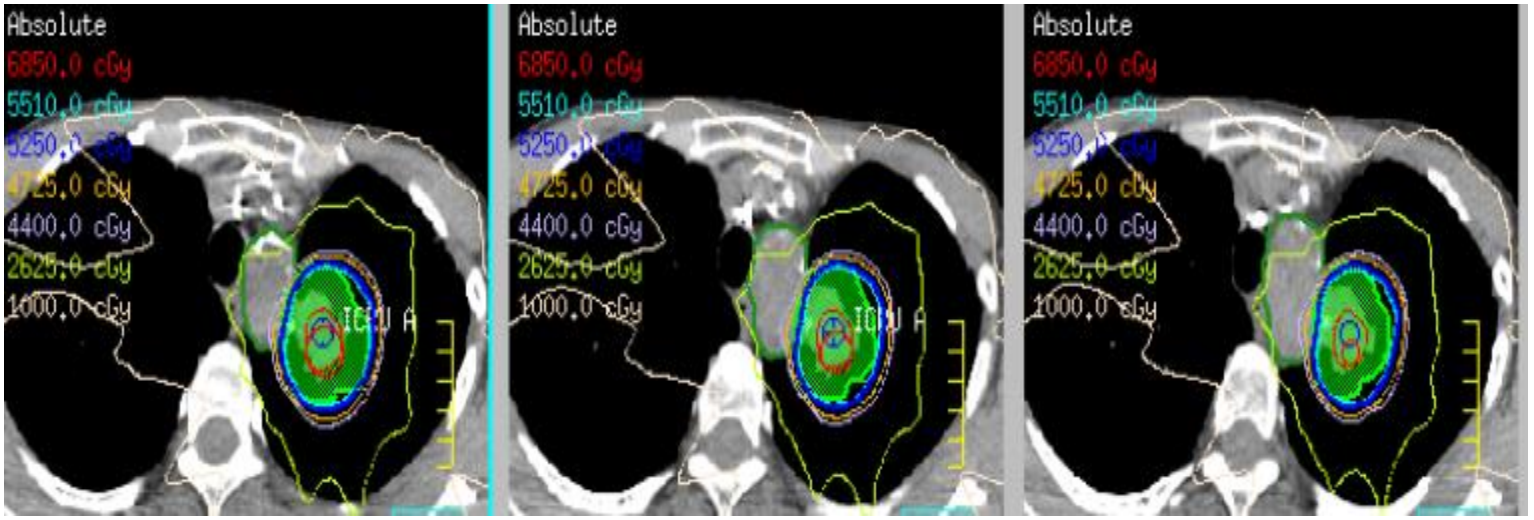
1 x bronchial fistula, mainstem bronchus received a maximum point dose of 49 Gy (**EqD2 not applicable**)

Adebahr et al , BJR 2015

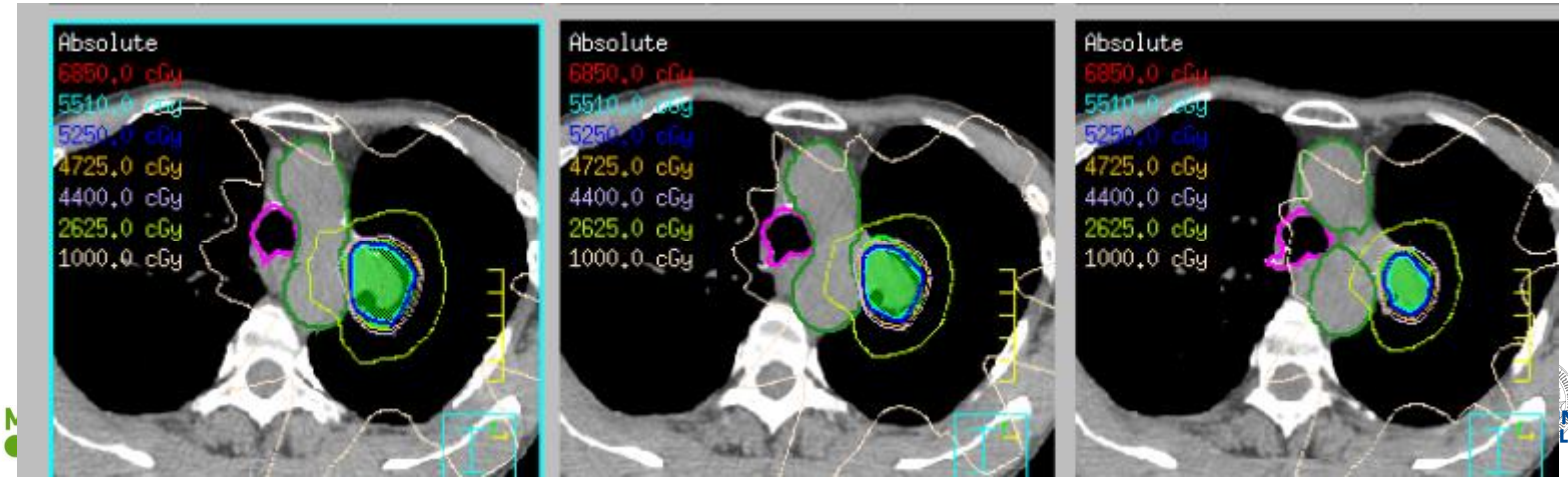
Large vessels: a case from A. Bezjak

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





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



Course post SBRT

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

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

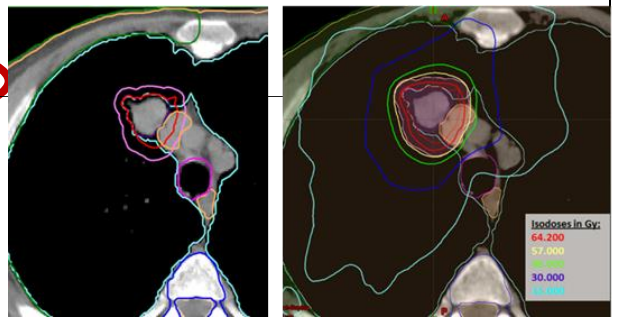
Next day blood - ? coughed or vomited – called ambulance – pt arrested within minutes of ambulance arrival –resuscitation attempts unsuccessful

Autopsy not performed

DOSE CONSTRAINTS: **LARGE 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

DOSE CONSTRAINTS LUNGTECH TRIAL: 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	Unacceptable 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

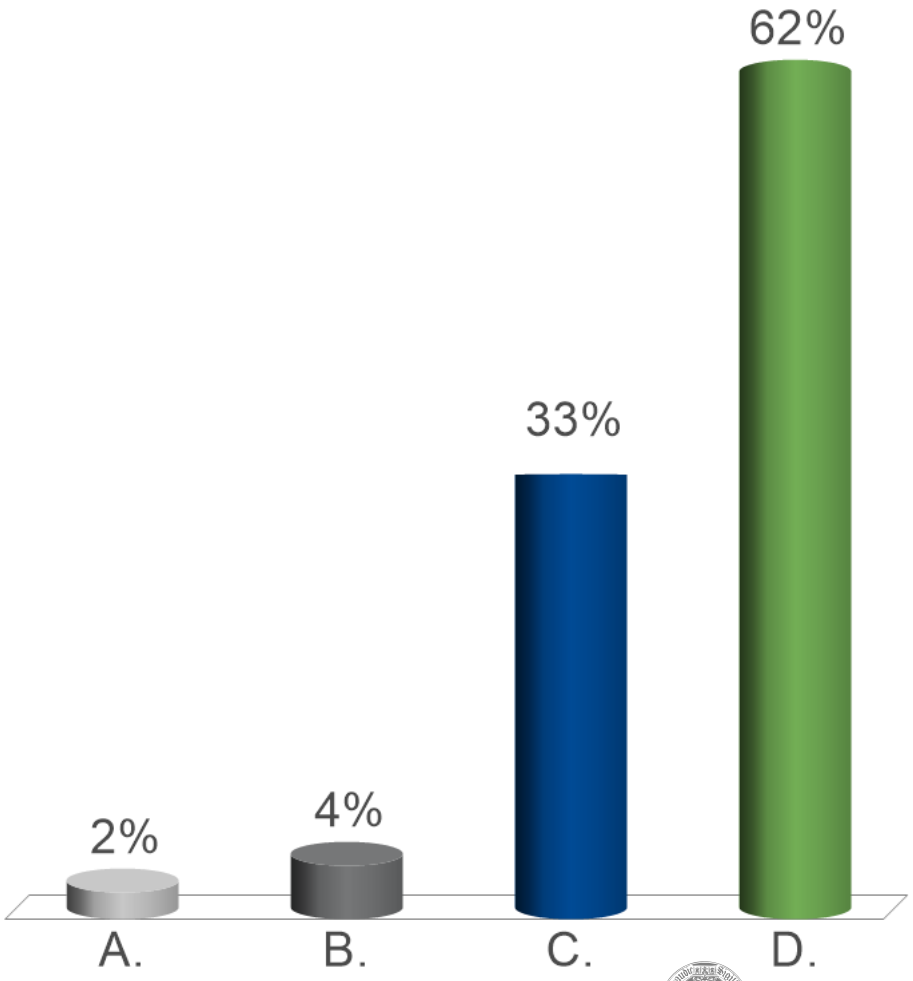
§ no restrictions are provided but recording of DVH data for toxicity evaluation is required

EORTC 22113-0813-LungTech RTQA Guidelines

Adebahr et al , BJR 2015

Q4: what do you do with critical normal tissues (NT) overlapping with a high-dose PTV, e.g. in SBRT?

A. We prioritize for the PTV, no respect to NT
B. We prioritize for the NT, no respect to PTV
C. We lower the dose (or change fractionation) to the whole PTV to reach the constraint of the NT
D. We somehow compromise in the part of the PTV which is near the NT



How can we cope with critical serial organs near to high-dose targets?

Strahlenther Onkol (2016) 192:886–894
DOI 10.1007/s00066-016-1057-x

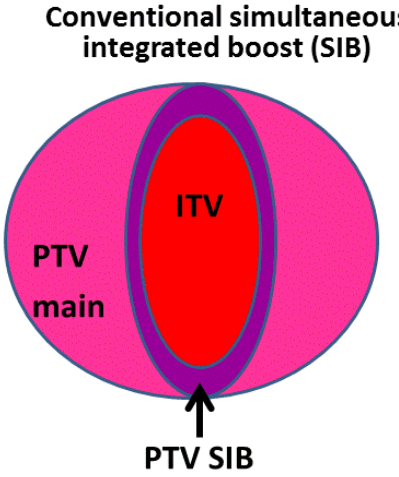
ORIGINAL ARTICLE

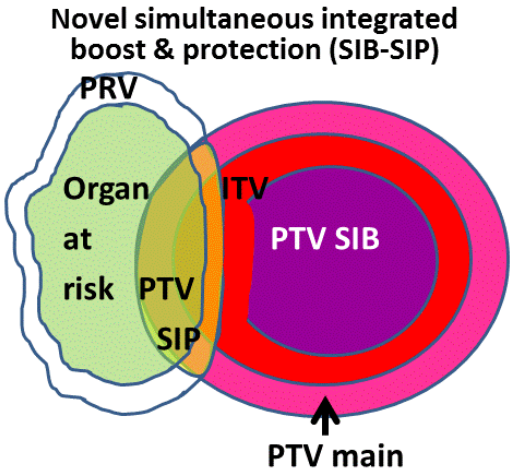
Simultaneous integrated protection

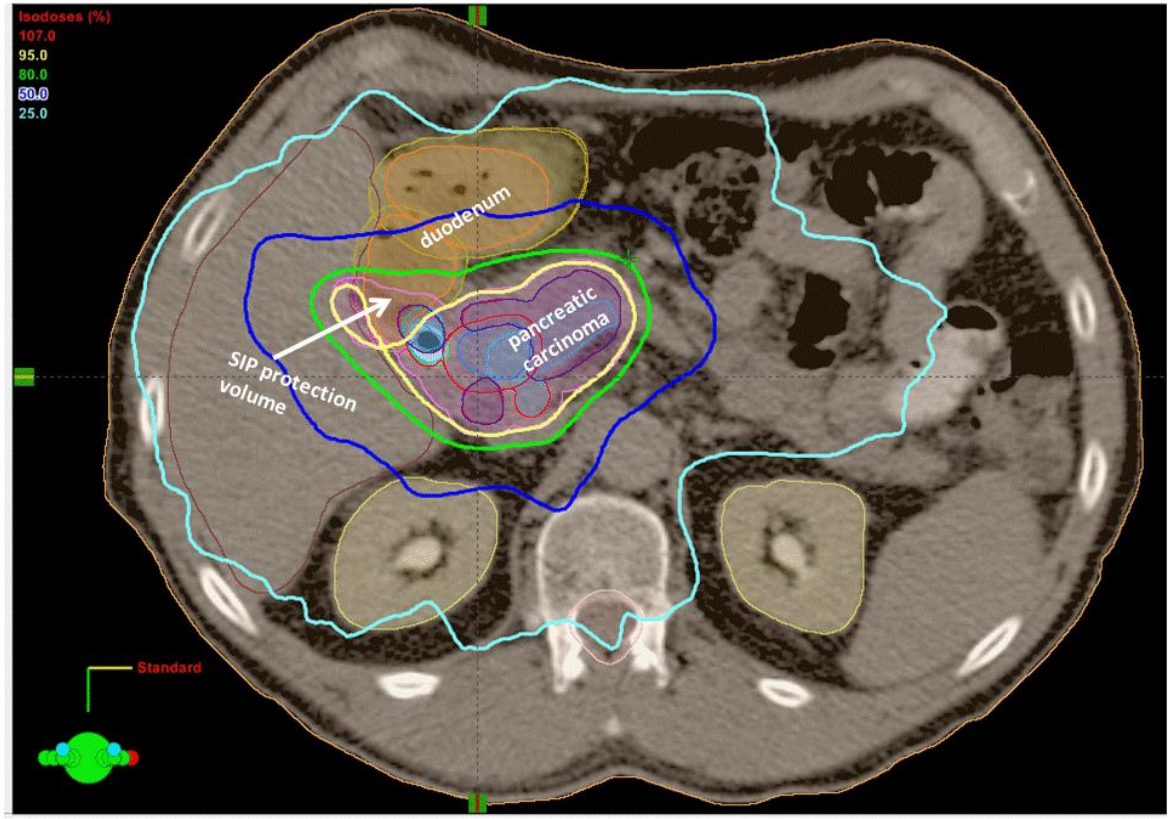
A new concept for high-precision radiation therapy

Thomas B. Brunner[1,2] · Ursula Nestle[1,2] · Sonja Adebahr[1,2] · Eleni Gkika[1,2] · Rolf Wiehle[1,2] · Dimos Baltas[1,2] · Anca-Ligia Grosu[1,2]

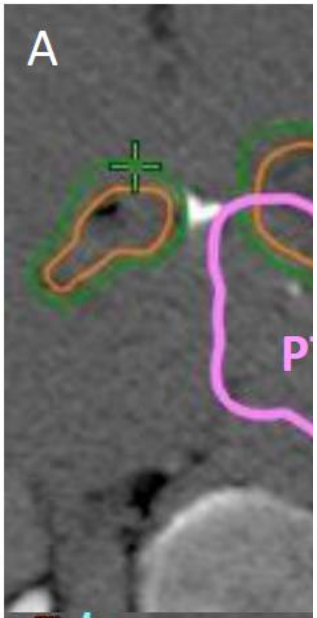
SBRT- SIB and SIP:
Concept to obtain highest TCP and low NTCP







Brunner, Nestle et al. Radiotherapy and Oncology 2016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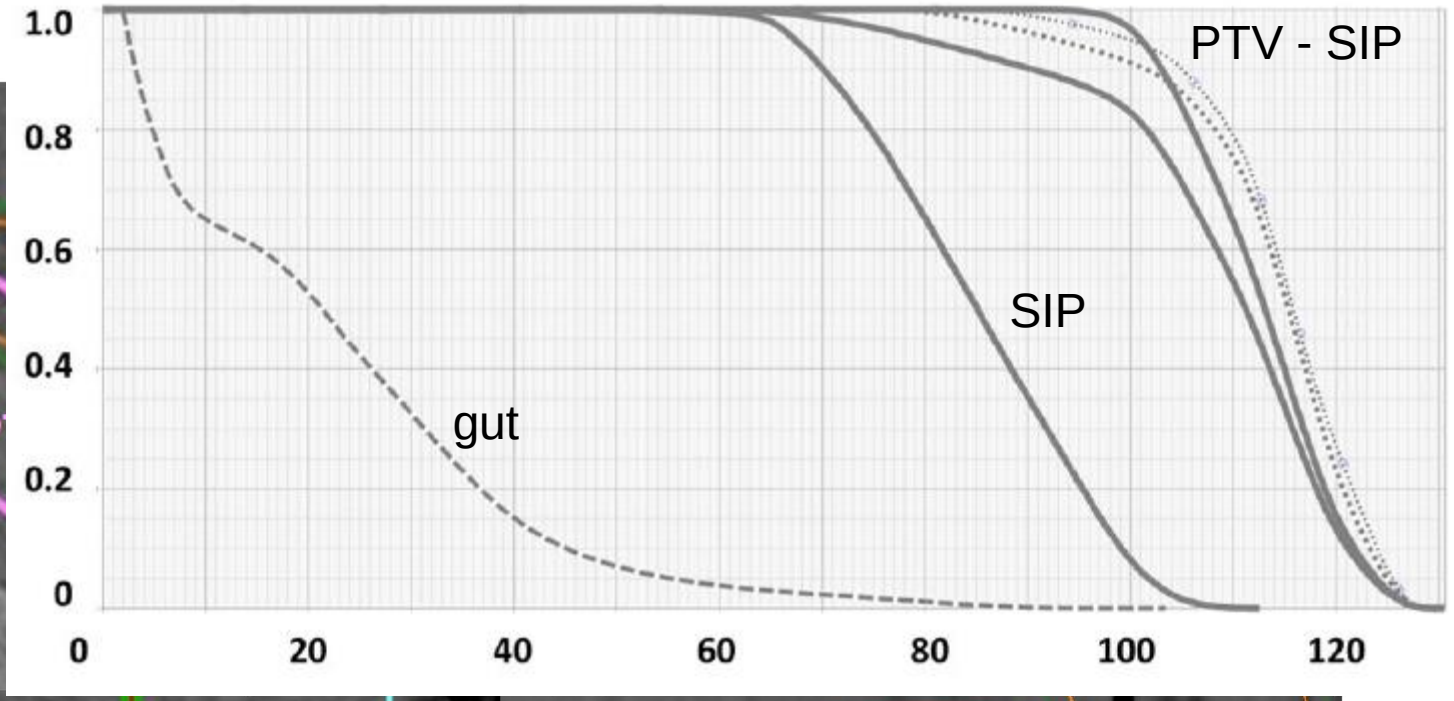
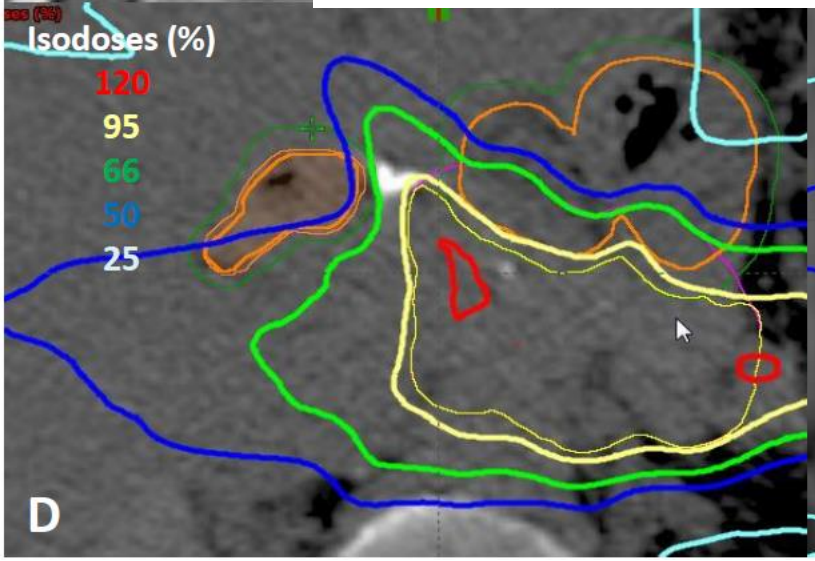
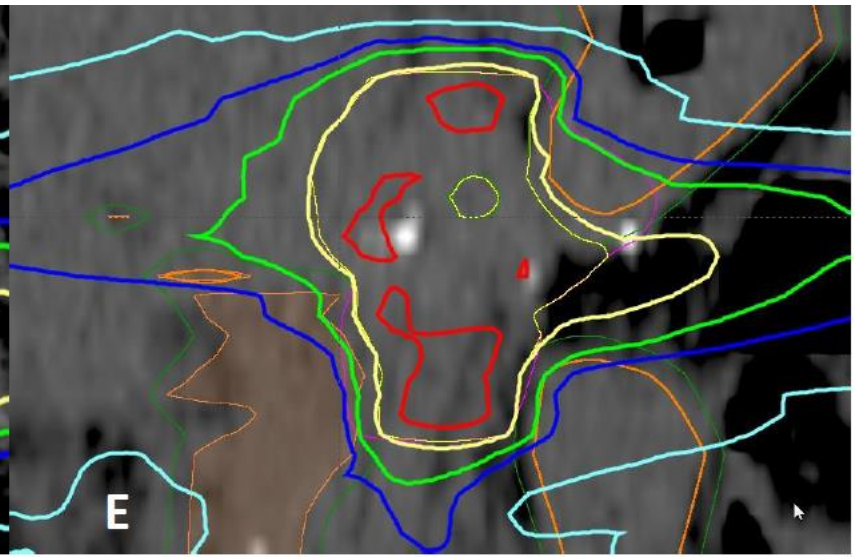

1.0
0.8
0.6
0.4
0.2
0
0
20
40
60
80
100
120
PTV - SIP
SIP
gut


Isodoses (%)
120
95
66
50
25
D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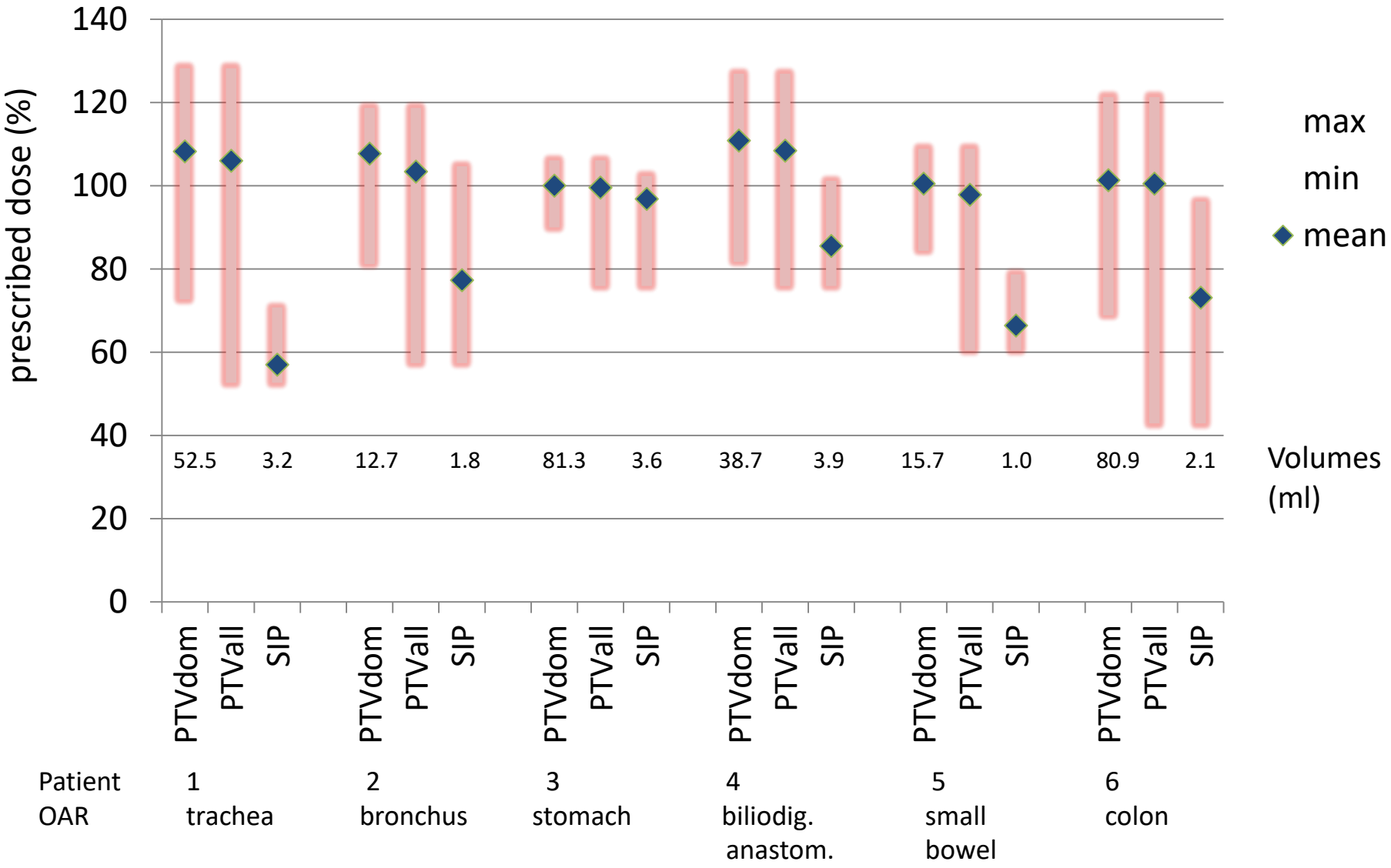

prescribed dose (%)
140
120
100
80
60
40
20
0
max
min
mean
52.5
3.2
12.7
1.8
81.3
3.6
38.7
3.9
15.7
1.0
80.9
2.1
Volumes (ml)
PTVdom
PTVall
SIP
Patient
OAR
1
trachea
2
bronchus
3
stomach
4
biliodig. anastom.
5
small bowel
6
colon

Summary

• in high-precision radiotherapy enabling hypofractionation, effective tumor doses often exceed normal tissue tolerances

• a relevant problem are critical serial normal tissues near high-dose targets, as exceeding tolerance doses here may lead to life-threatening consequences for the patient

• advanced treatment strategies therefore need the discussion of compromises

• beyond adapting dose and fractionation, local strategies may help to ensure high TCP

Physical and biological optimisation

Gert Meijer

ESTRO
European Society for Therapeutic Radiology and Oncology

Physical optimisations

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

  prescribed and calculated dose distribution

Advantages

Physical optimisations

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

Limitations

Physical optimisations

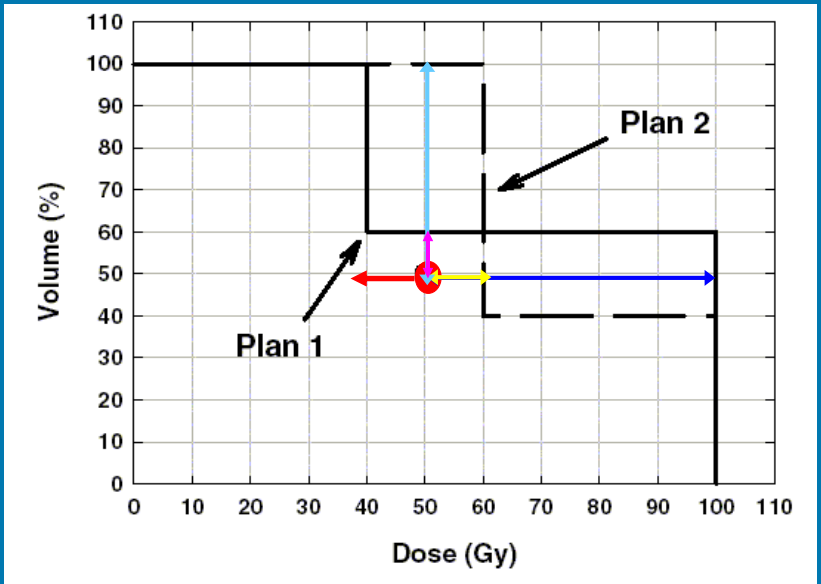
- Quadratic dose difference may not reflect clinical objective
- Properly ranking plans based on dose-volume objectives may fail

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

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

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

Result: Plan 1 is rejected!



Courtesy of Aswin Hoffmann

Limitations

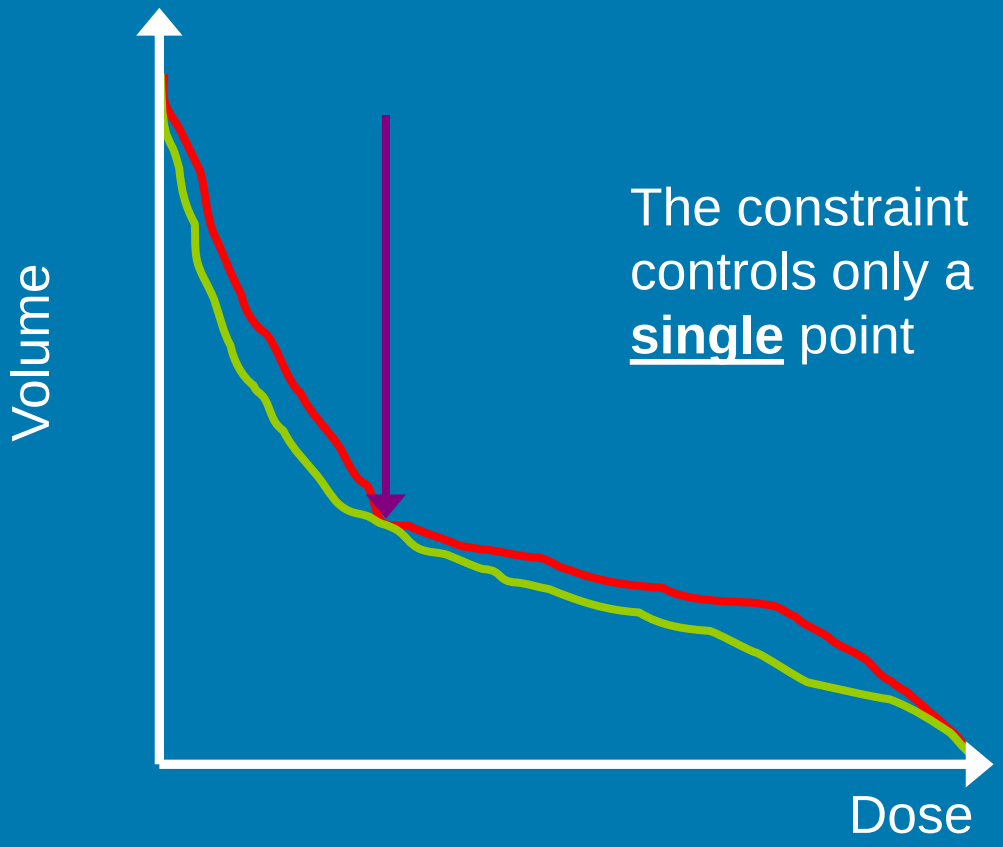
Physical optimisations

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

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

Limitations

Physical optimisations



The constraint controls only a **single** point

Optimization in the biology domain

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

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

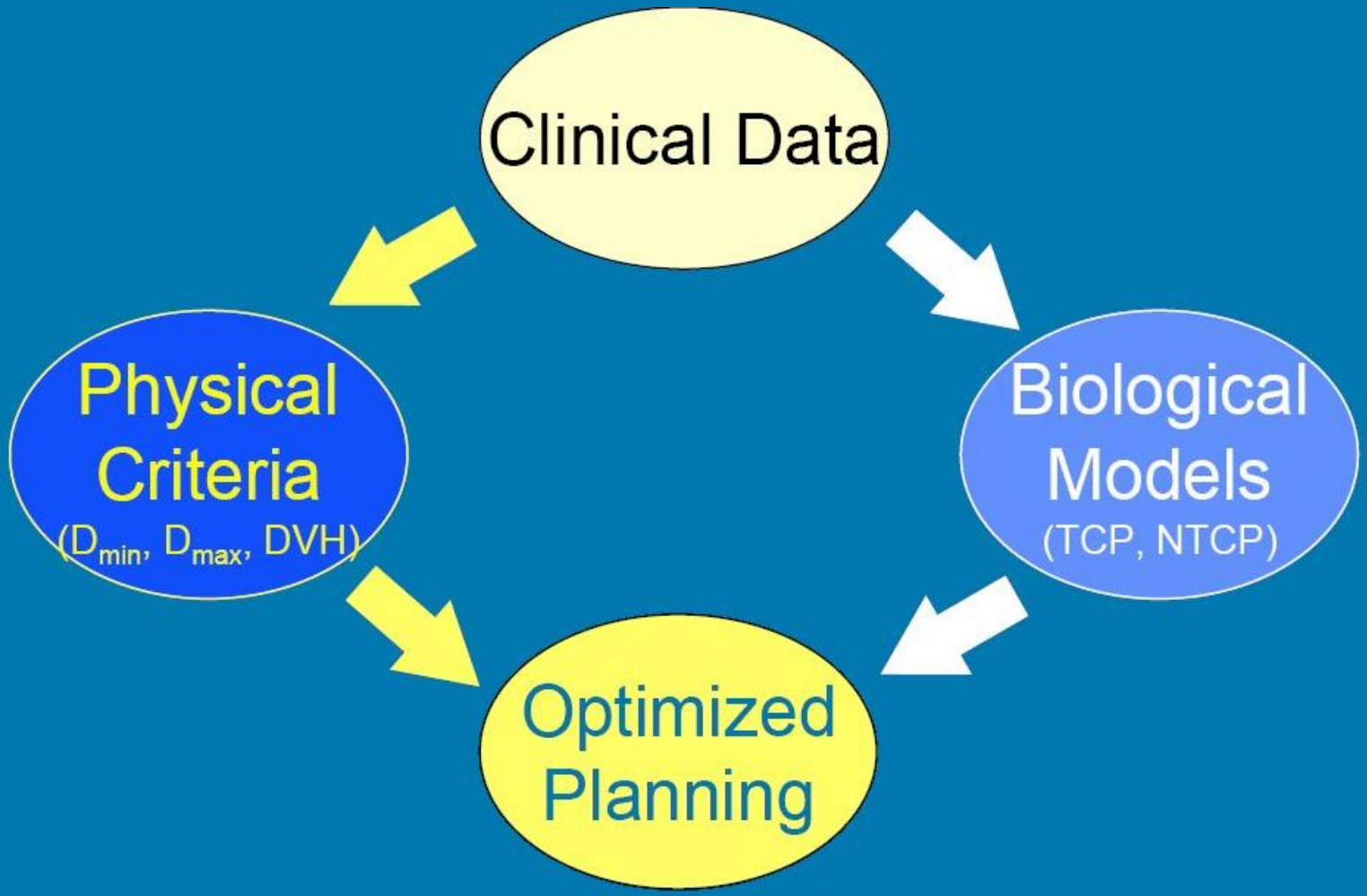
- **Method:** Use an adequate model to quantify the biological effect of dose deposition

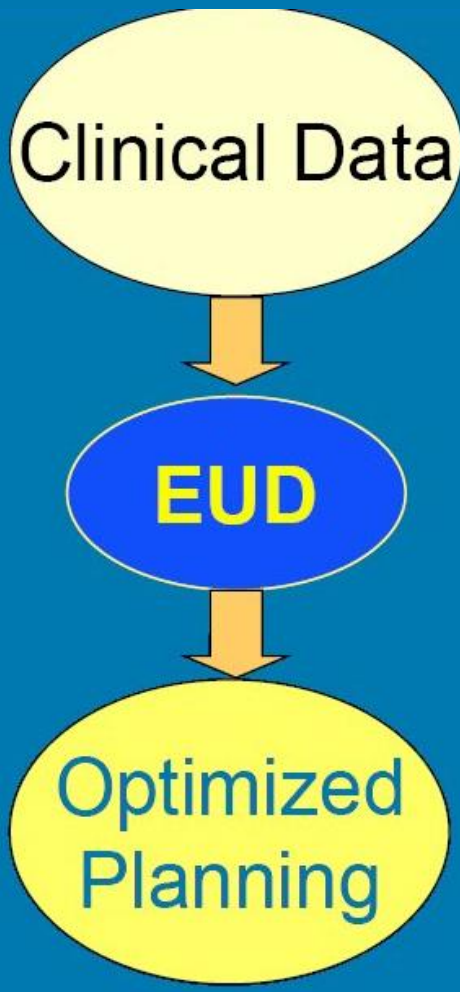
Radiobiological dose-response models

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

this is merely a dream

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

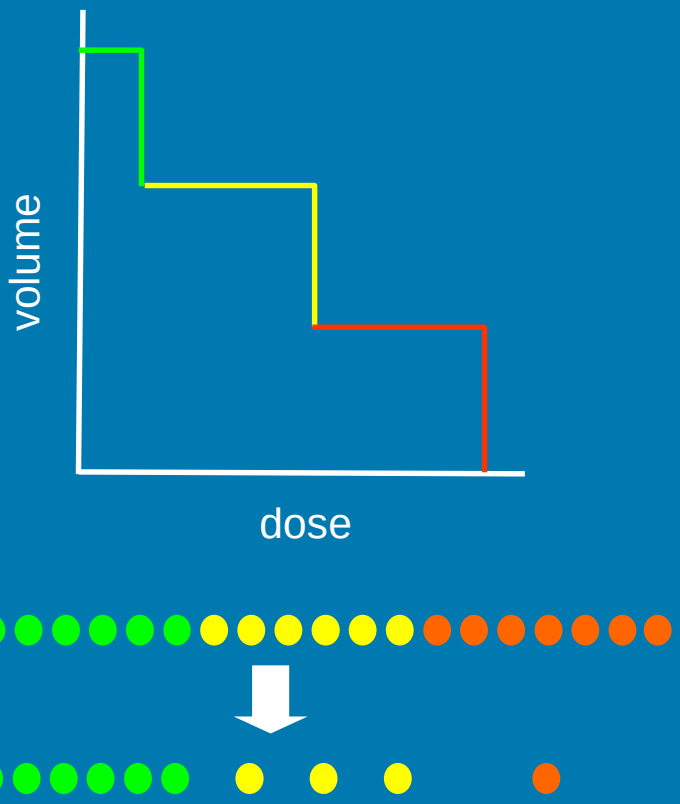


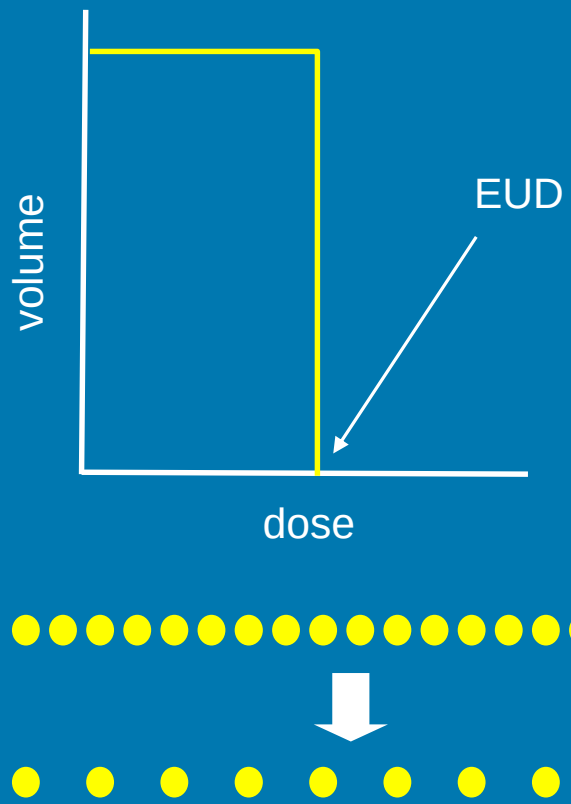


Equivalent uniform dose

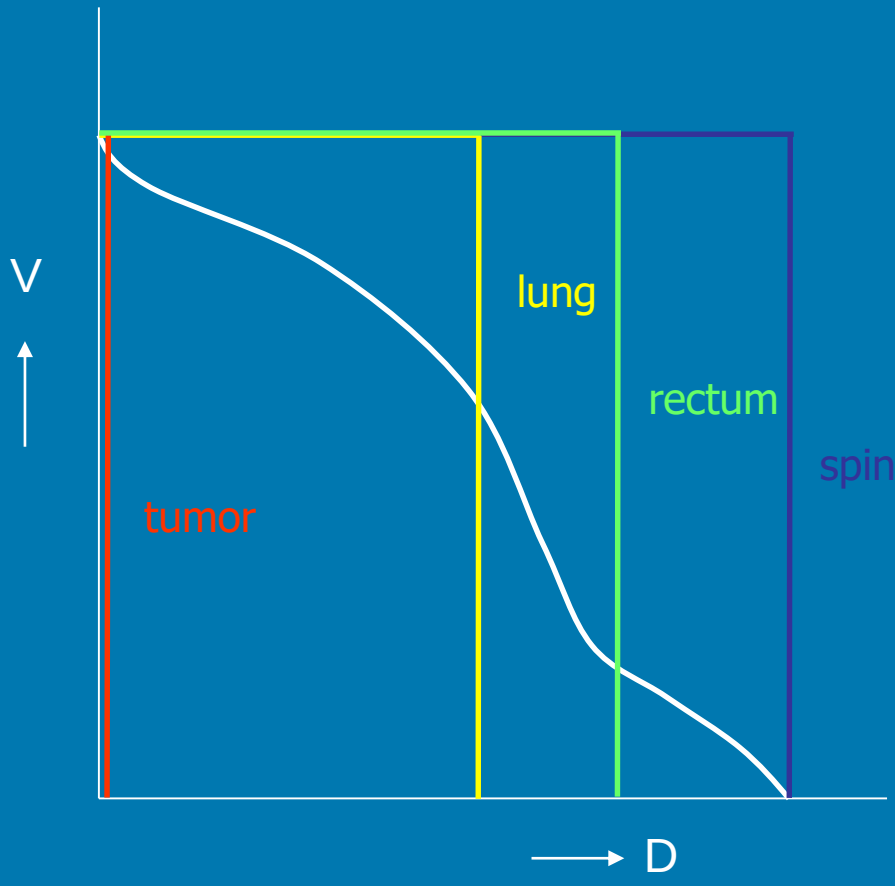
the EUD represents a uniform dose,
which leads to the same probability
of a radiobiological effect as
the corresponding inhomogeneous dose

Equivalent uniform dose





Equivalent uniform dose



Question:

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

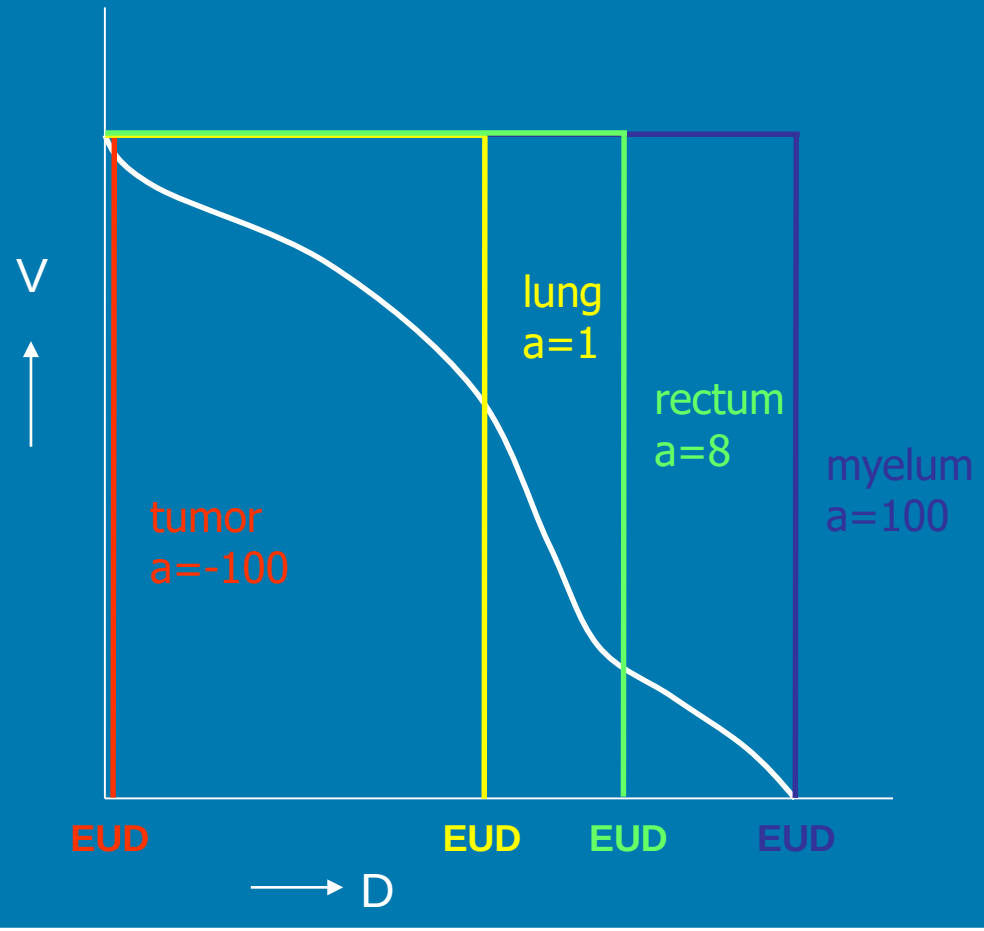
Equivalent uniform dose

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

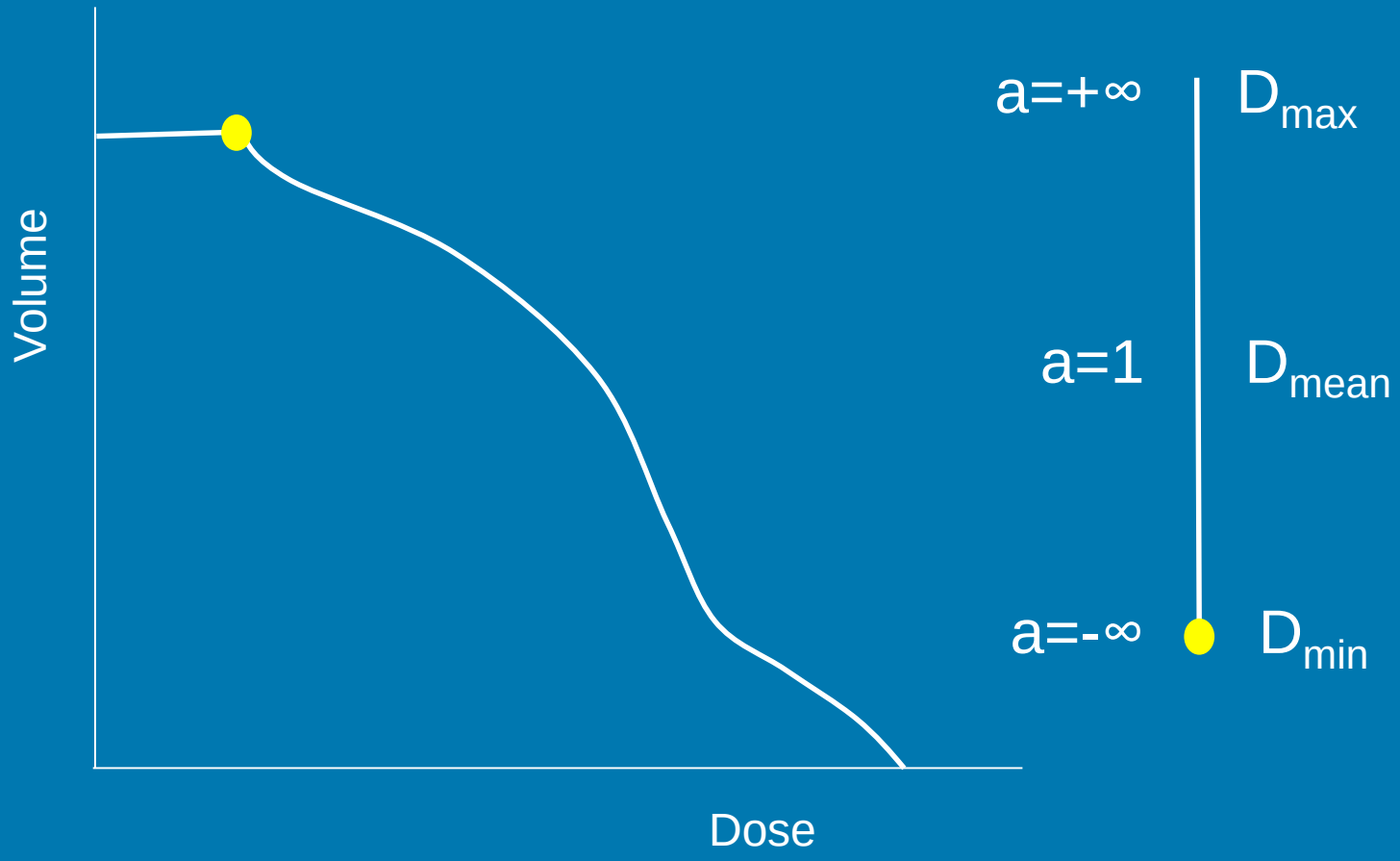
$$\mathrm{EUD} = \frac{1}{N} \sum_{\mathrm{i}=1}^{N} d_{\mathrm{i}}$$

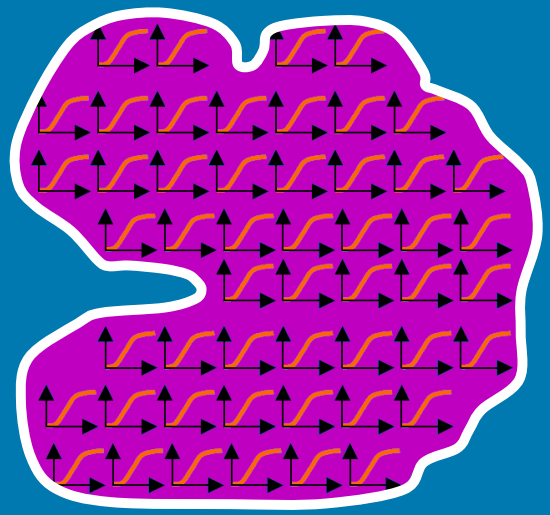
	Effect	Suitable organs
$a < 1$	Lower doses are given higher weight, so that cold spots affect the EUD to a large extent.	Targets.
$a = 1$	This corresponds to the mean dose. Cold and hot spots are given equal weight.	Parallel organized normal tissue, such as lung and liver.
$a > 1$	Larger doses are given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

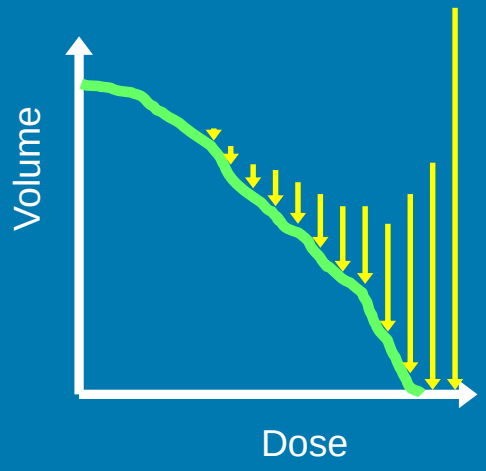
Equivalent uniform dose



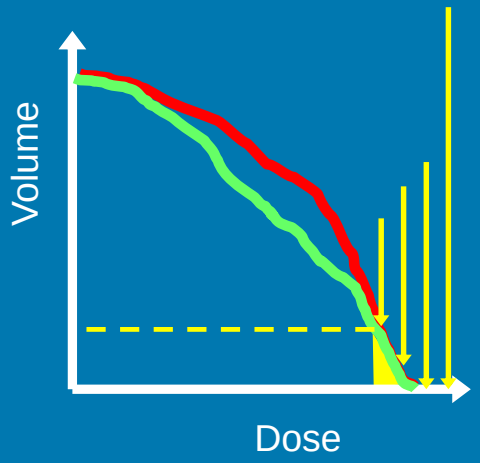
Equivalent uniform dose



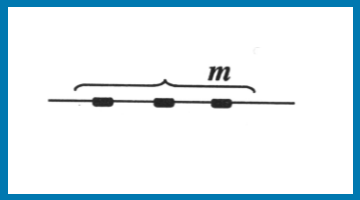


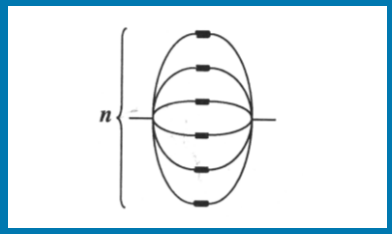


in contrast
d_{max}

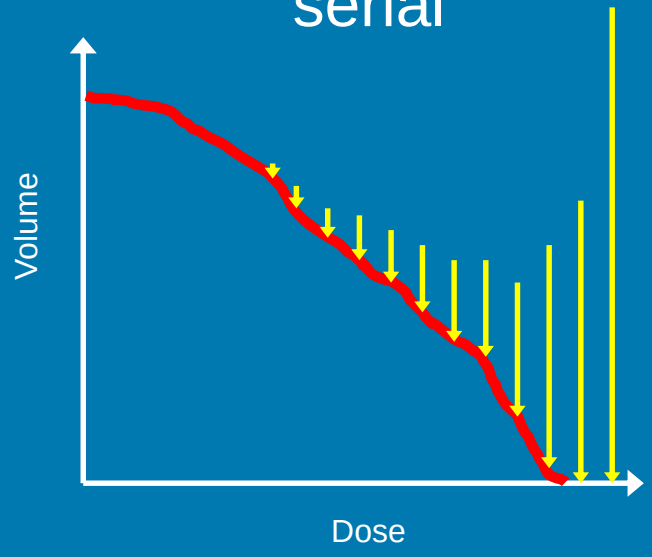


Essentially, a biological cost function is applied to each volume element of a structure
The total effect is described in the resulting DVH

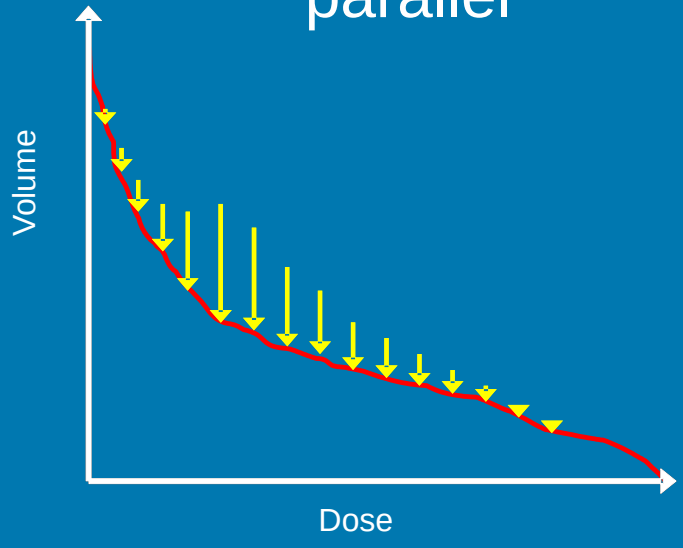




serial

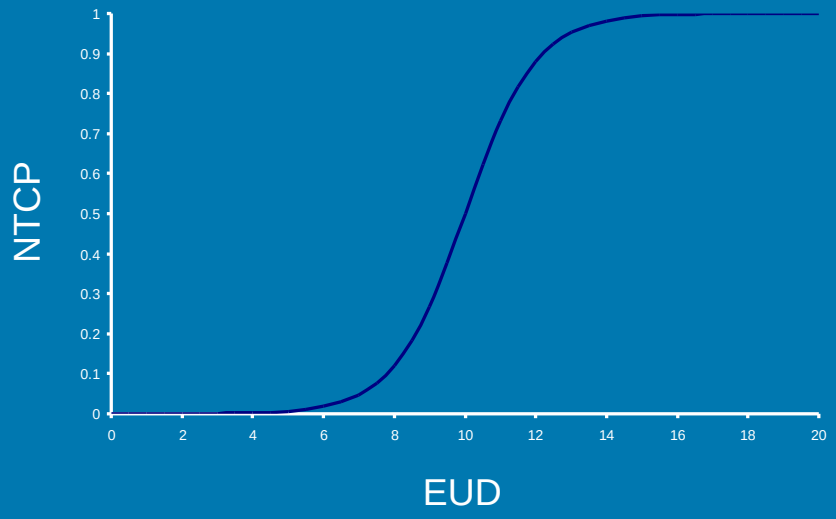


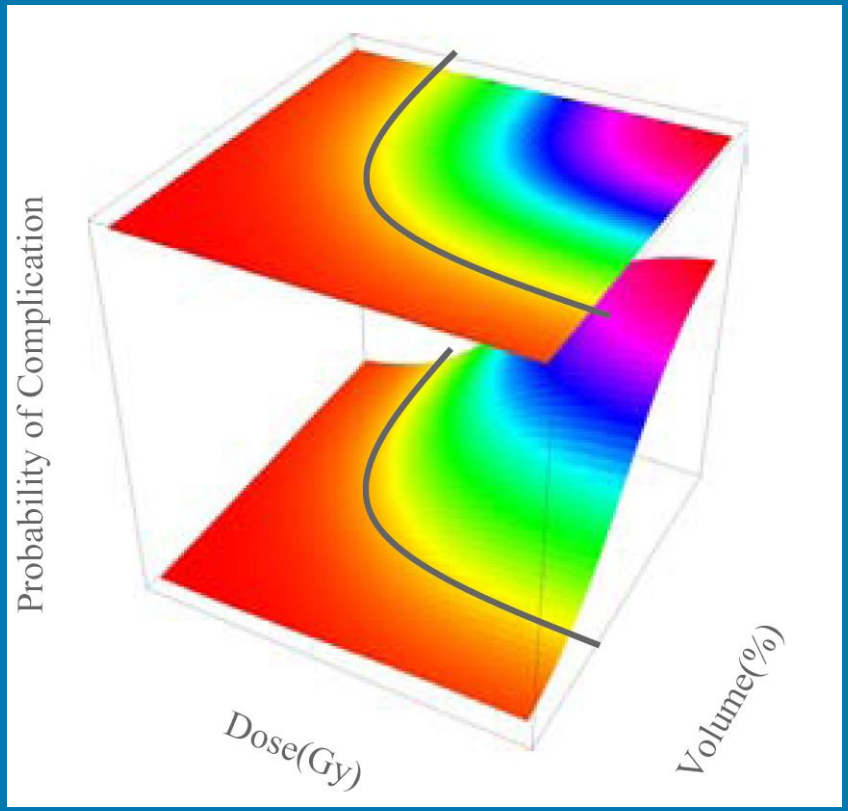
parallel



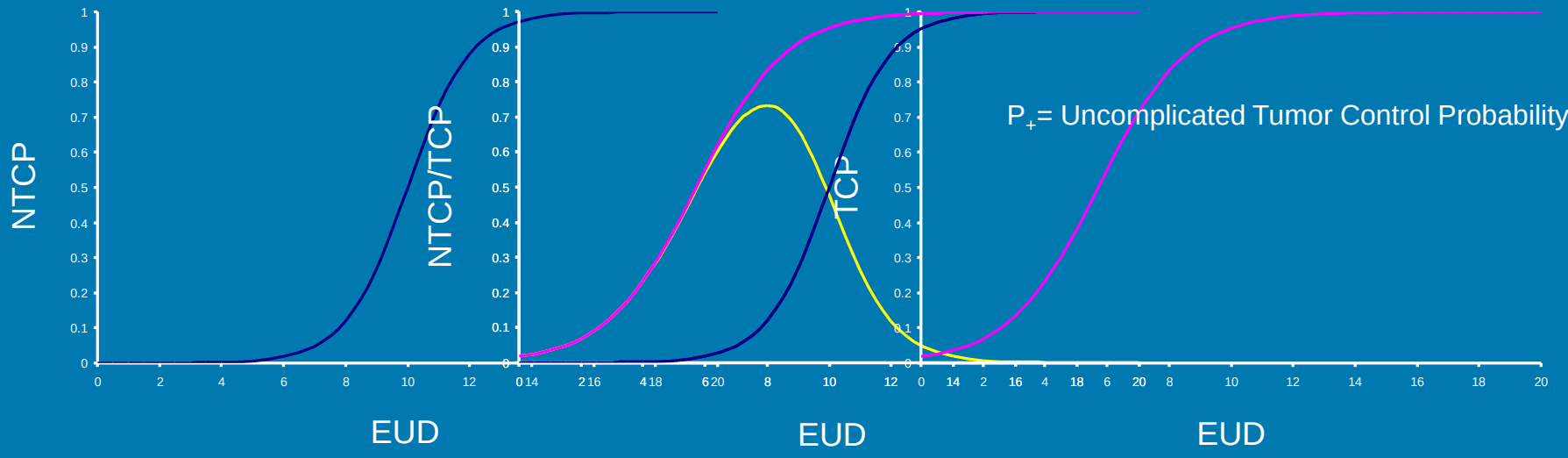
Can we go beyond EUD?

NTCP =
normal tissue complication probability





Can we go beyond EUD?



Limitations

Biological optimisations

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

Advantages

Biological optimisations

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

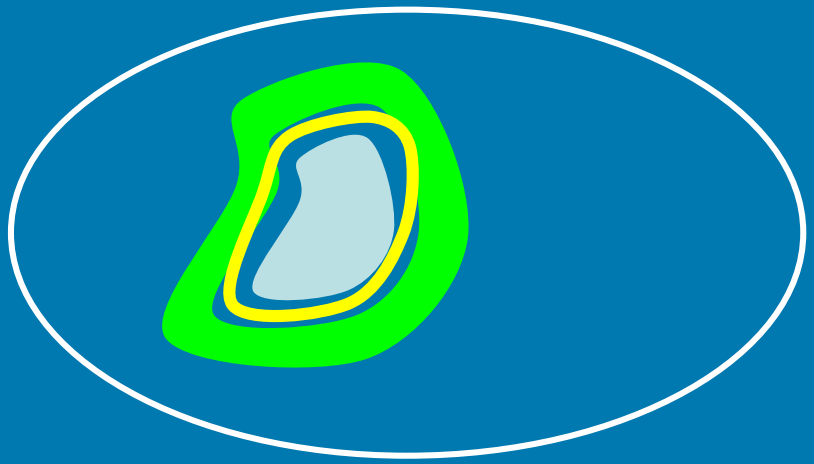
Conclusions

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

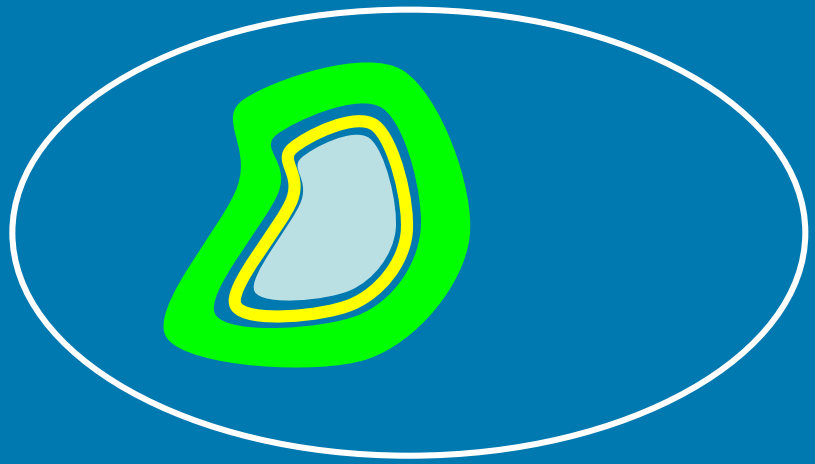
- **Radiobiological optimisation** will become more trustworthy by judicious use of more accurate dose-response models

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

Special acknowledgements to Aswin Hoffmann who kindly provided many slides



α=8
EUD = 40



α=8
EUD = 35

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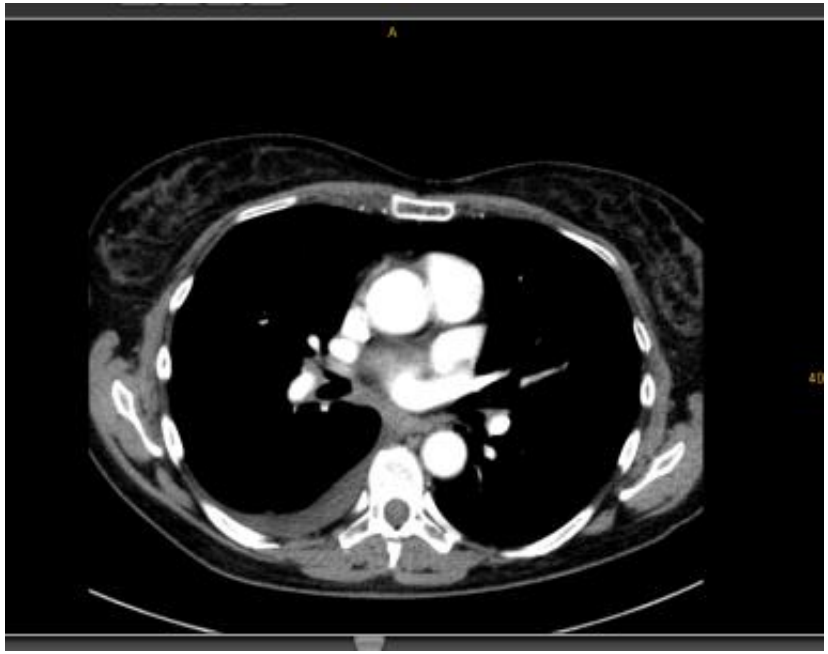
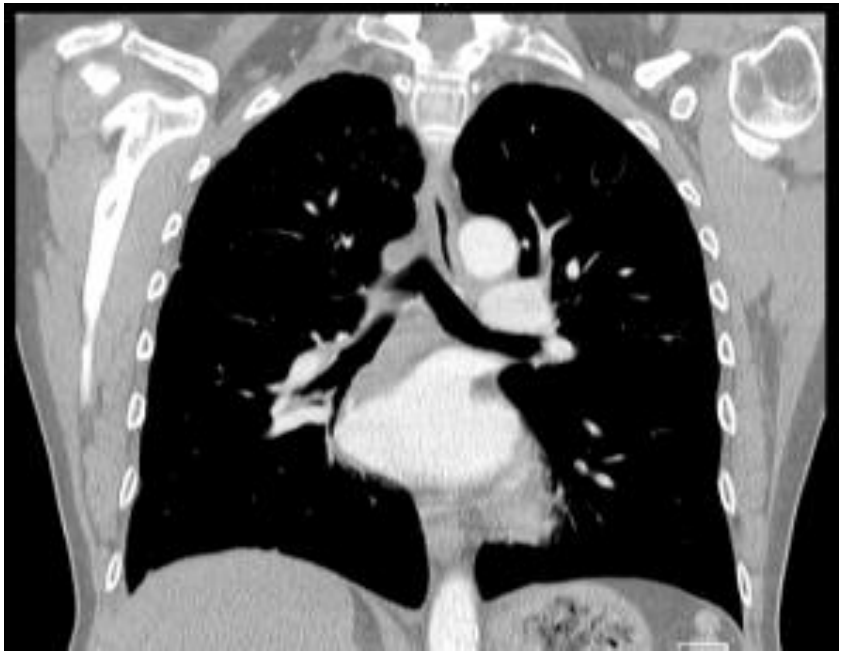
Lung case discussion

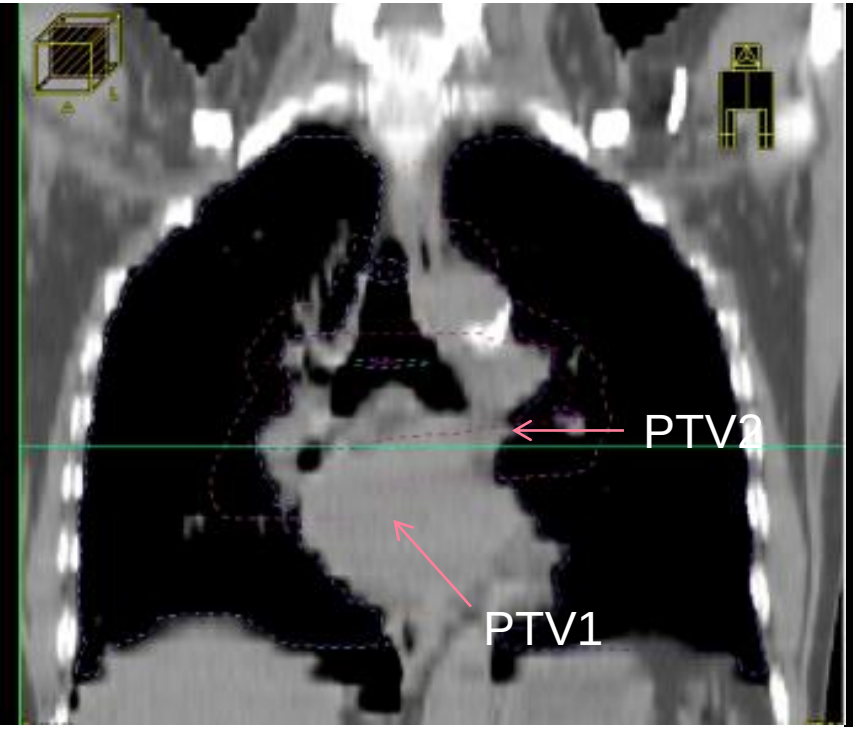
ESTRO ATP Athens
September 2018

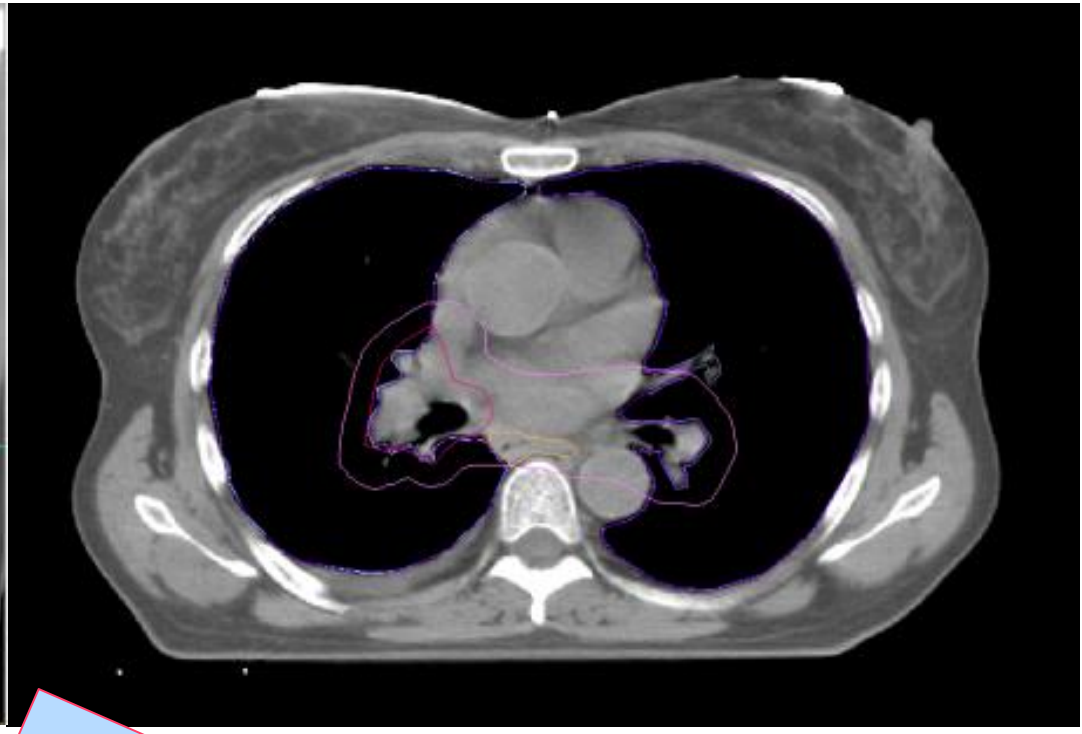
Case 3 (lung)

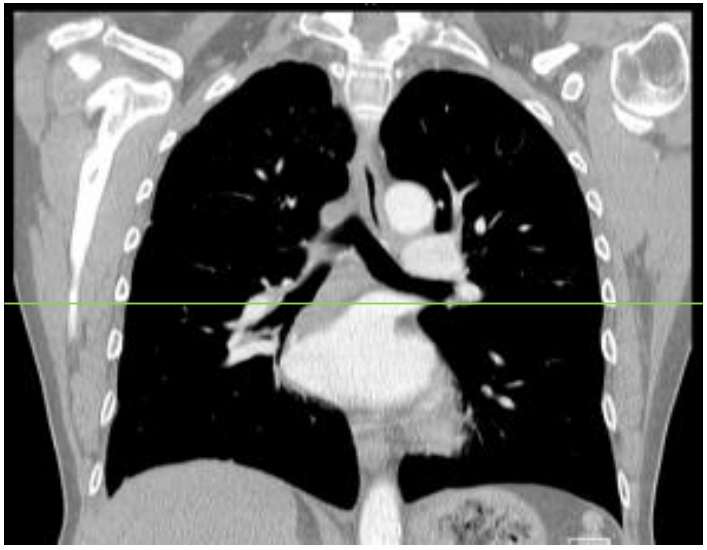




Female pt. *1952;
SCLC diagnosed in 2009
cT4 cN3 Mx
(suspected liver metastasis, lateron excluded)
finally: M0 = limited disease
before 08/2009 6 x CE, partial remission
referred for consolidating radiotherapy of mediastinum







Your challenge!

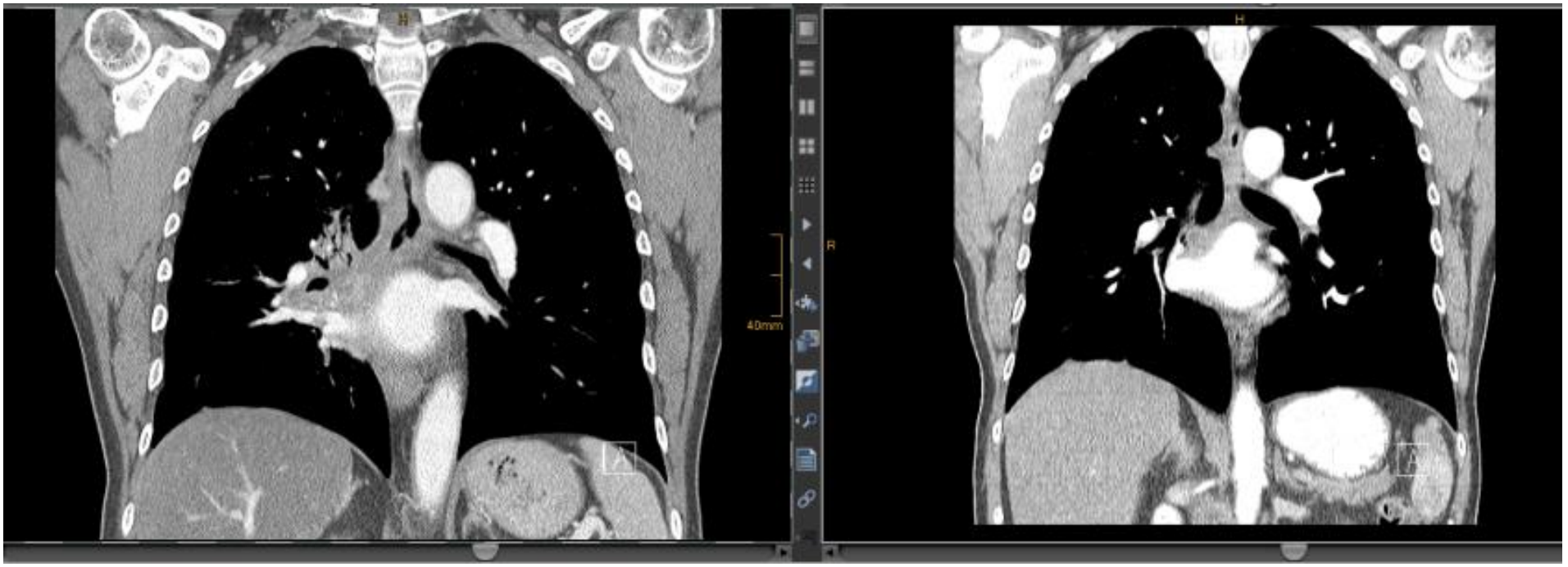
ing and administration:

initi… …escription:

„not possible“

final PTV and dose prescription:
PTV2, 45/1.8 Gy

Case 3 (lung): further development of disease



01/2010: local recurrence right hilum, brain metastasis

brain radiotherapy, chemotherapy

pat. died in 2010

Case 3 (lung): your planning task

Please try to design a RT treatment plan for
59.4 Gy 1.8 Gy to the whole PTV1 (ICRU)

NT restrictions

- *lung* — V20% < 35%
  and MLD < 18 Gy
  V5 of both lungs < 60%
- *spinal cord (PRV)* D_{max} — < 48 Gy
- *esophagus* — V55Gy < 35 %
  or D_{mean} < 35 Gy

Further considerations:

if constraints cannot be reached, a **compromise** may be needed.

Possible trade-offs for compromise:

- discuss to **loosen PTV coverage** from lower constraint 99% receiving 95% of the prescribed dose to 95%

- as pneumonitis may kill the patient soon, try to keep the **lung** constraints without compromise

- allow up to 50 Gy point dose to the **spinal cord** and/or steep dose gradients near to the spine, if IGRT is available

- allow more dose to the **esophagus**, as this will affect acute toxicity, which can be monitored and treated clinically

Individual planning

Enjoy !

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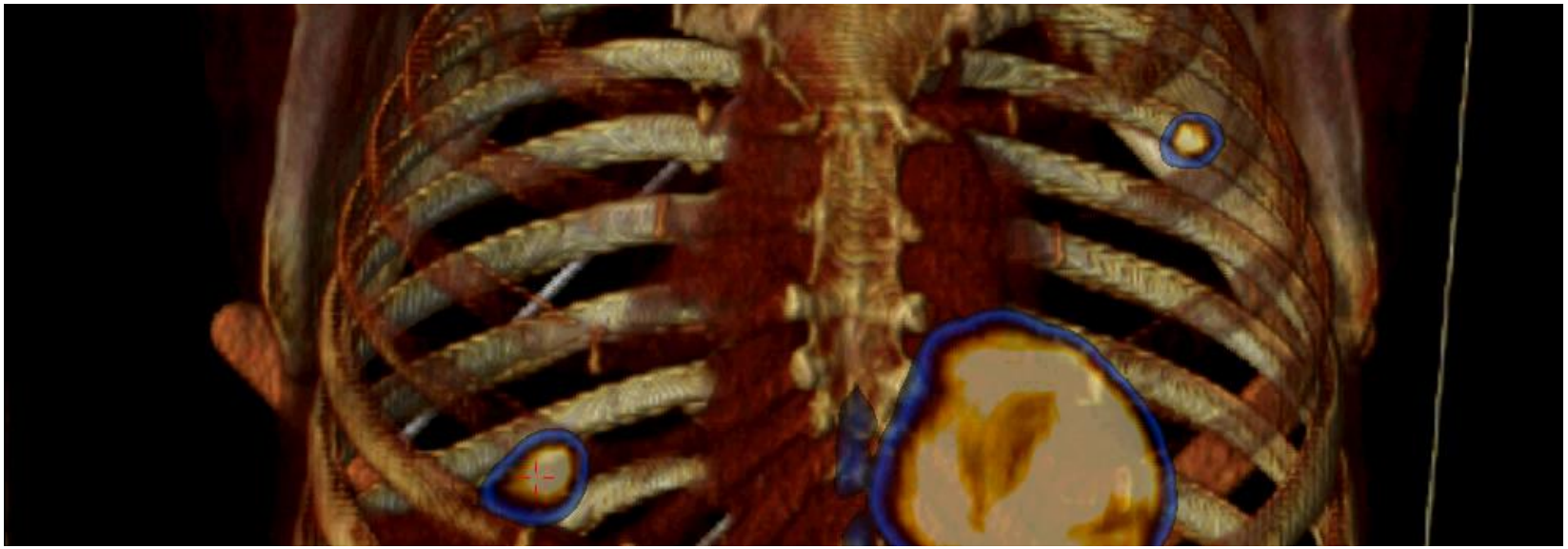
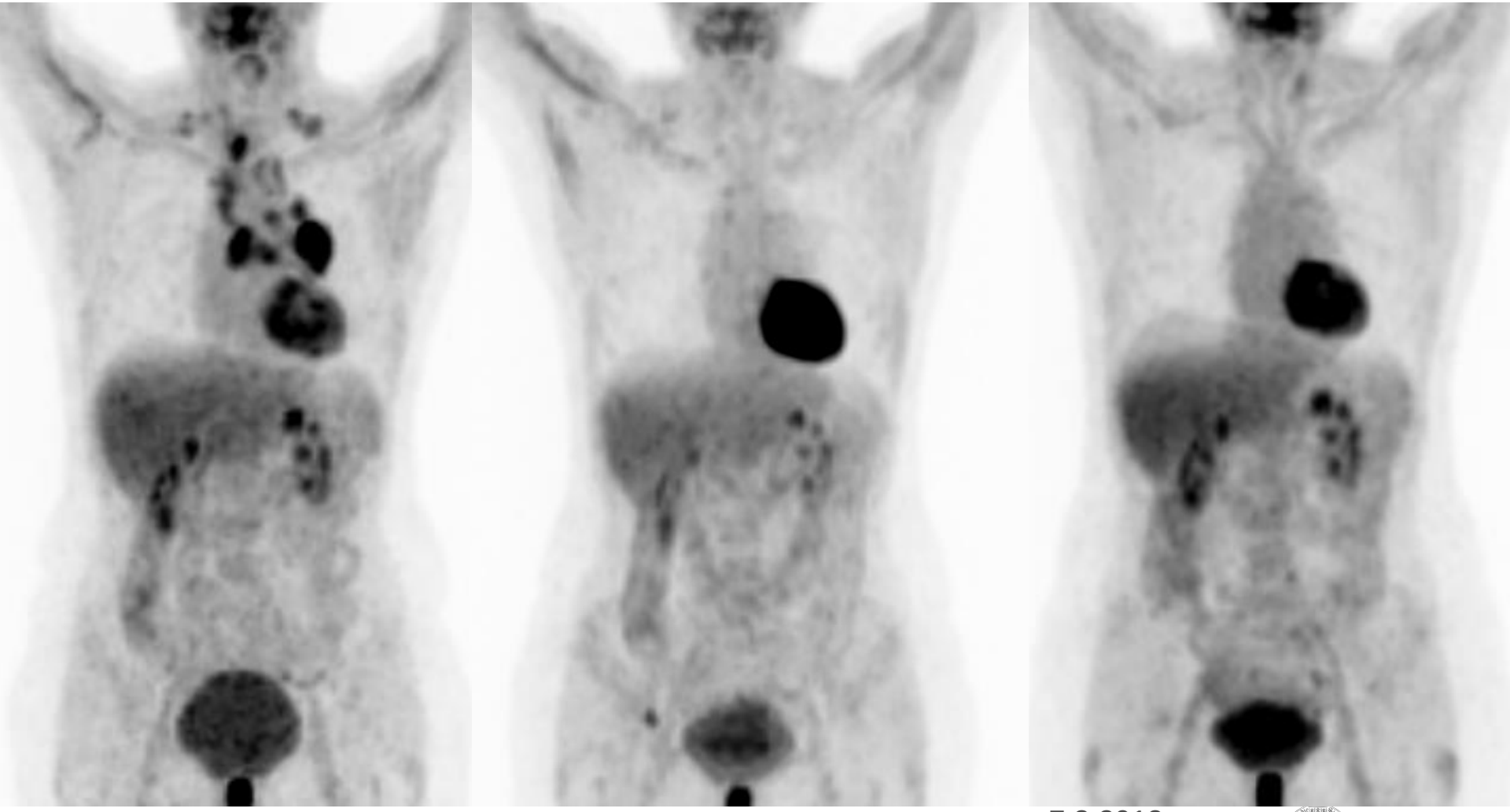


Molecular imaging in treatment planning

Prof. Ursula Nestle
Klinik für Strahlenheilkunde Universitätsklinikum Freiburg, Germany
and Klinik für Strahlentherapie und Radioonkologie Kliniken Maria Hilf Mönchengladbach

ESTRO ATP Athens 2018

Cure with the help of multimodal imaging …



9.3.2010 20.12.2010 7.3.2012

Kliniken Maria Hilf Mönchengladbach

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MCQ 1 - Improvements in medical imaging will impact on:

A. The GTV
B. The CTV
C. The PTV
D. all of the above

Applications of multimodal imaging in radiation therapy: outline

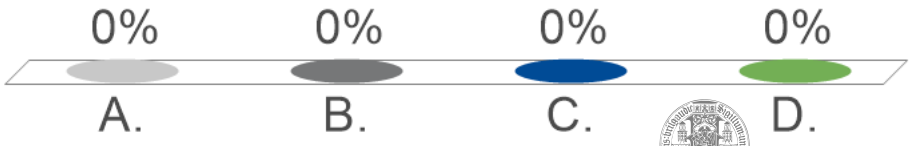
- Primary tumor: GTV
- Nodal volumes: CTV
- Movements: PTV
- Perspectives, caveats

Applications of multimodal imaging in radiation therapy: outline

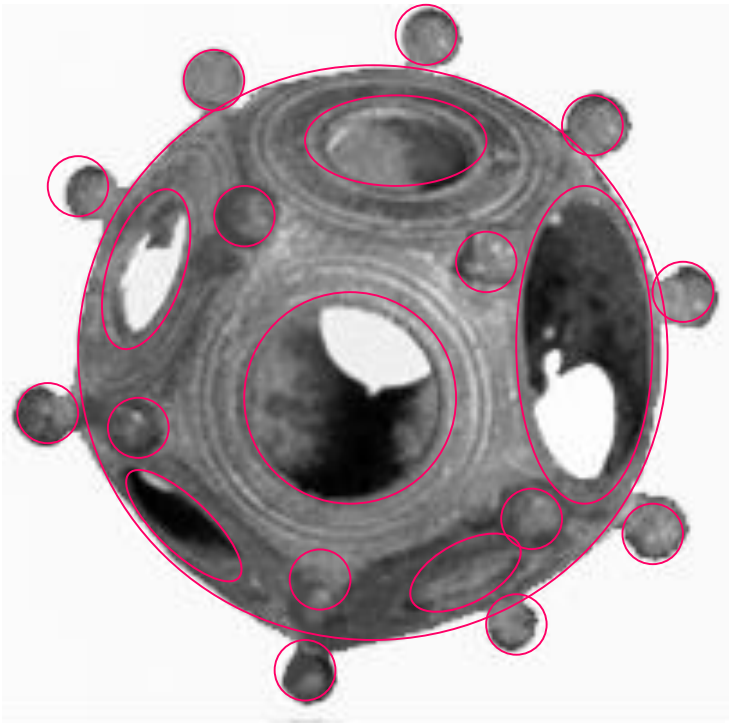
- **Primary tumor: GTV**
- Nodal volumes: CTV
- Movements: PTV
- Perspectives, caveats

MCQ 2 - Molecular imaging for GTV delineation:

A. May help to better identify the tumor
B. May depict normal tissue and inflammation
C. May enable dose painting concepts
D. all of the above



Imaging for GTV-Definition



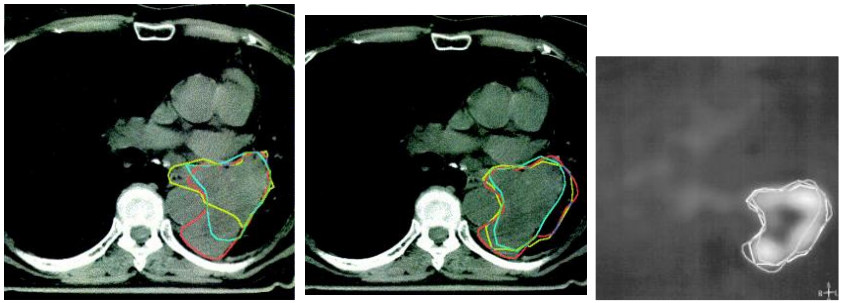
diagnostic imaging:

What is that?

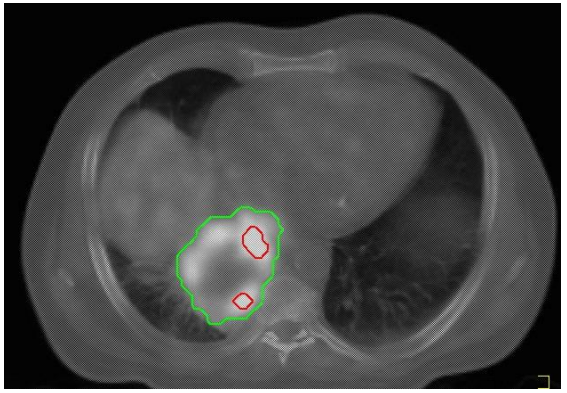
Treatment planning:

Where is that?

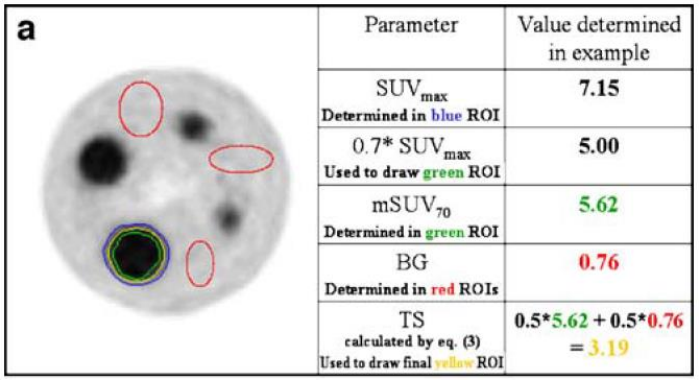
Volume definition using molecular imaging-data: Chance and Challenge



Caldwell, C. et al. IJROBP 2001

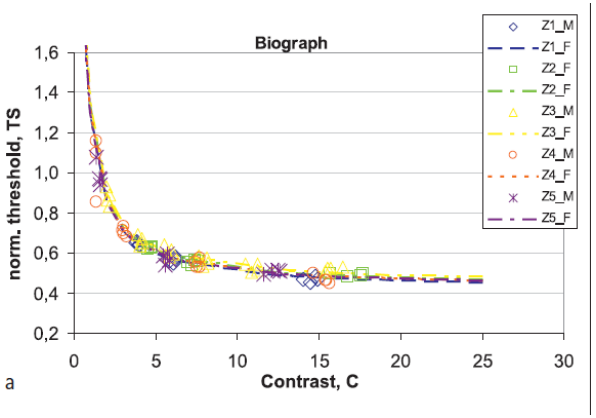


Nestle, U. et al; JNM 2005



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.	median rank 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

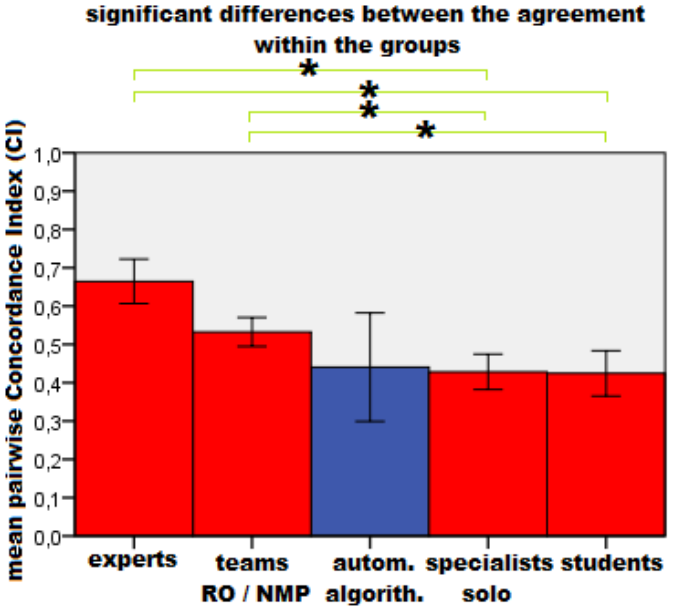
Shepherd, T. et al. IEEE 2013

Observer variability vs. method variability

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

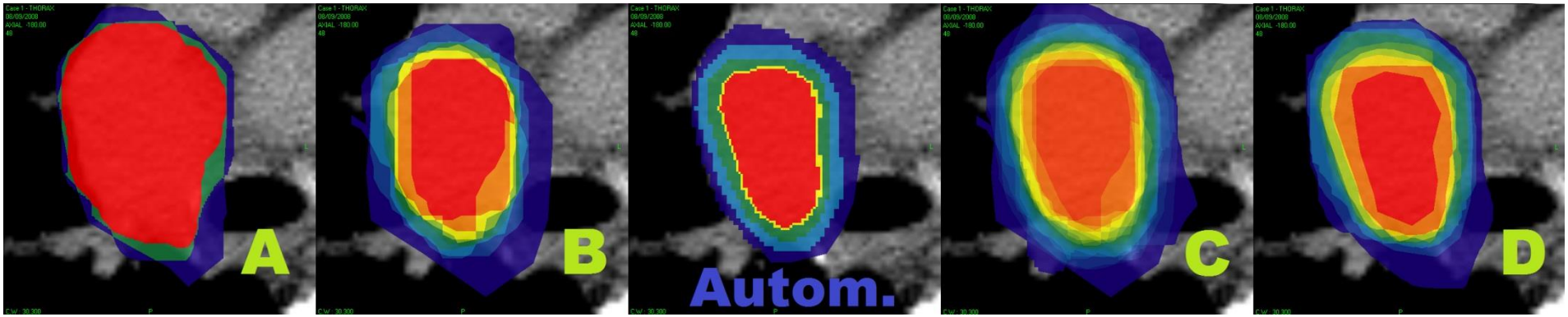
- IOV Specialists (**C**) vs. students (**D**): n.s.
- „PET-years“ n.s.

- IMV of automatic algorithms = IOV of students

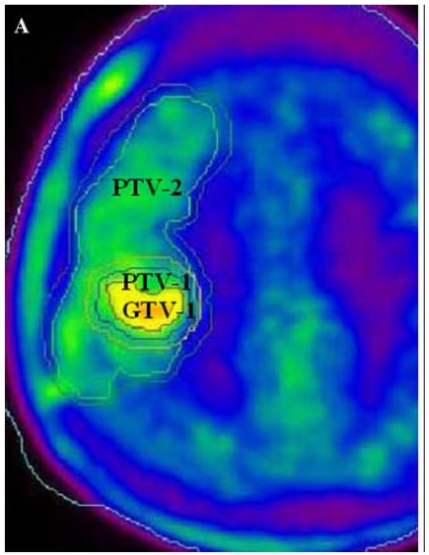


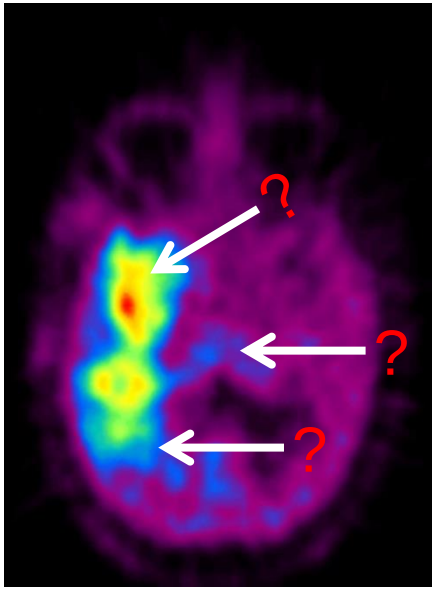
	A	B		C	D
C I	0,67	0,53	0,44	0,43	0,42
Kappa Index	0,80	0,69	0,59	0,57	0,57

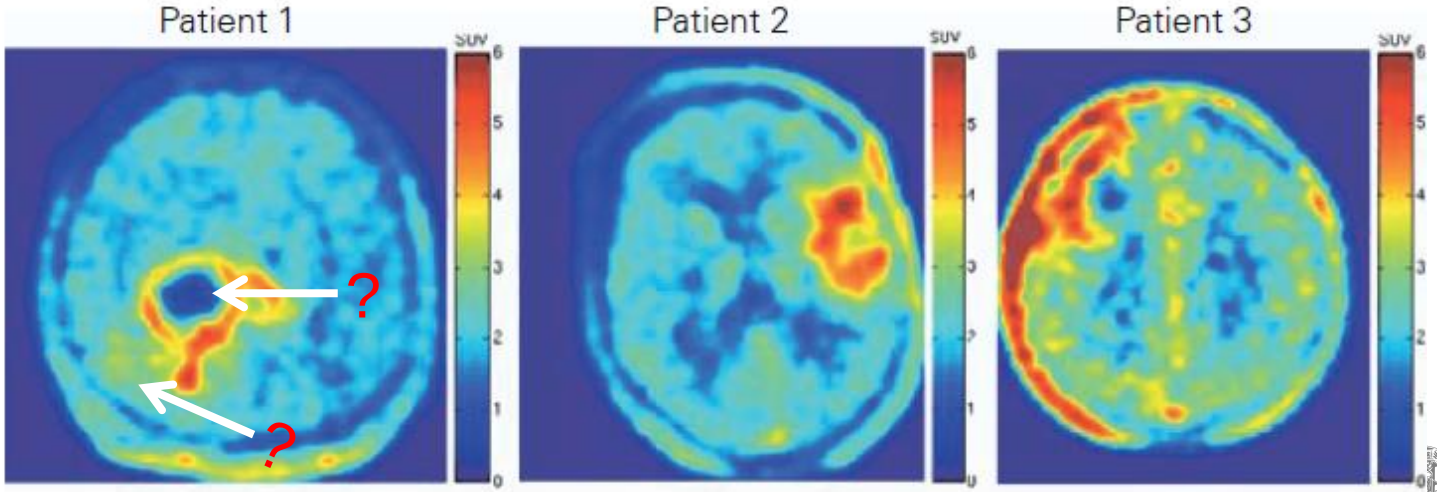
C. Doll et al. Strahlentherapie 2012



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, 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

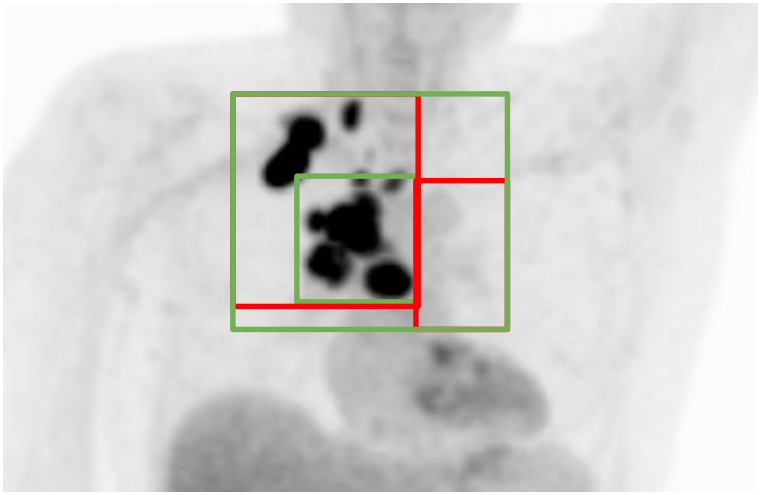
Applications of multimodal imaging in radiation therapy: outline

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

MCQ 3 - With improved imaging, the clinical target volume…

A. Will be abandoned
B. Will not change, as it is about non-detectable spread
C. Will be replaced by newly detectable parts of the GTV
D. May be subject to changing concepts due to improved but still imperfect diagnostic accuracy

CTV: where are the nodes?



diagnostic imaging:

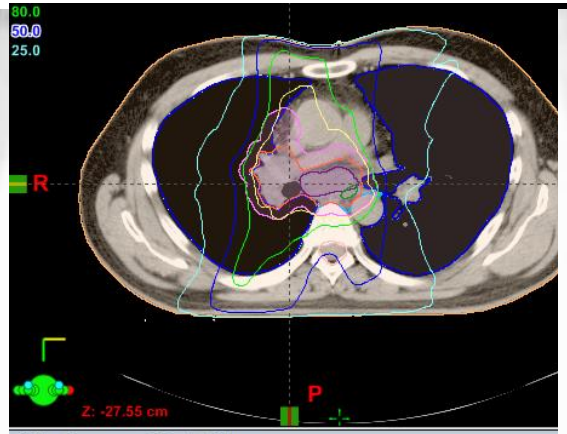
N2

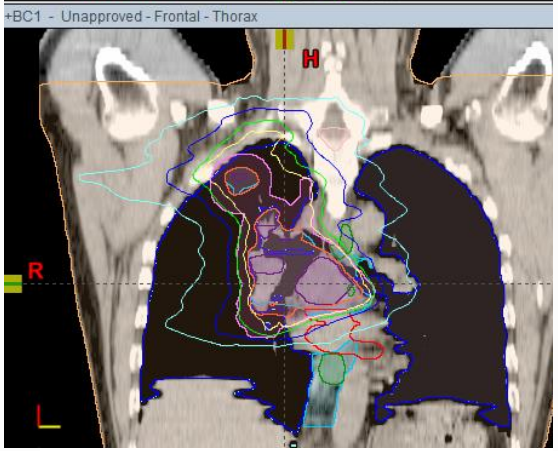
RT treatment planning:

Treat what?

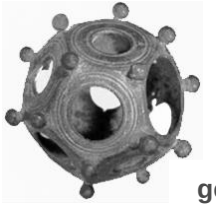
19.4.2012

14.12.2012

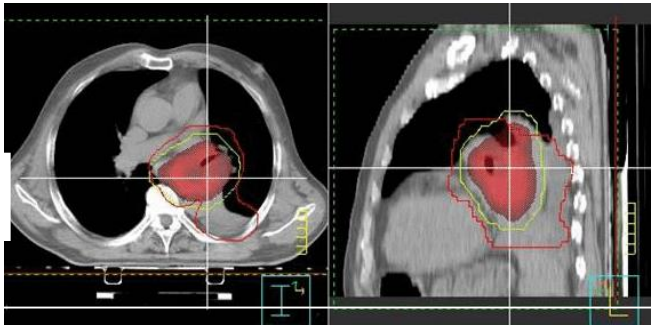




NSCLC (SCC) IIIb;
RCT 07/2012; Platin,
66 Gy/2 Gy

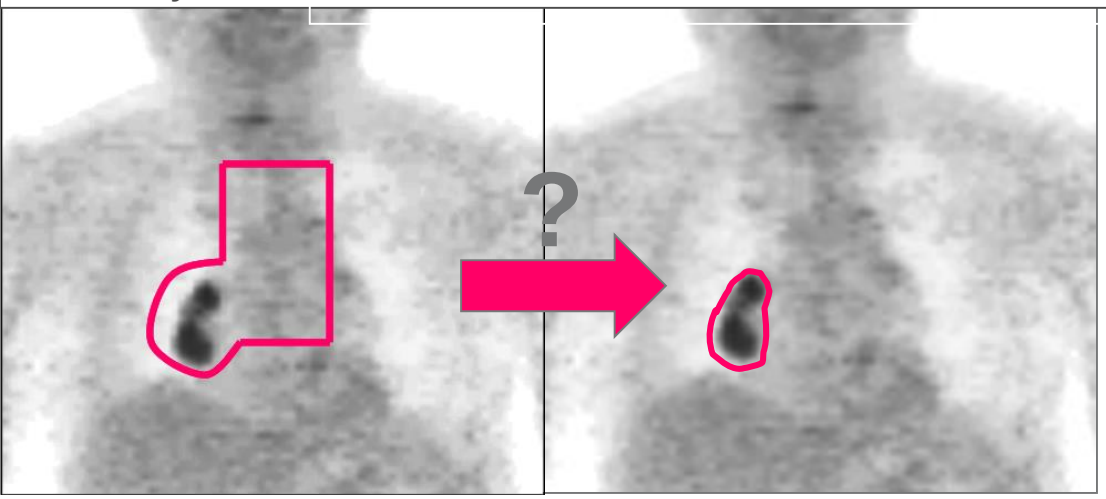


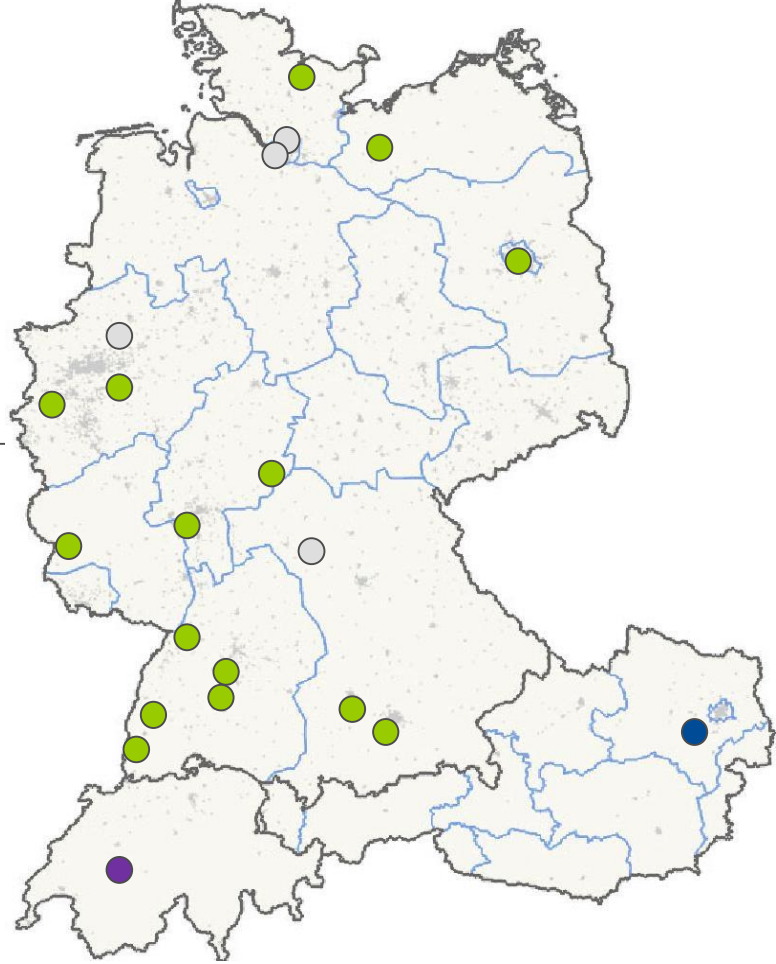
gefördert durch die Deutsche Krebshilfe

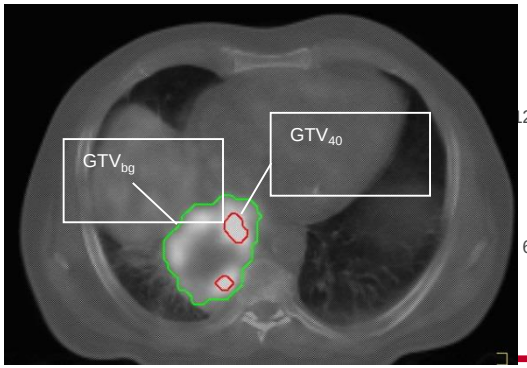


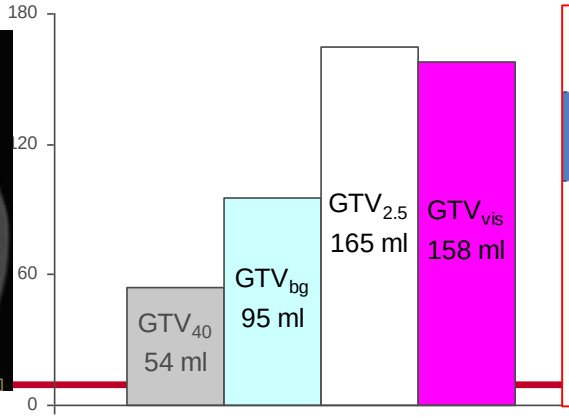
PI: U. Nestle, Freiburg, Germany

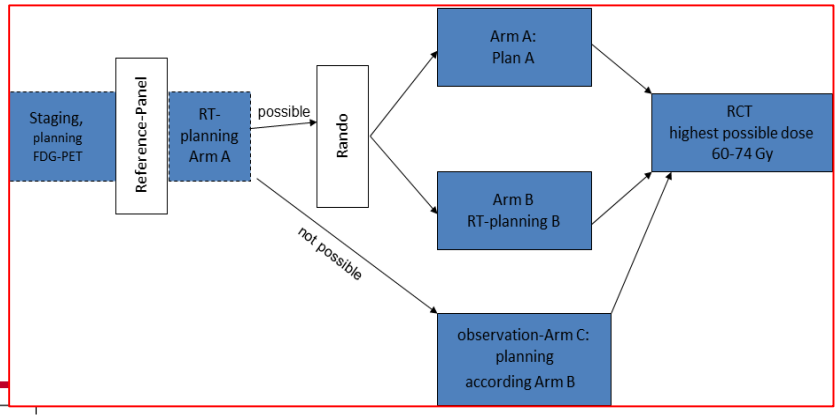
PET - Plan



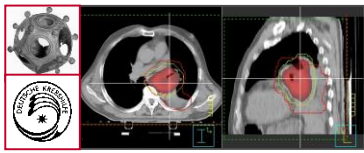


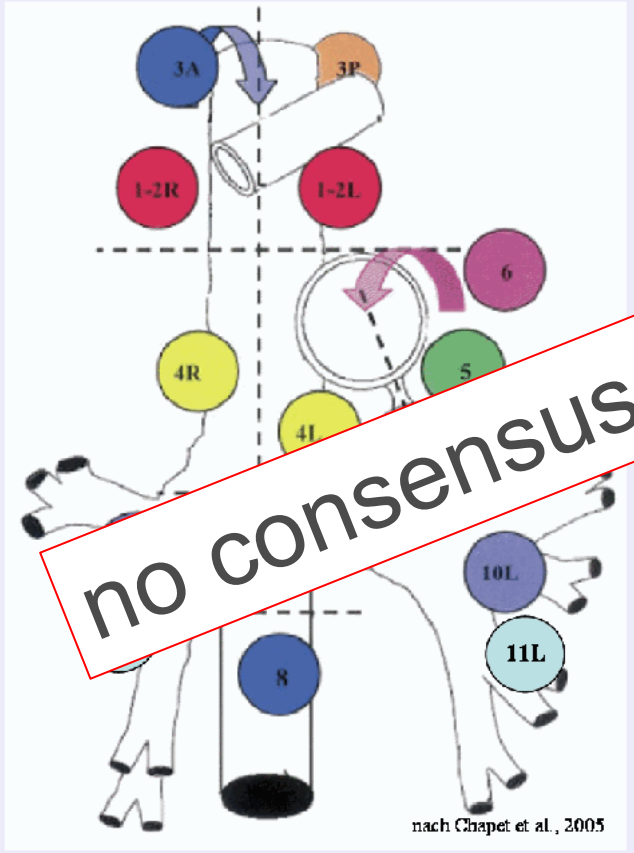






PET-Plan Study: diagnostic expert-panel



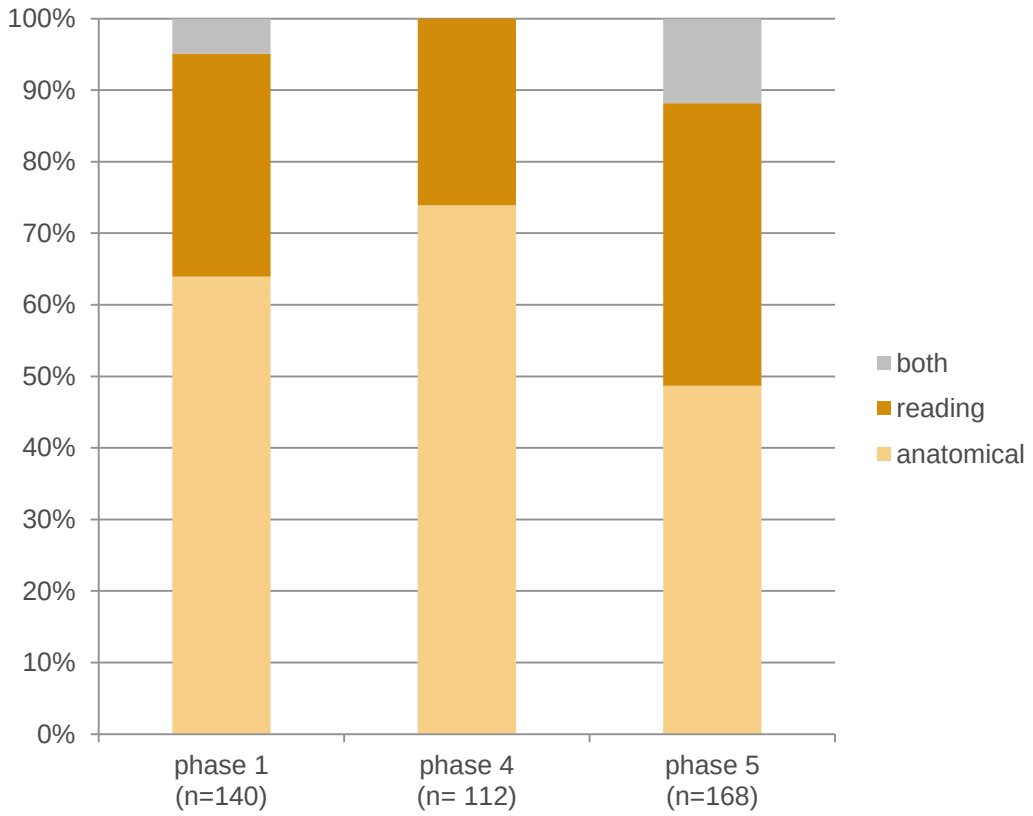


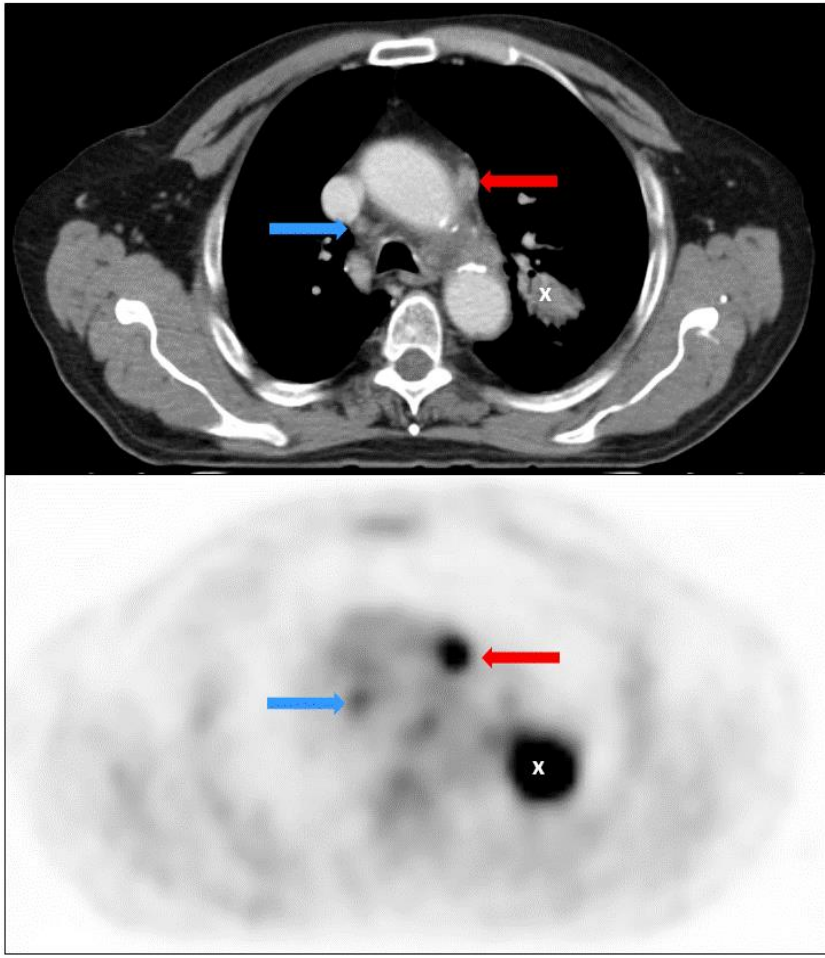
Station	Findings study center	Findings Review 1	Findings Review 2	Consensus Reviewer 3
1R*	neg	neg	pos	
1L*	neg	neg	neg	
2R*	pos	pos		
2L*	neg			pos
3A*	neg		neg	neg
3P*			neg	neg
4R*		pos	pos	pos
4L*		pos	neg	pos
5*	neg	neg	pos	neg
6*	neg	neg	neg	neg
7*	pos	pos	pos	pos
8*	neg	neg	neg	neg
10R*	neg	pos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

What are the reasons for reporting disagreements?





Kliniken Maria Hilf Mönchengladbach

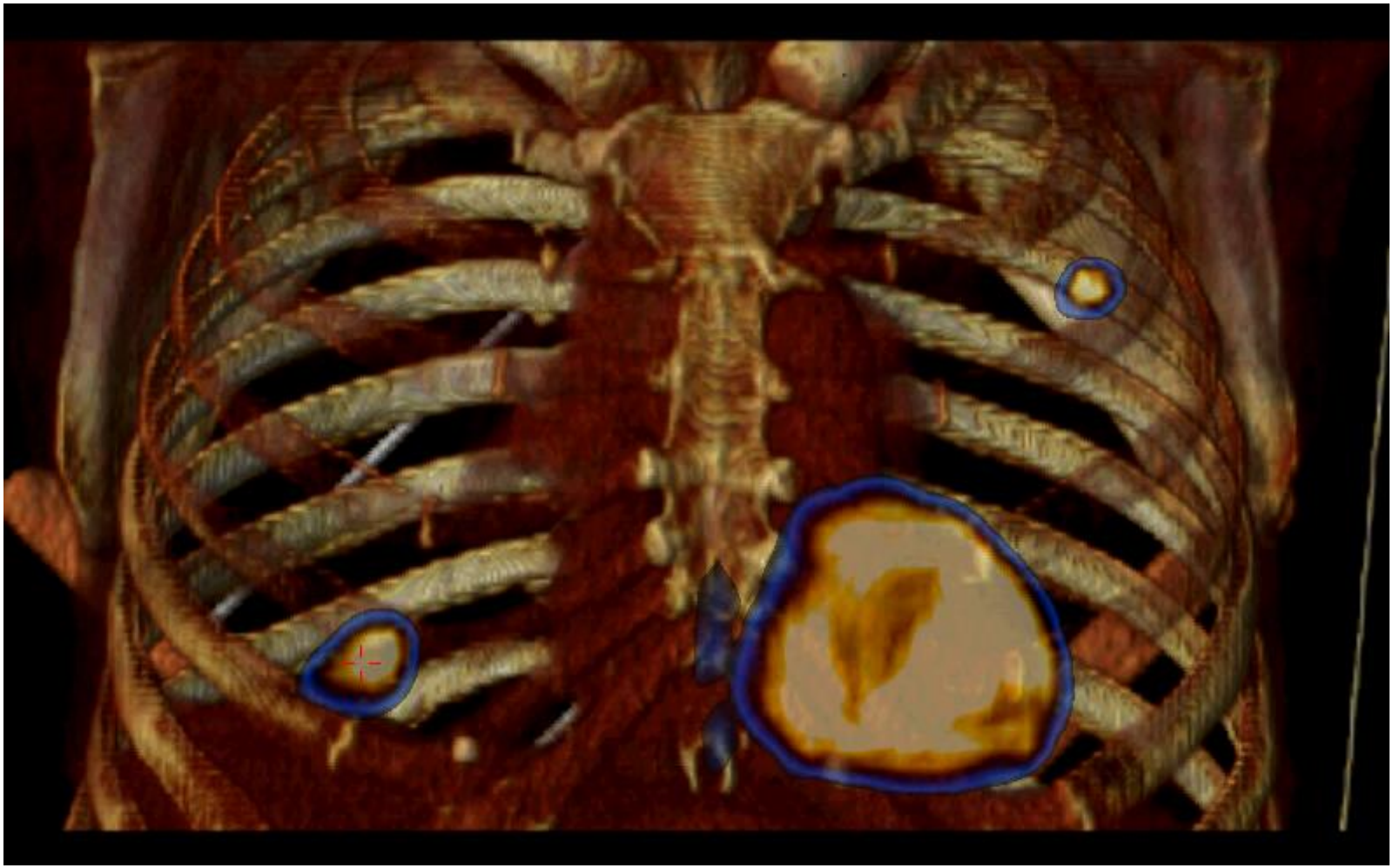
UNIVERSITÄTS KLINIKUM FREIBURG

Nestle et al. EJC 2015

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…

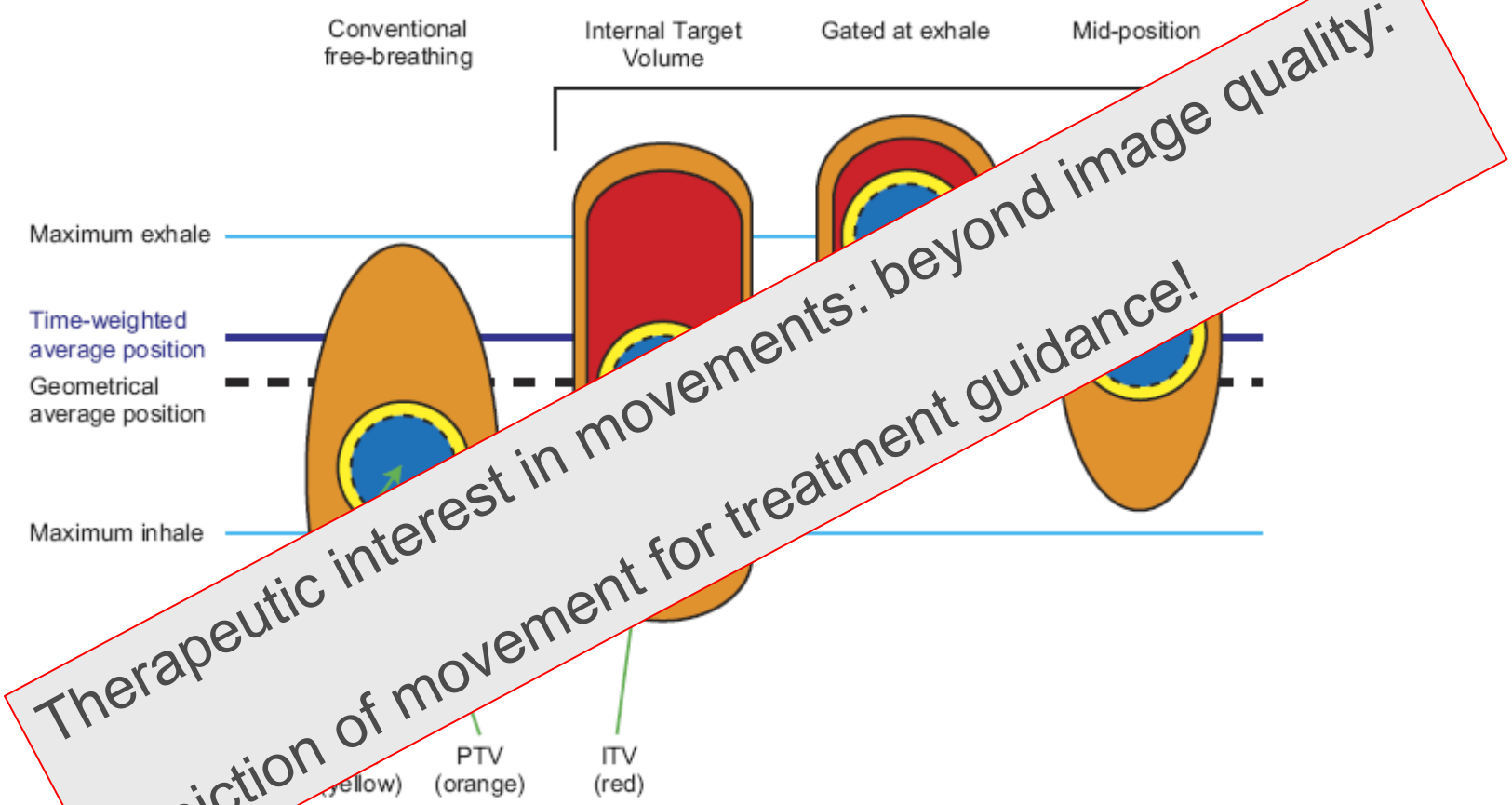


Kliniken Maria Hilf
Mönchengladbach

UNIVERSITÄTS KLINIKUM FREIBURG

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

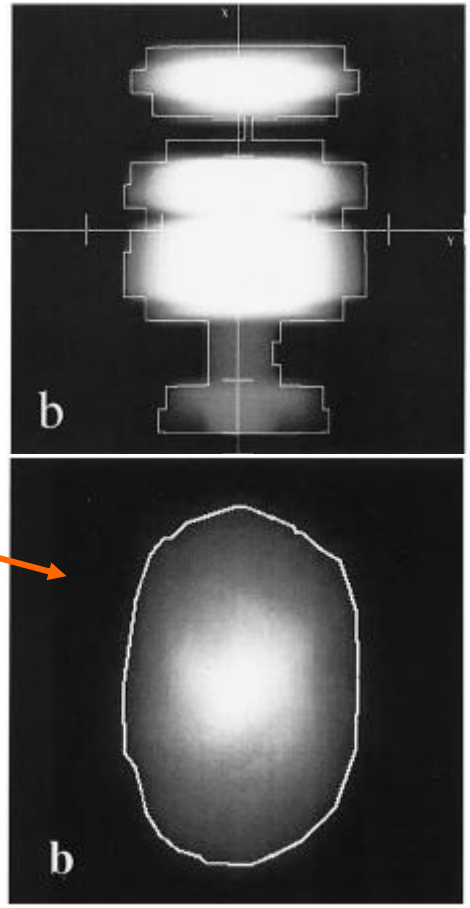
Wolthaus *et al.* (IJROBP 2008)

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

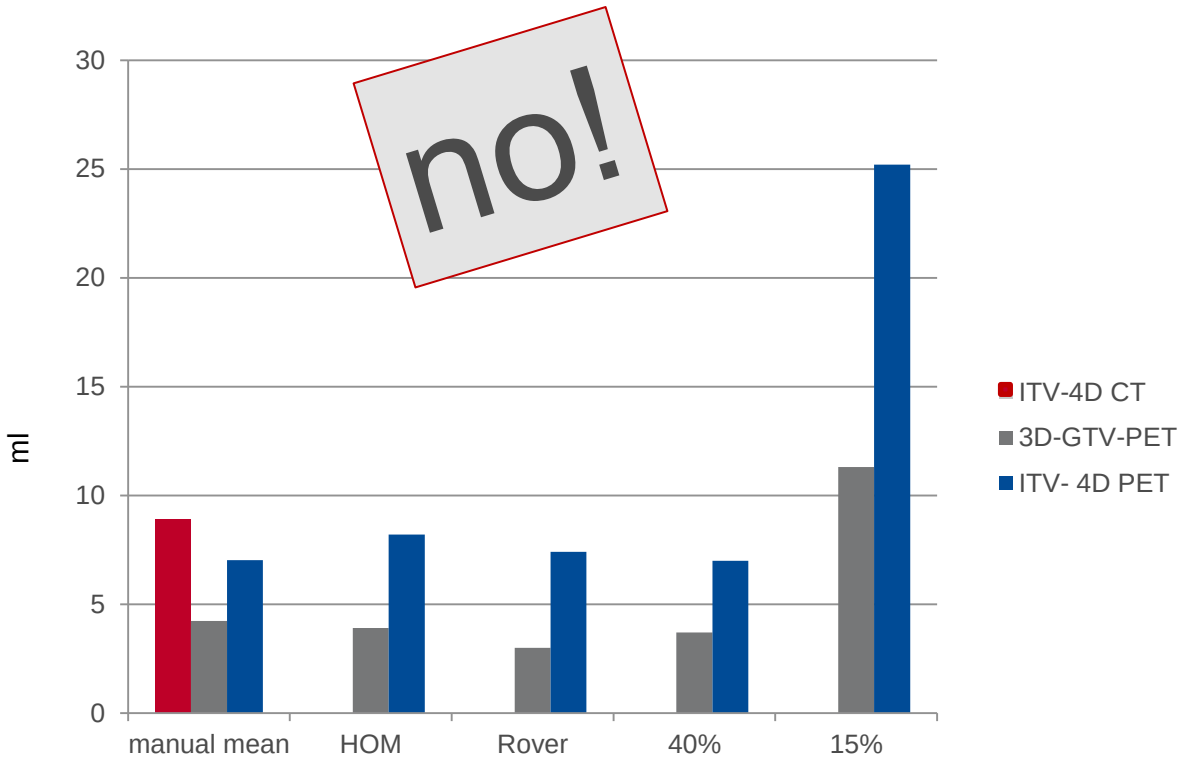
Can we derive an internal target volume from 3D PET?

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

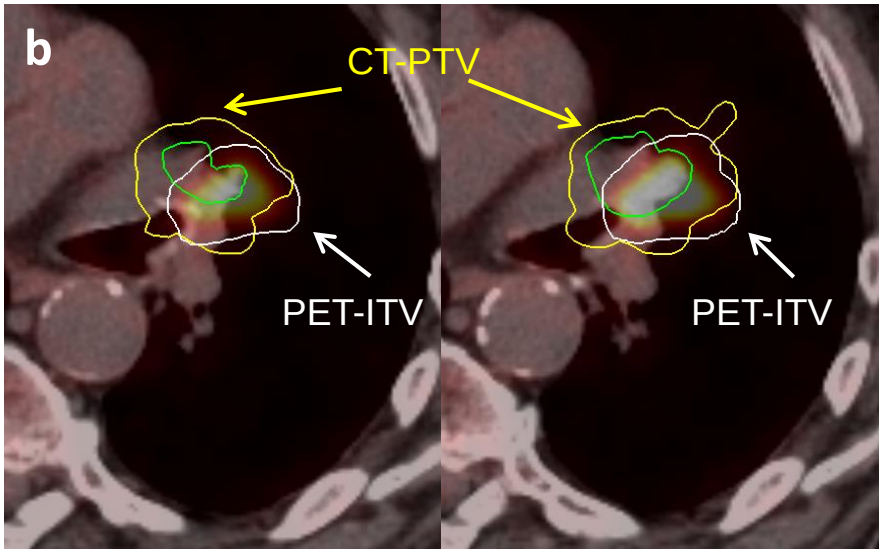


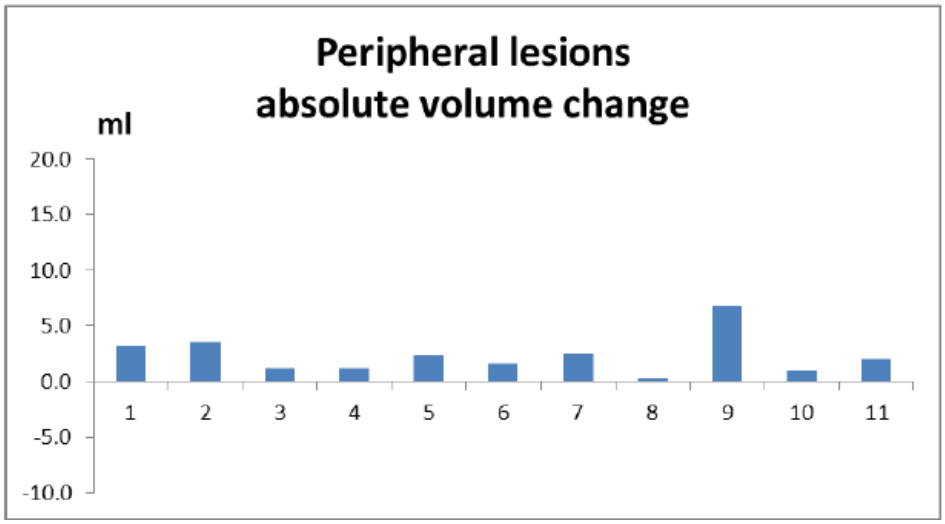
Impact of 4D PET-CT in SBRT-planning

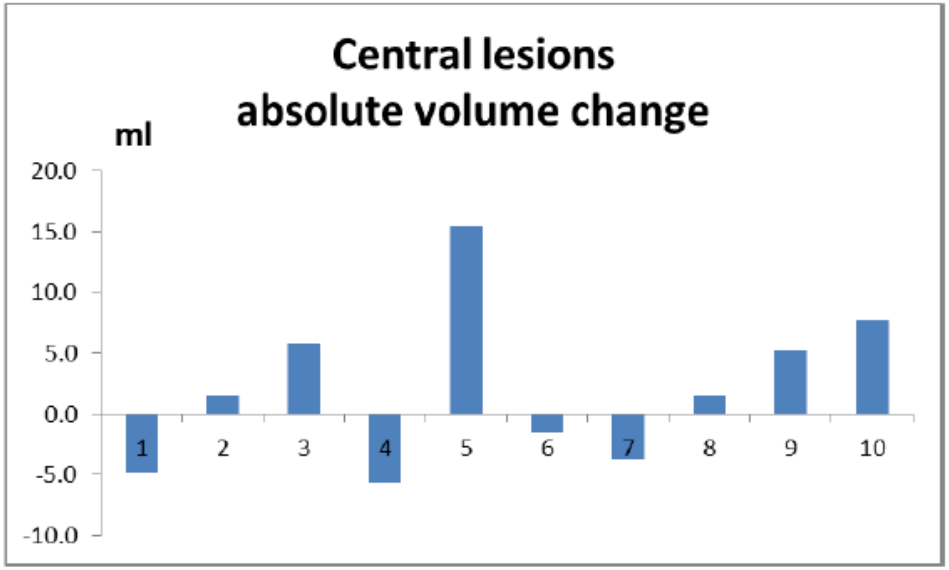
central (n = 10) vs. peripheral (n=11) NSCLC

contouring ITV, 4 observers:

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

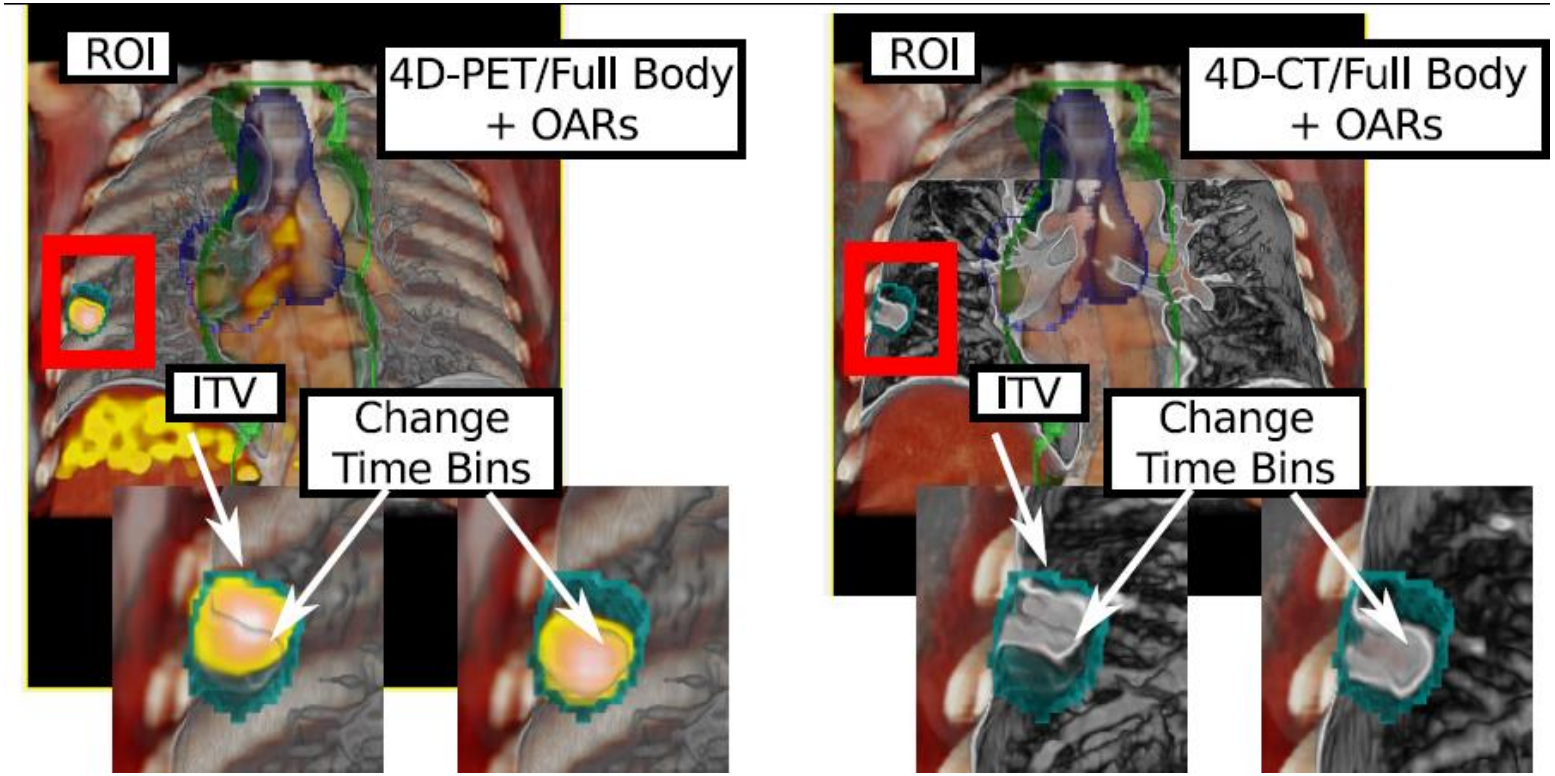


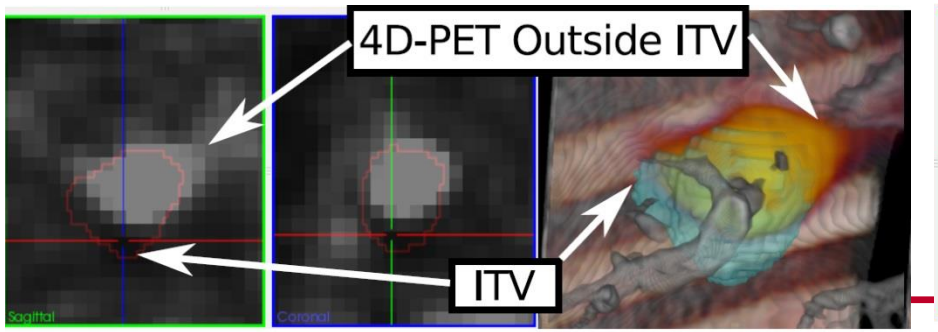


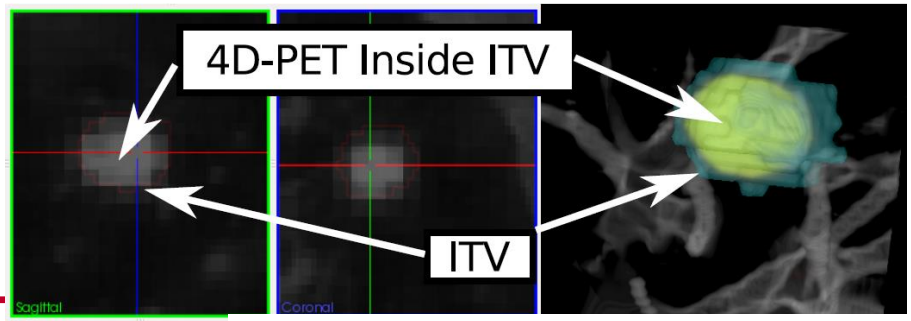


Chirindel et al. R&O 2015

4D PET/CT Delineation: needs automation…





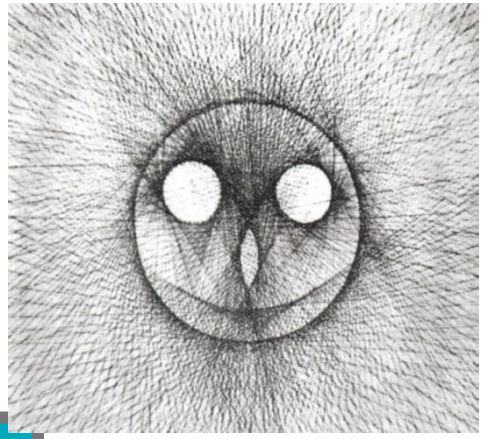


Schlachter, M., et al.IEEE TMI 2017

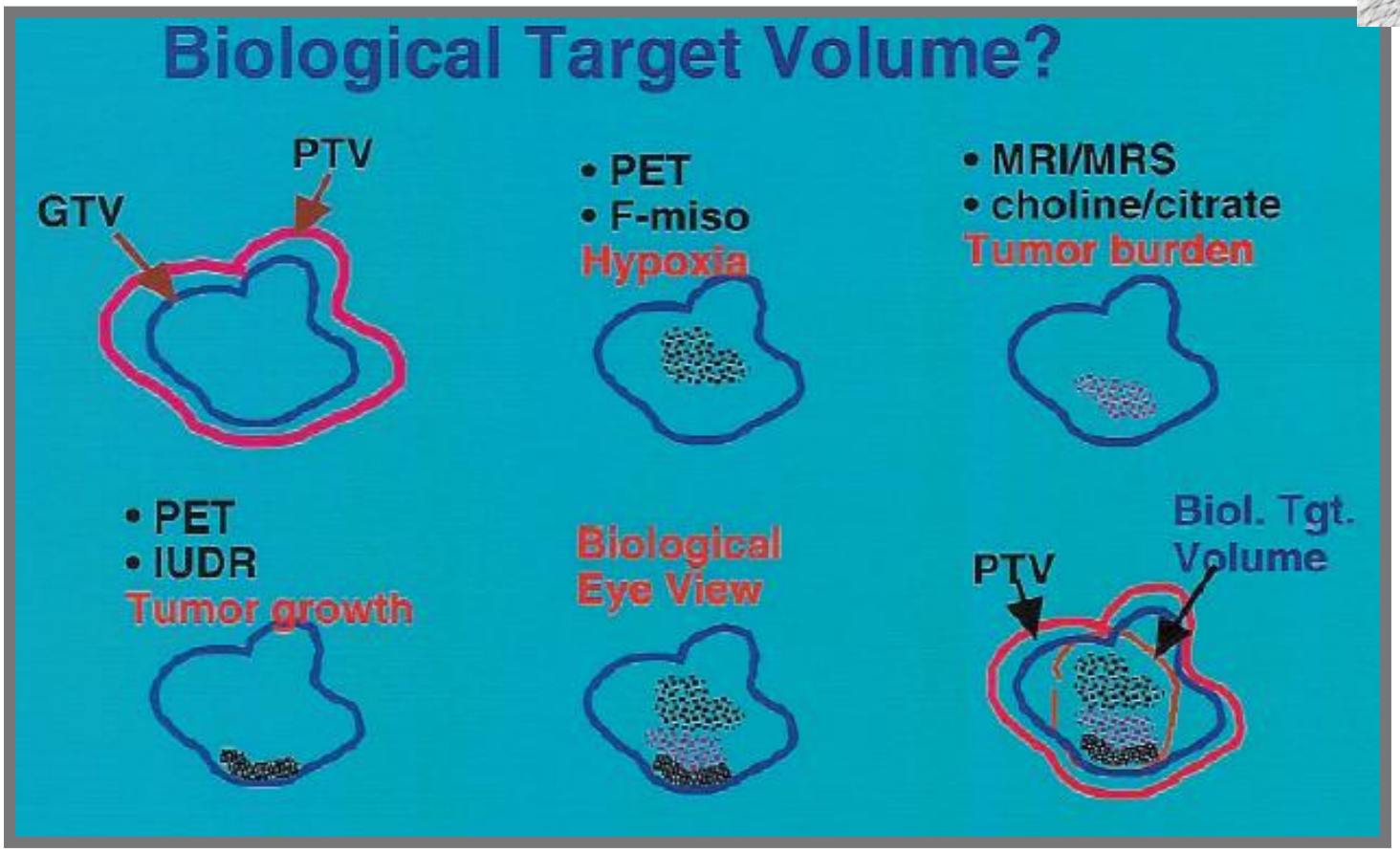
Applications of multimodal imaging in radiation therapy: outline

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

... dose painting



Birkhoff G 1940.

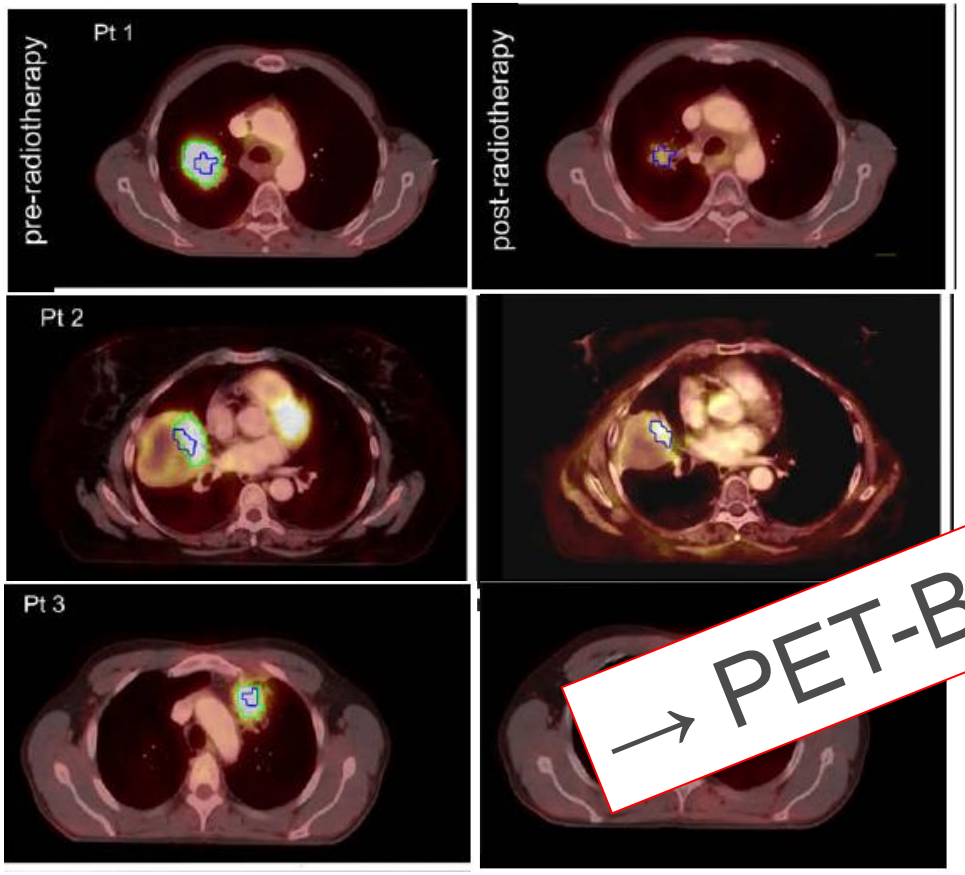


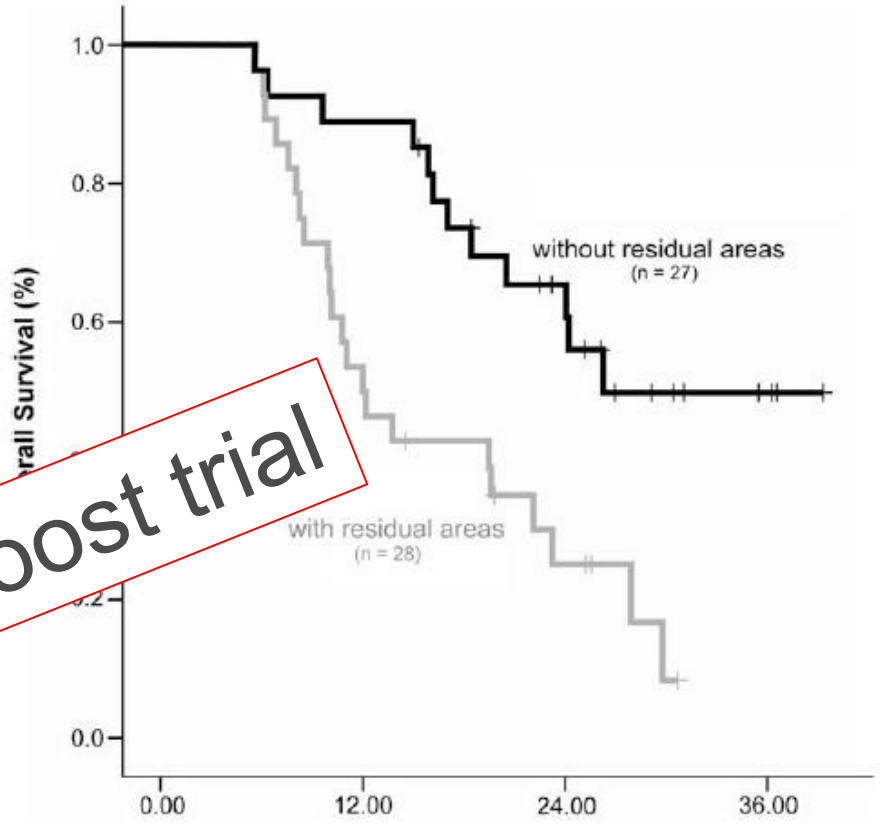
Ling 2000

MCQ 4 - What is your personal / institutional approach to dose painting?

A. A dream, hope to soon have it available…
B. We use it in clinical routine
C. we‘re involved in clinical trials
D. Sceptic, too many problems, will never work

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

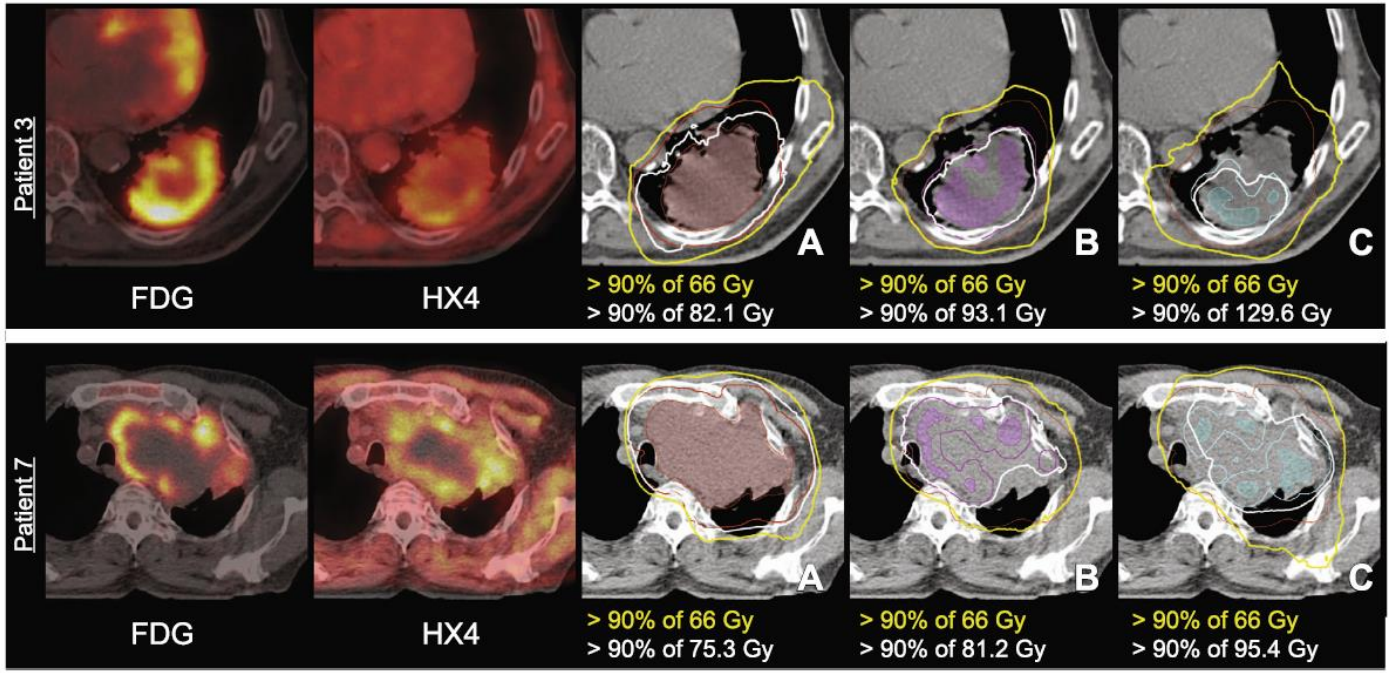
journal homepage: www.thegreenjournal.com

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*.

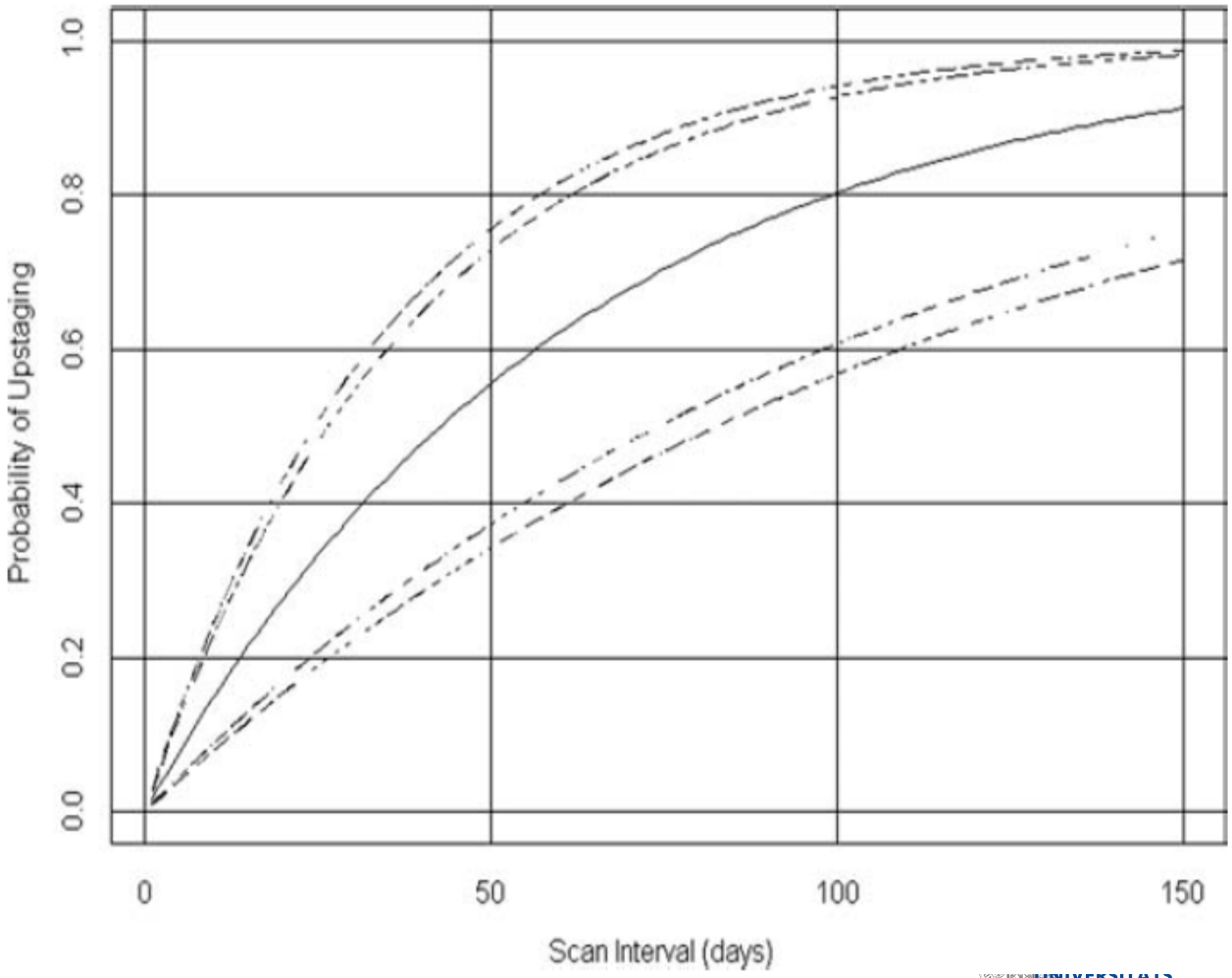
Imaging for RT-planning: soon before treatment!

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

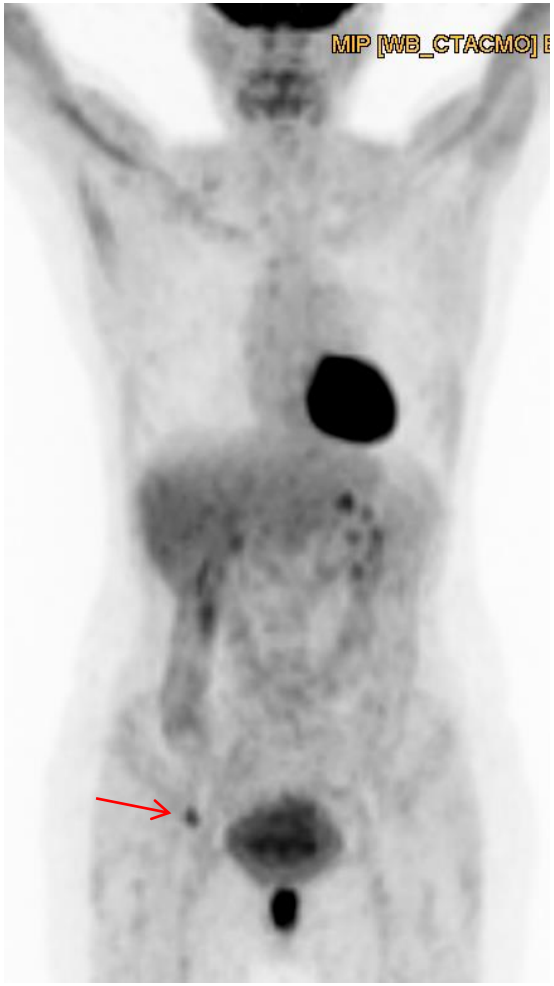
progression in 39%

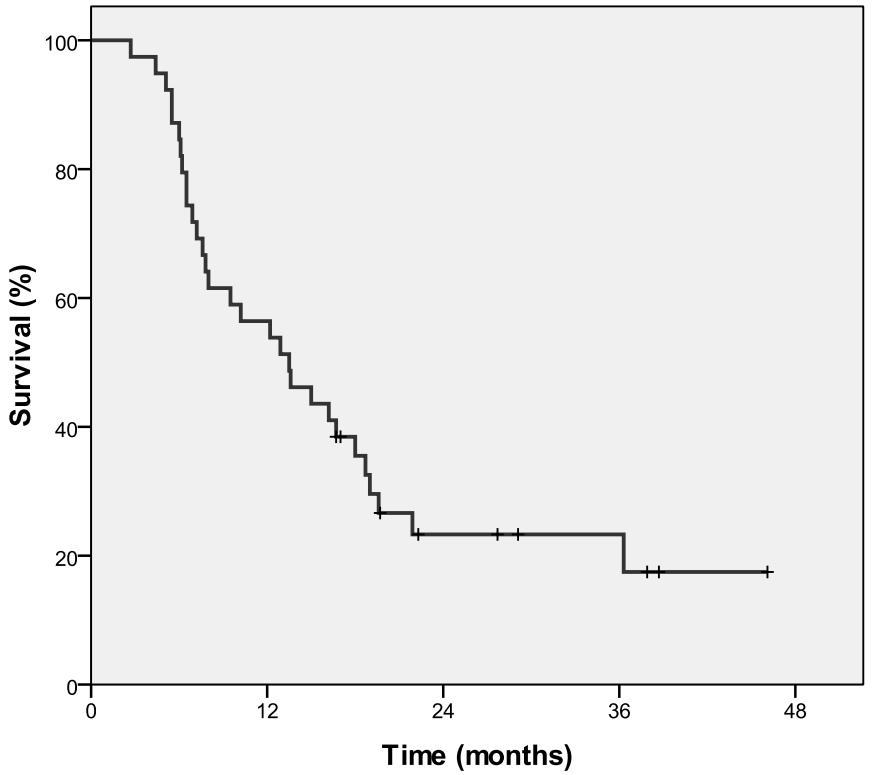
upstaging probability
within 24 days: **32%**

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

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

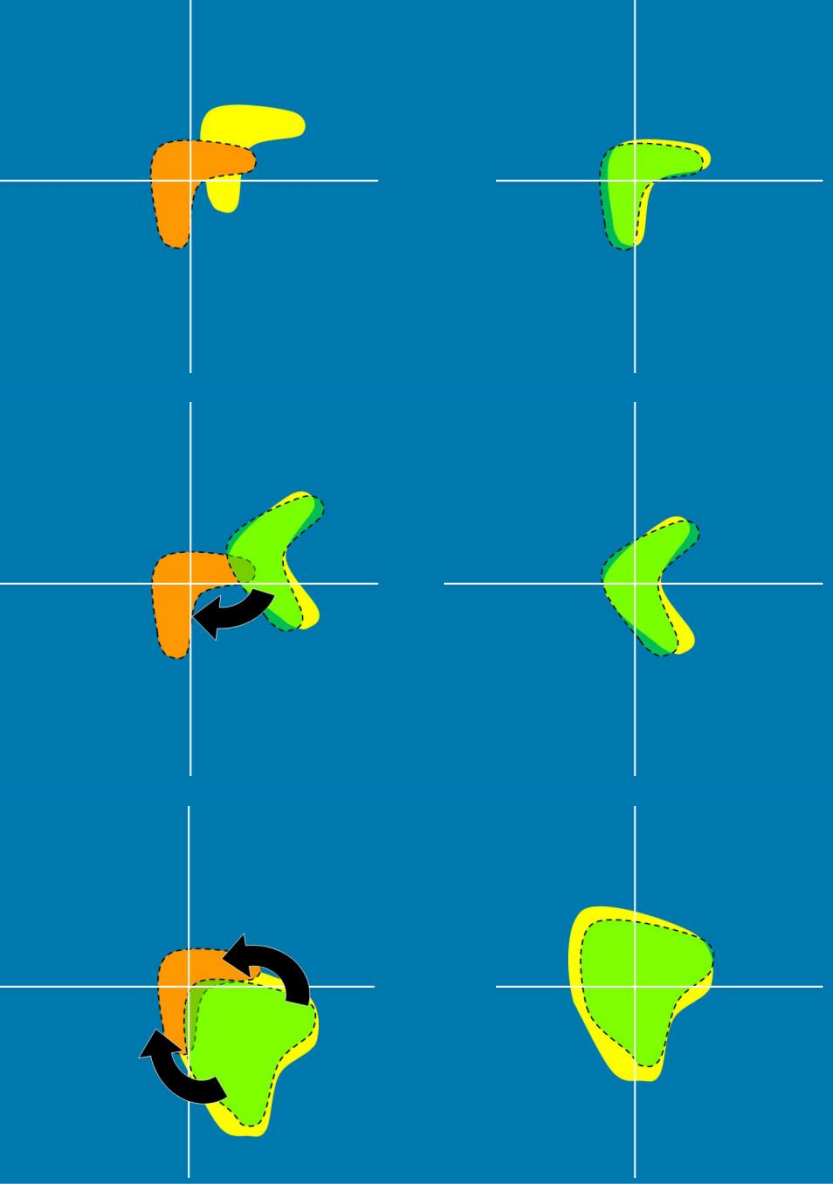
To seriously show patients benefit by the use of new imaging modalities in different clinical situations, clinical trials are mandatory

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

Library planning

Gert Meijer

ESTRO
European Society for Therapeutic Radiology and Oncology



adapting postion

ART

plan of the day

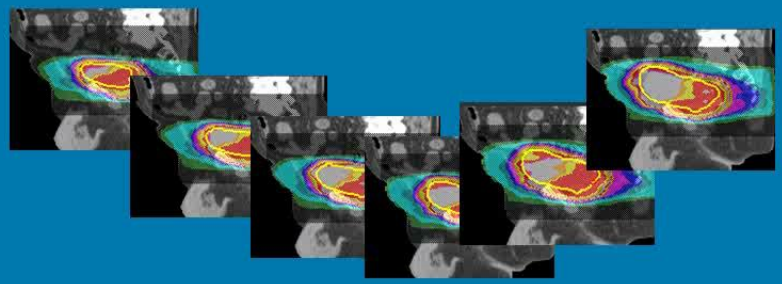
plan of the day

1

online (re)planning

2

library of plans

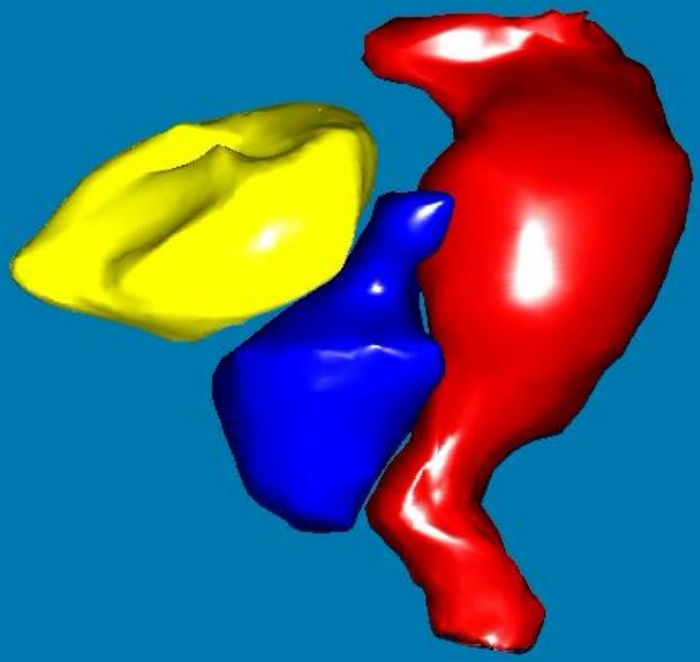


issues with library planning delivery

- how to prospectively generate a set of plans?
  - sampling prior to treatment
  - sampling during treatment
- target visualisation during treatment
- shift in responsibilities
  - who will select the plan of the day?

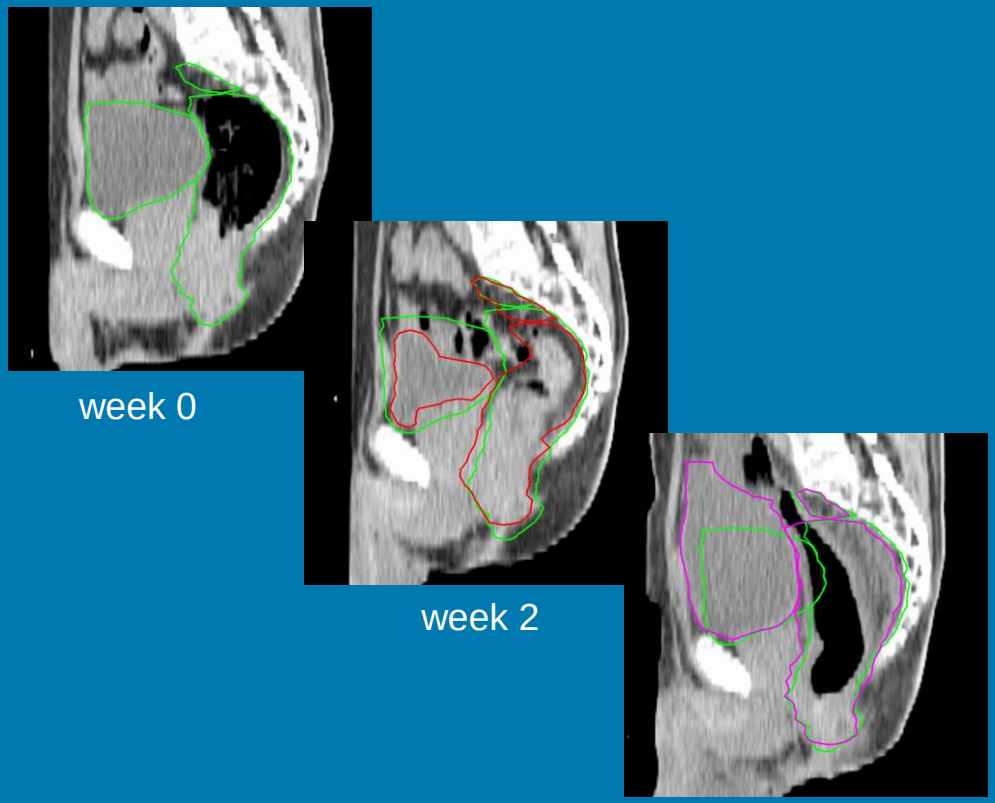
potential tumour sites for online adaptive strategies

- **prostate cancer**
- rectal cancer
- cervical cancer
- bladder cancer



potential tumour sites for online adaptive strategies

- prostate cancer
- **rectal cancer**
- cervical cancer
- bladder cancer

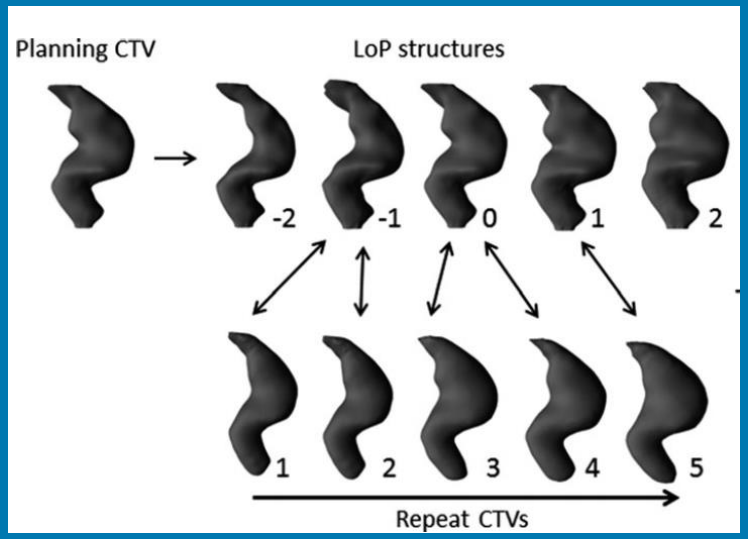


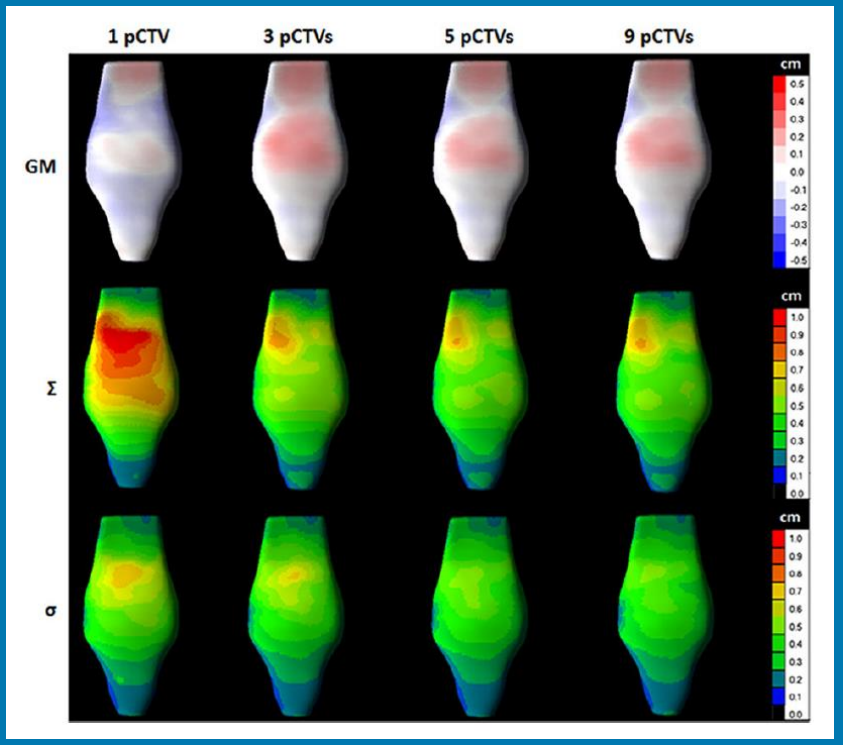
courtesy of Jasper Nijkamp, NKI

Rectal cancer

Library created based on population statistics

33 patients x 5CTs

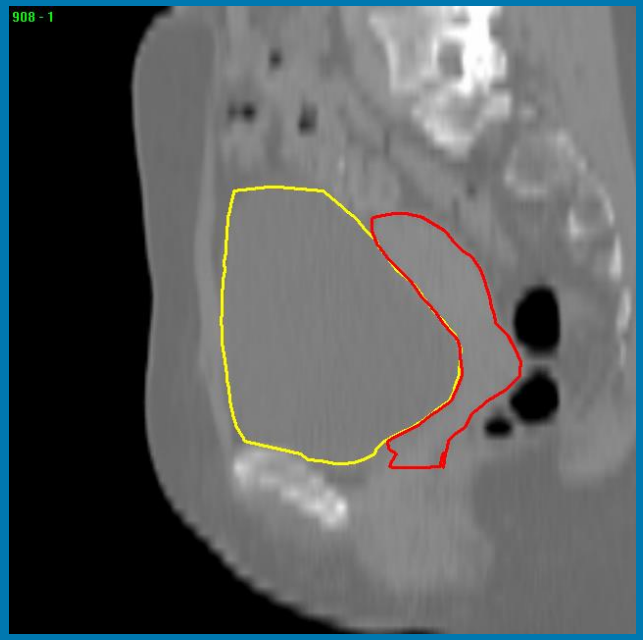




Beekman *et al. Med. Phys. 2018*

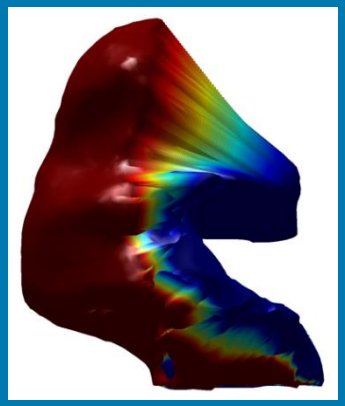
potential tumour sites for online adaptive strategies

- prostate cancer
- rectal cancer
- **cervical cancer**
- bladder cancer

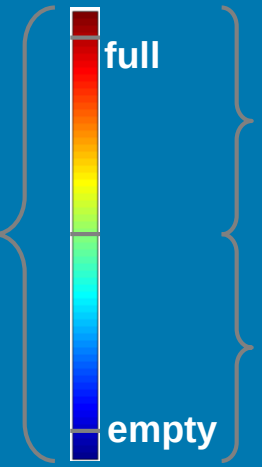


cervical cancer

bladder volume as a surrogate for uterus geometry

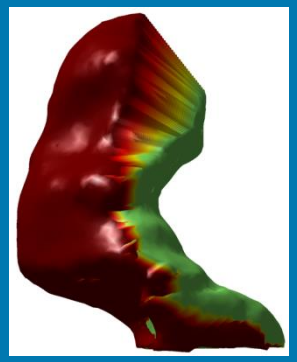


ITV

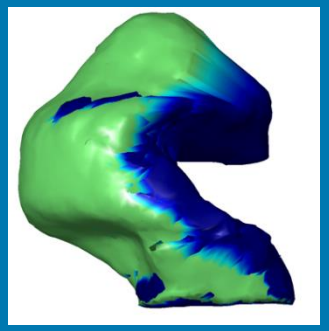


ITV1

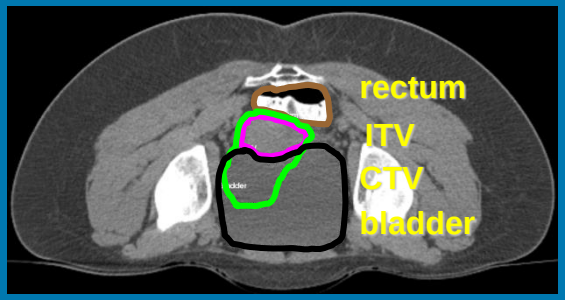
ITV2

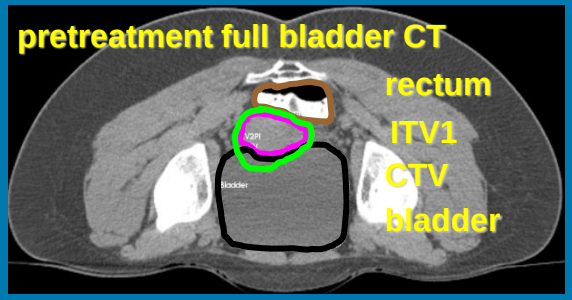


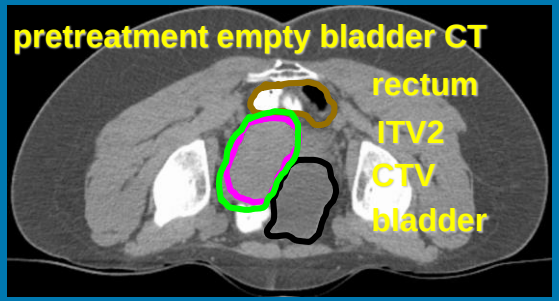
ITV1- large bladders



ITV2- small bladders







Luiza Bondar *et al*, Rotterdam

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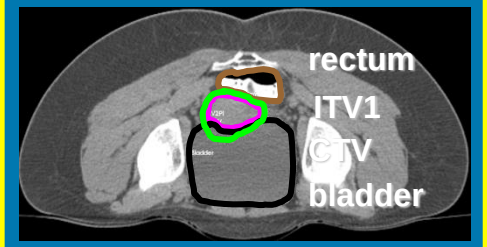
bladder volume used for plan of the day selection

full

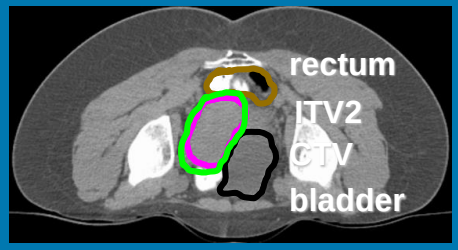
empty

ITV1

ITV2

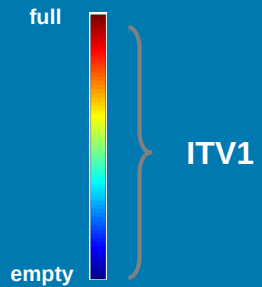


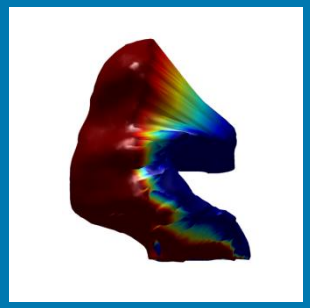
ITV1 - large bladders

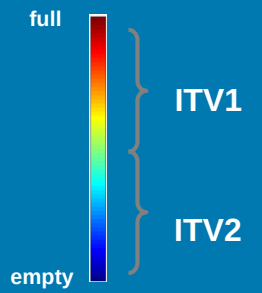


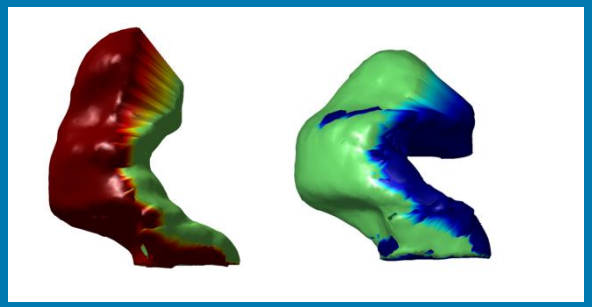
ITV2 - small bladders

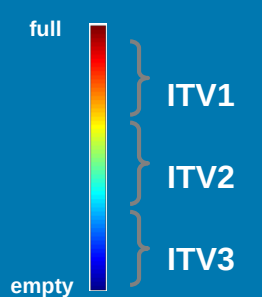
with courtesy of Luiza Bondar Erasmus MC

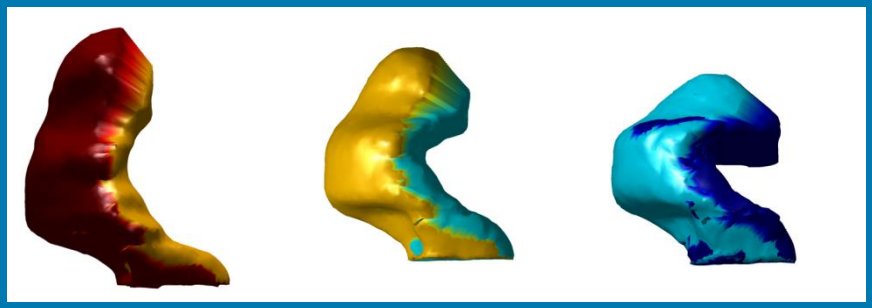












with courtesy of Luiza Bondar Erasmus MC

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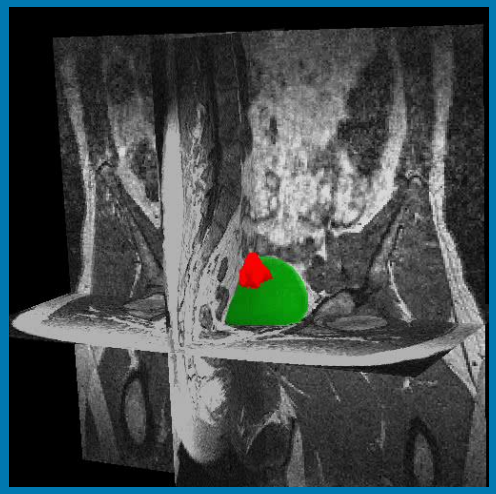
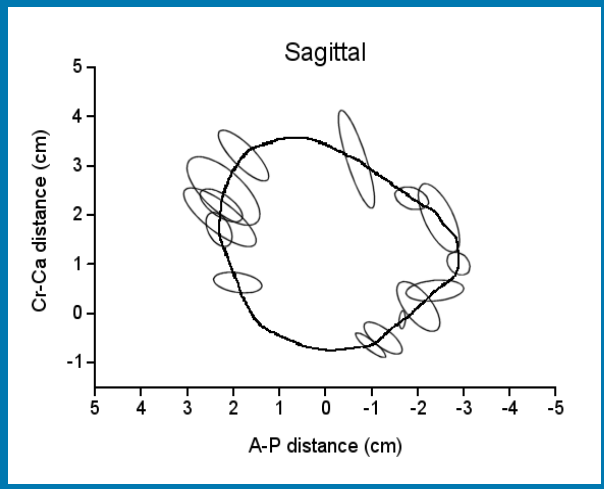
potential tumour sites for online adaptive strategies

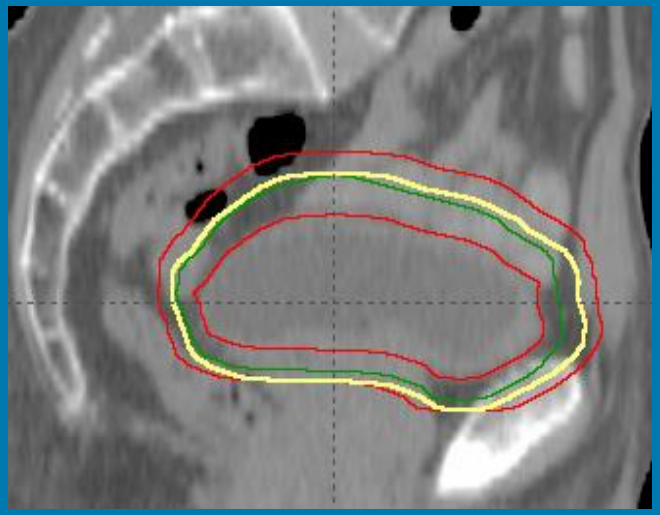
- prostate cancer
- rectal cancer
- cervical cancer
- **bladder cancer**





Lotz *et al.* IJROBP 2003

bladder cancer



library based on different margins

library generation

# CT scans	#CBCT scans	groups
1	**0**	**Vestergaard, Aarhus** **Burridge, Christy Hospital**
1	multiple	Vestergaard & Wright, Aarhus
multiple	0	Lalondrelle, Royal Marsden Meijer, Catharina

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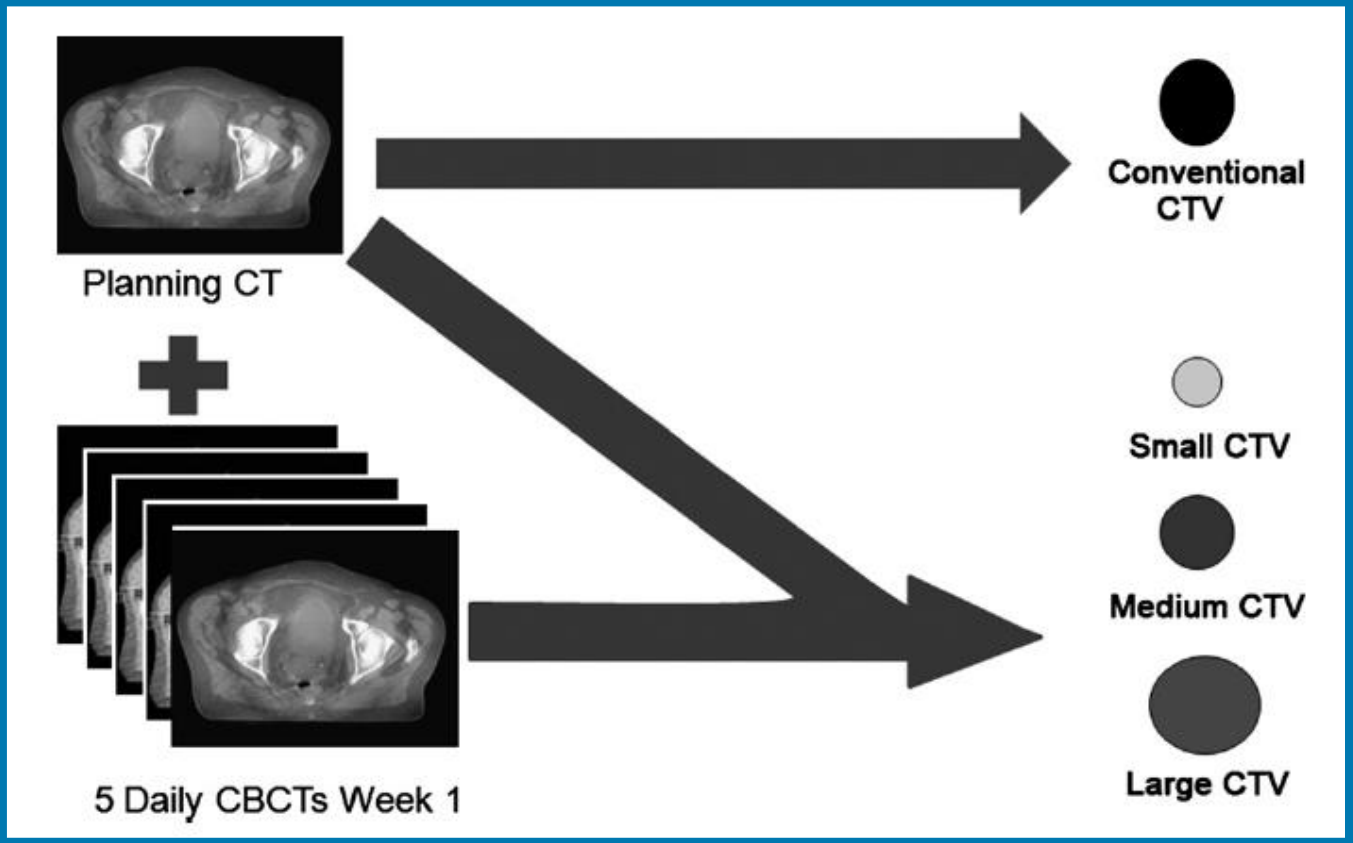


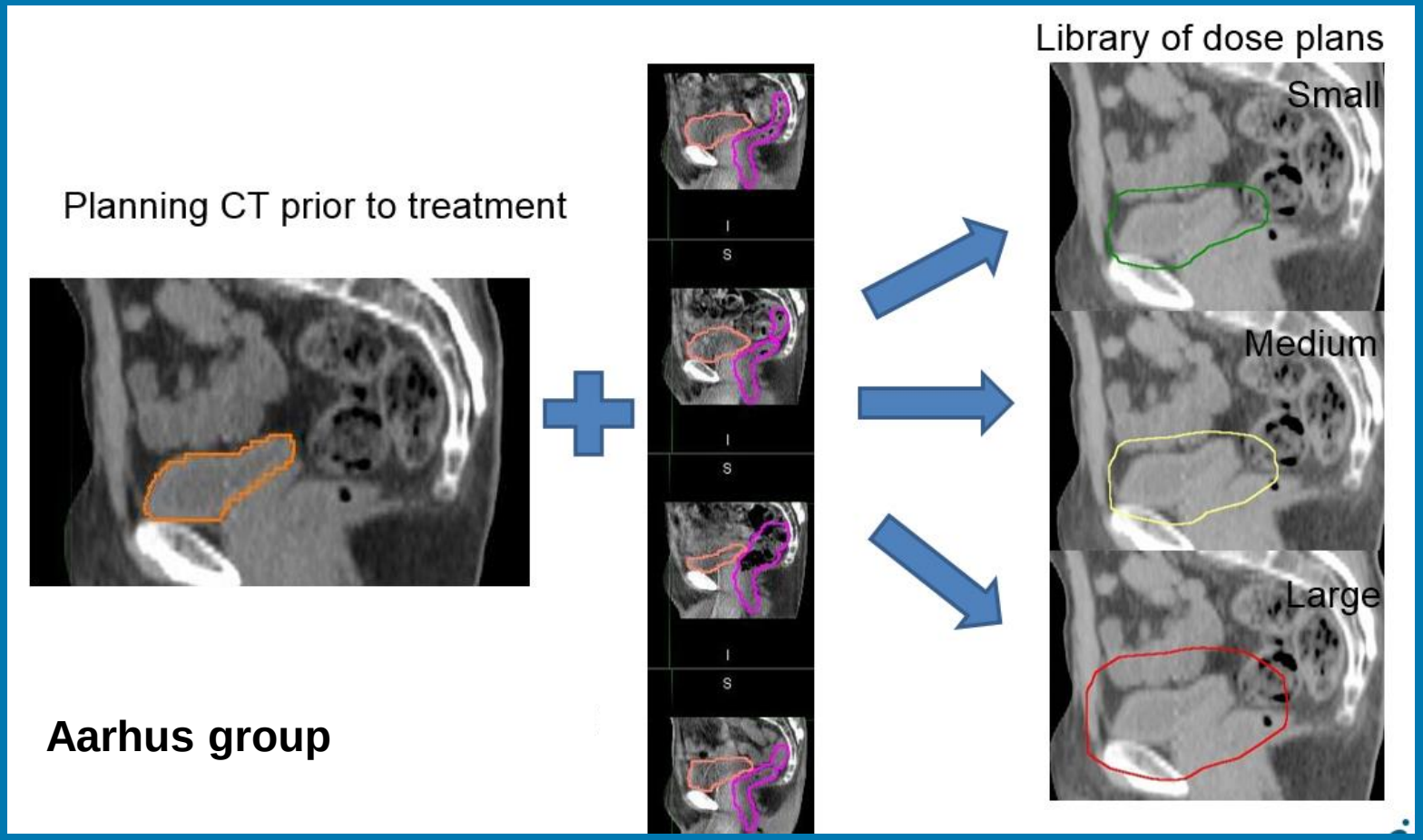
+ 1.5 cm margin

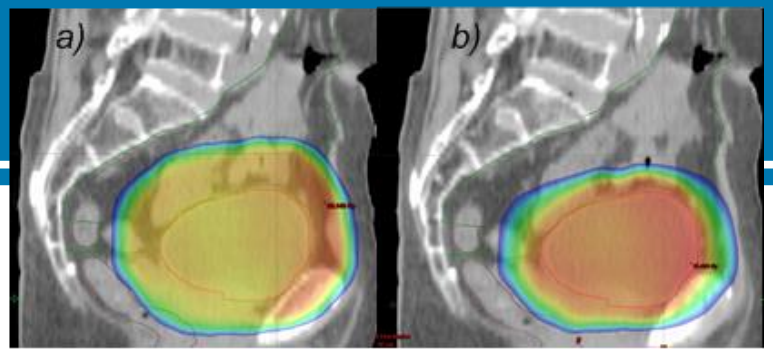
+ 0.5 cm margin

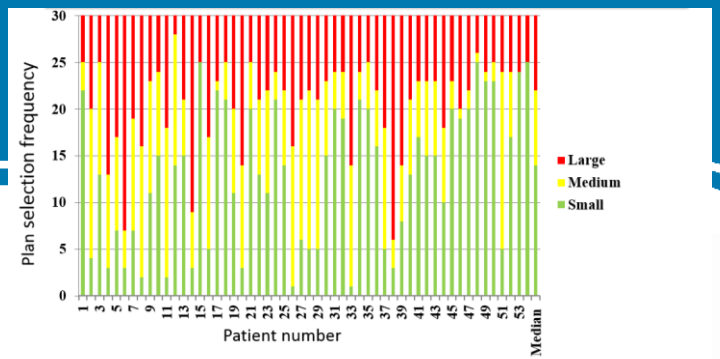
manual

summation

Foroudi *et al.* (IJROBP 2010)

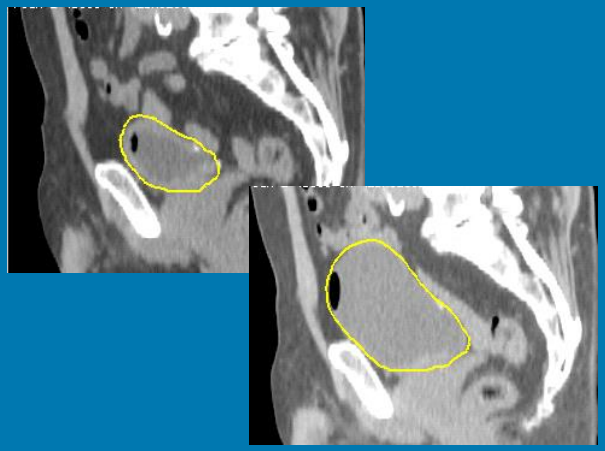






olume ratio of course averaged PTV: PTV_{ART} /PTV_{nonART} Median 0.68[0.43;0.93]

bladder cancer



prospectively generating target volumes

library generation

# CT scans	#CBCT scans	groups
1	0	Vestergaard, Aarhus Burridge, Christy Hospital
1	multiple	Vestergaard & Wright, Aarhus
multiple	**0**	**Lalondrelle, Royal Marsden** **Meijer, Catharina**

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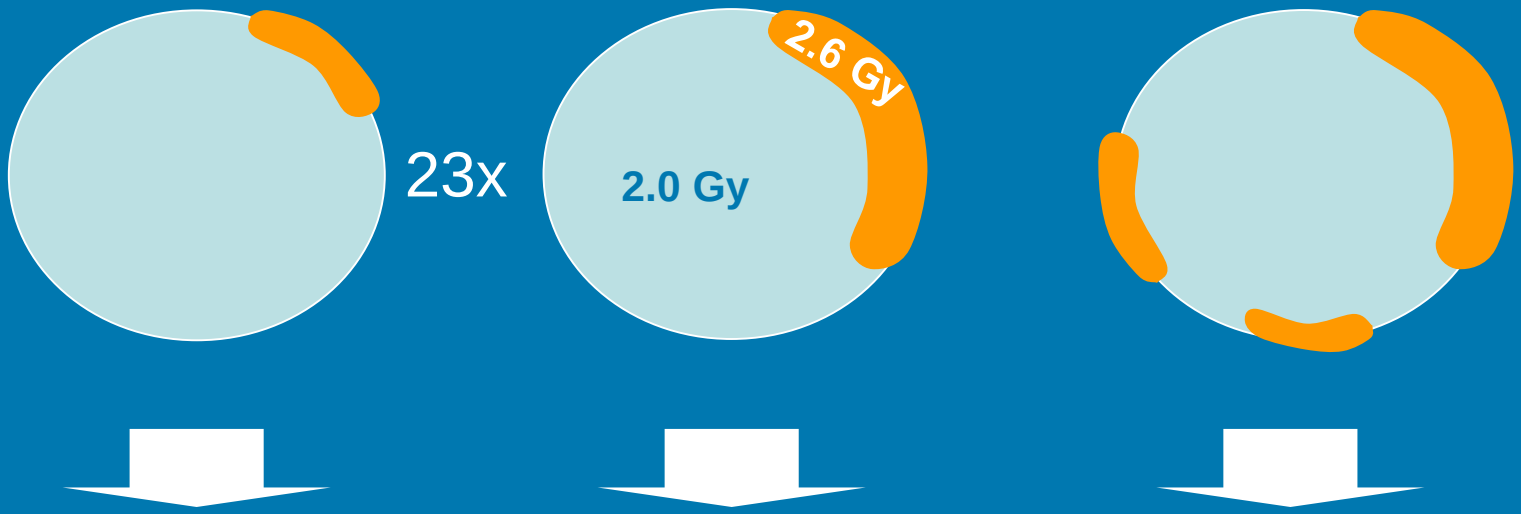
Bladder RT at Catharina Hospital

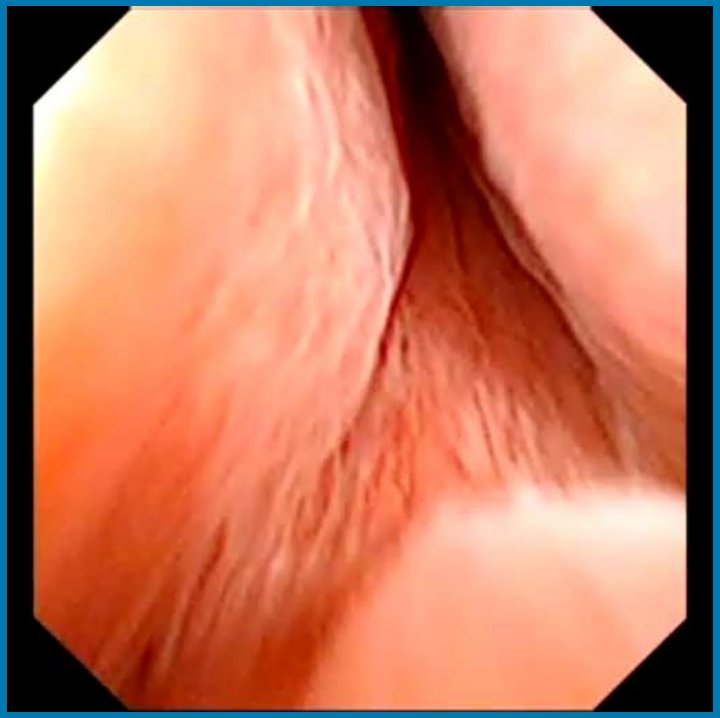


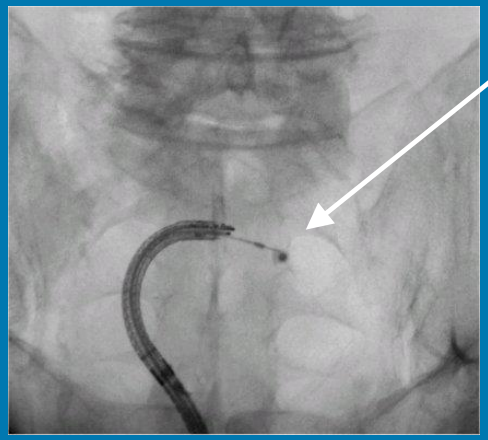
brachytherapy

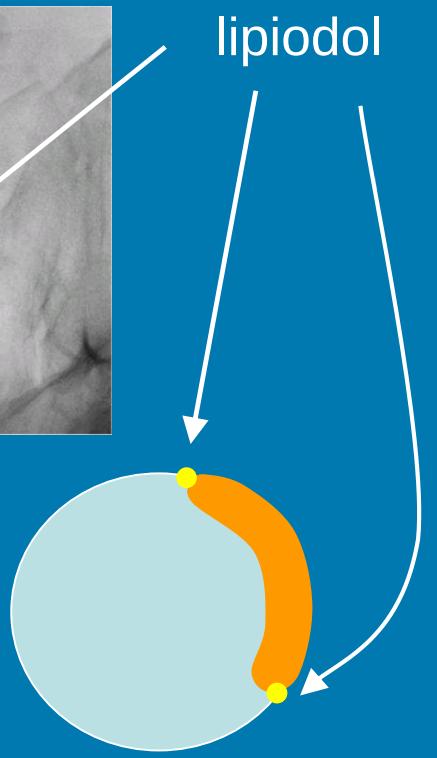
IGART
concomitant boost

EBT whole bladder

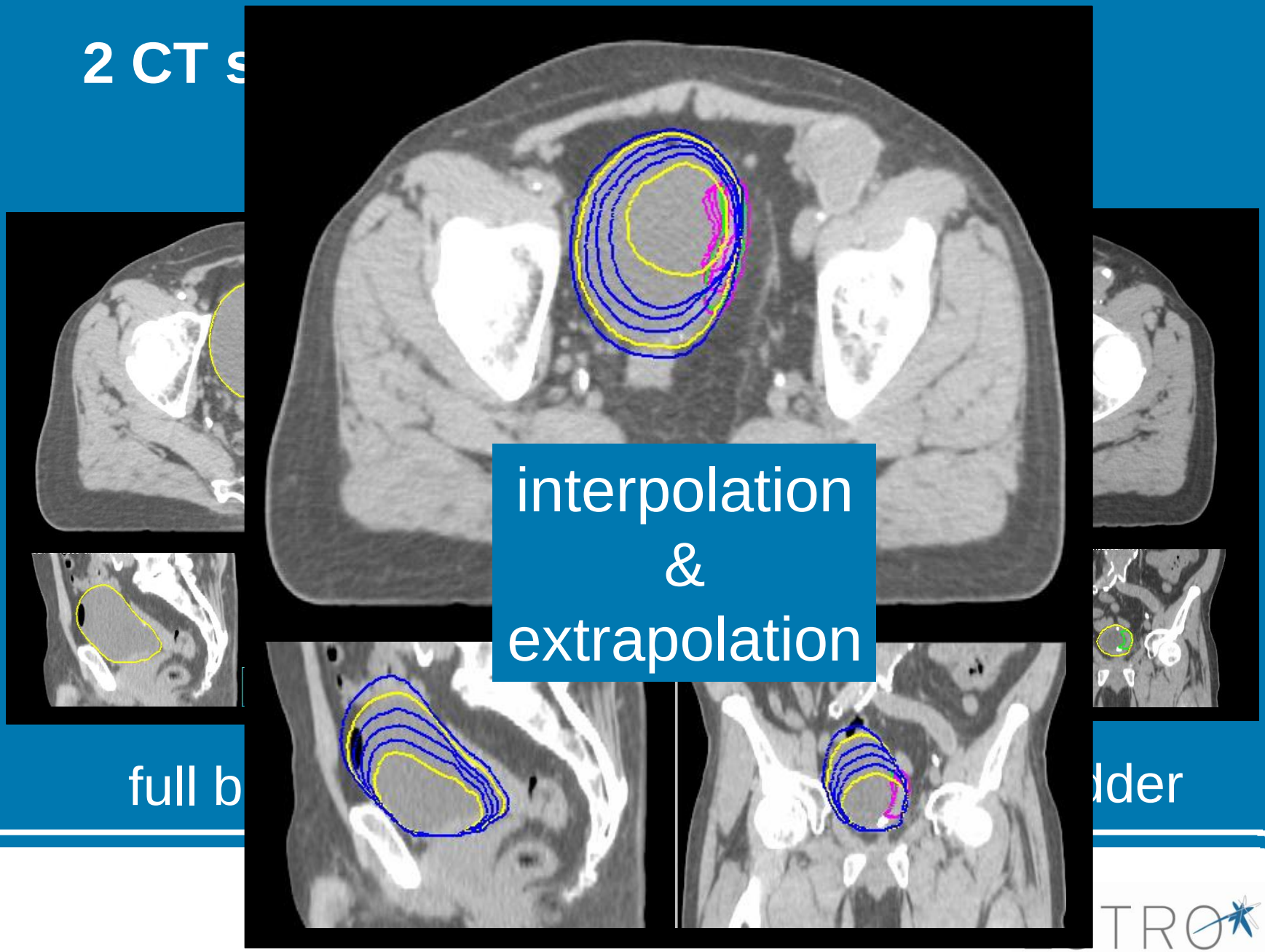
Endoscopic lipiodol demarcation of the GTV







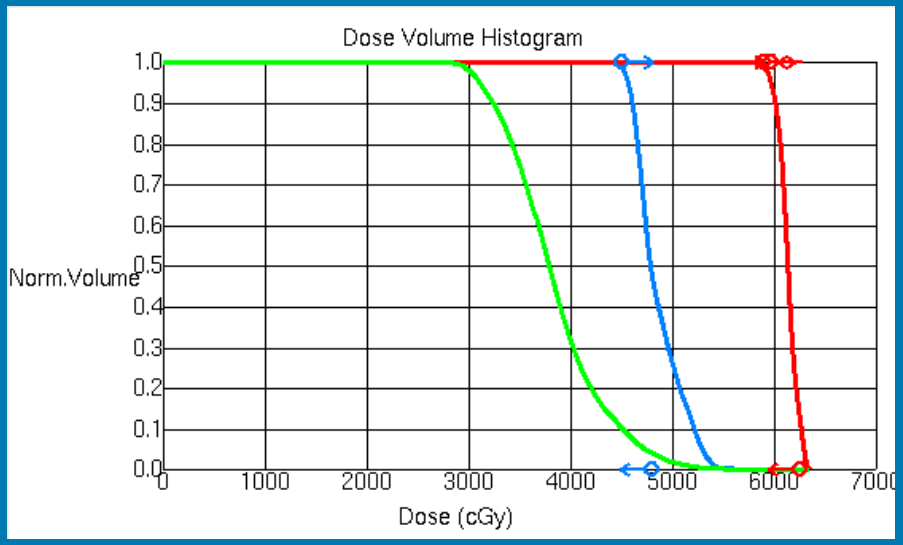
2 CT s



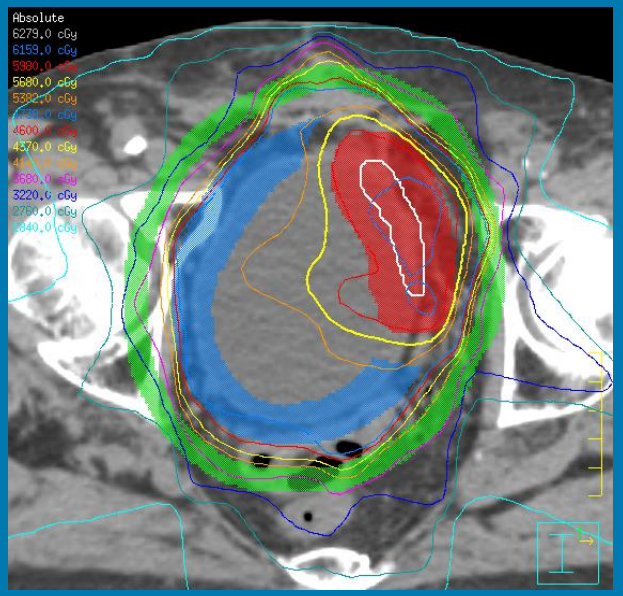
full b

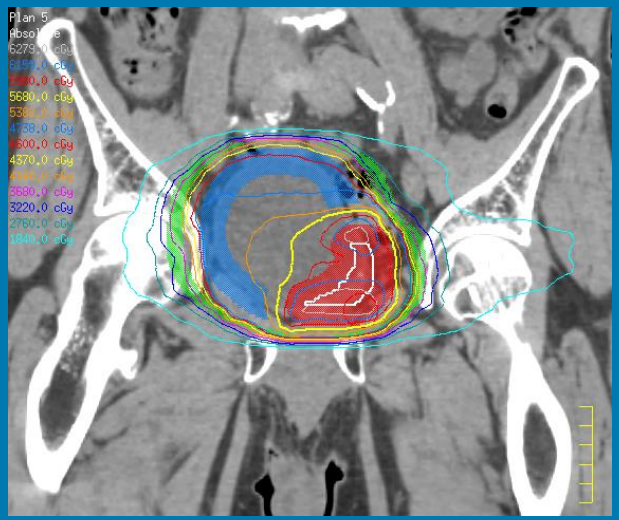
dder

automated planning



PTV GTV	min dose 100	59.0 Gy	
PTV GTV	max dose	62.5 Gy	30
PTV GTV	uni dose	59.8 Gy	1
PTV Bladder*	min dose 100	45.0 Gy	
Ring	Min EUD (a=5)	59Gy	1





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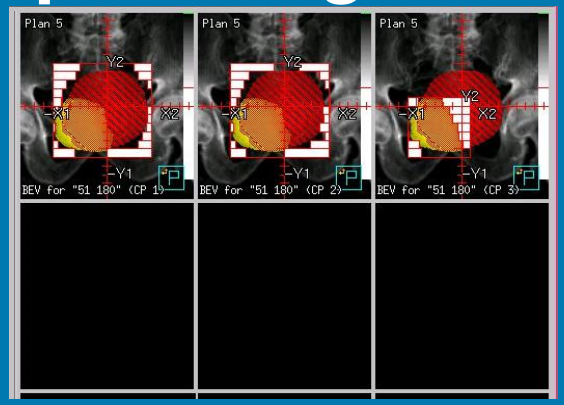
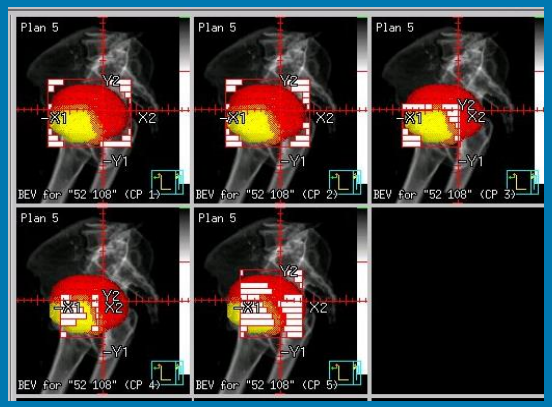
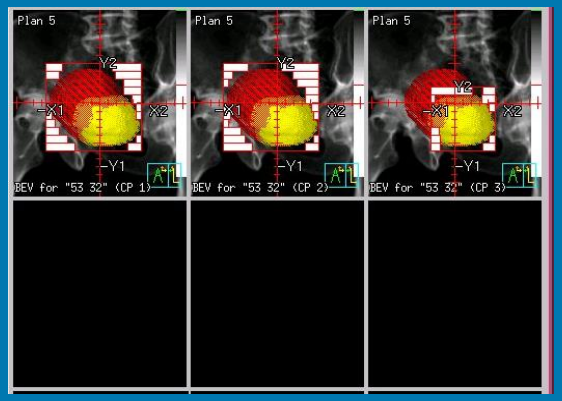
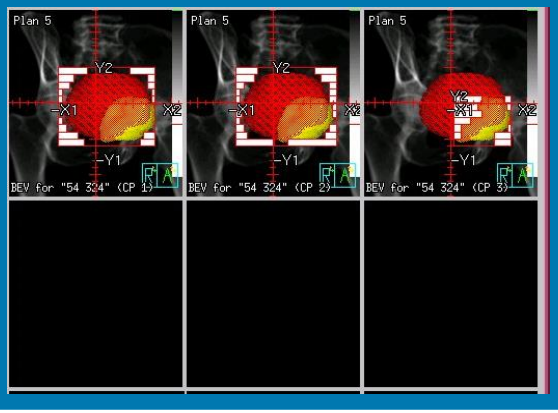
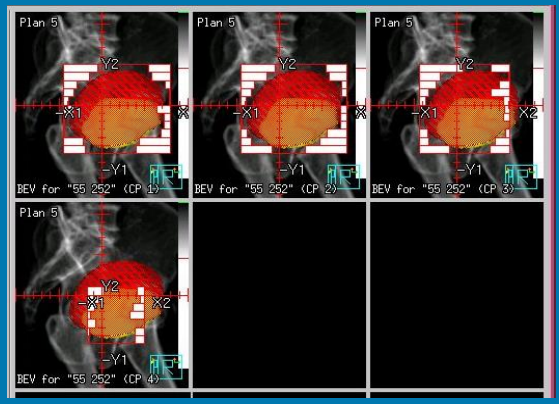
automated planning











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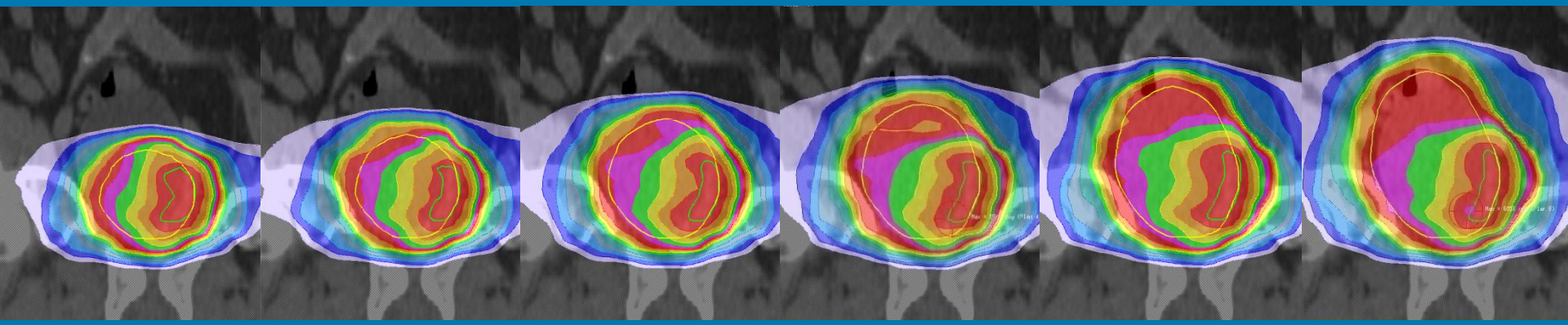
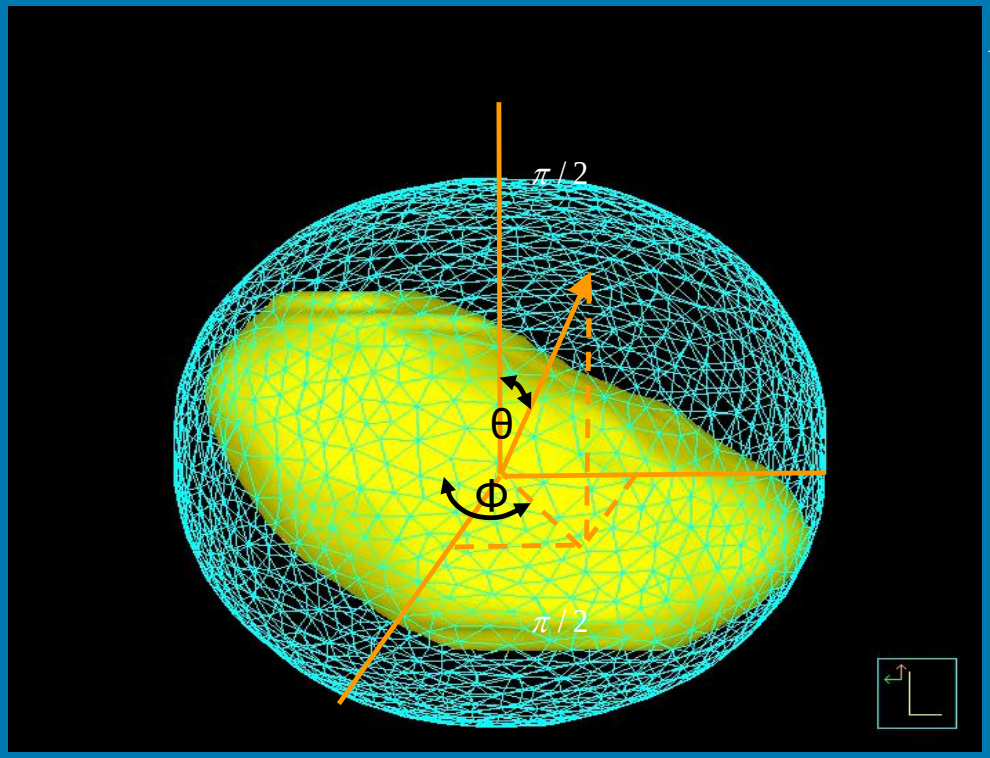
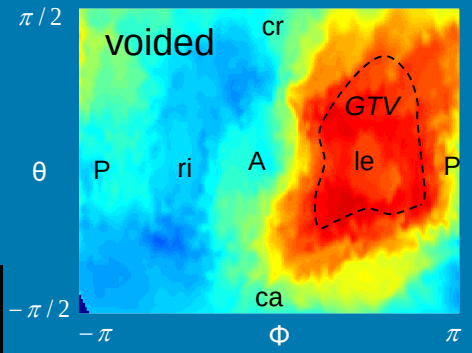
multiple ‘simple’ IMRT plans

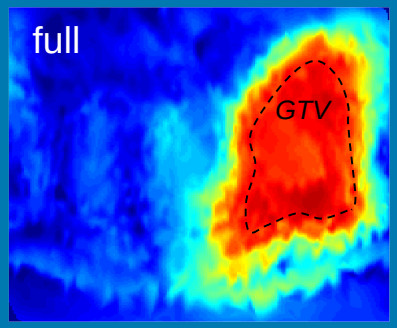


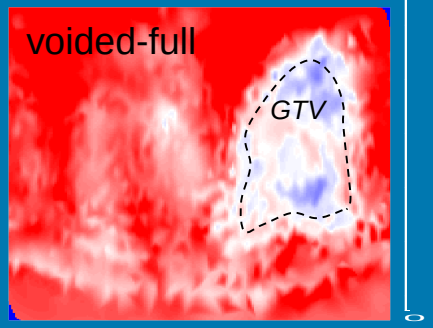
coronal views

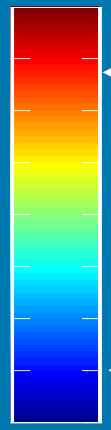
dose wall maps of voided and full bladder plans











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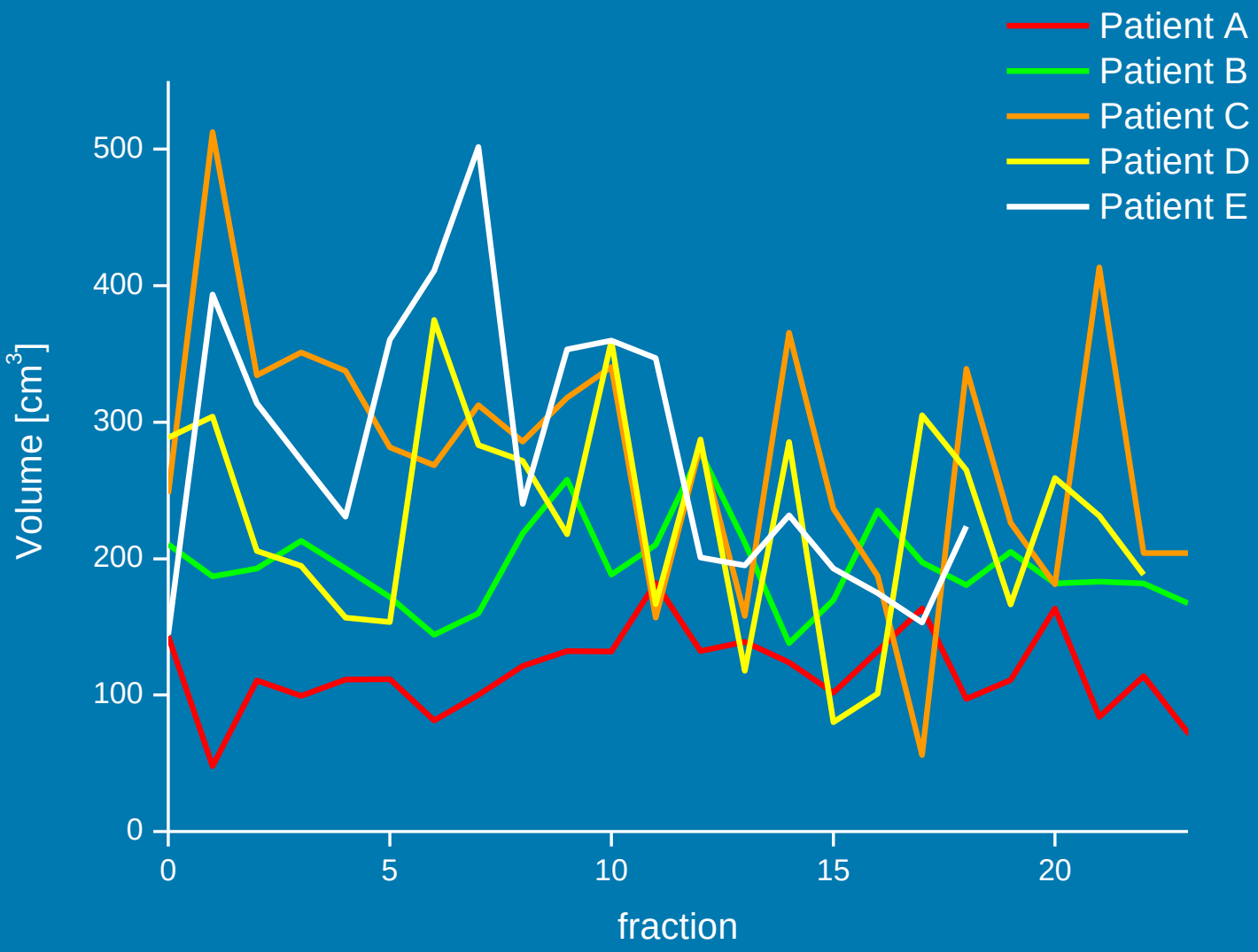
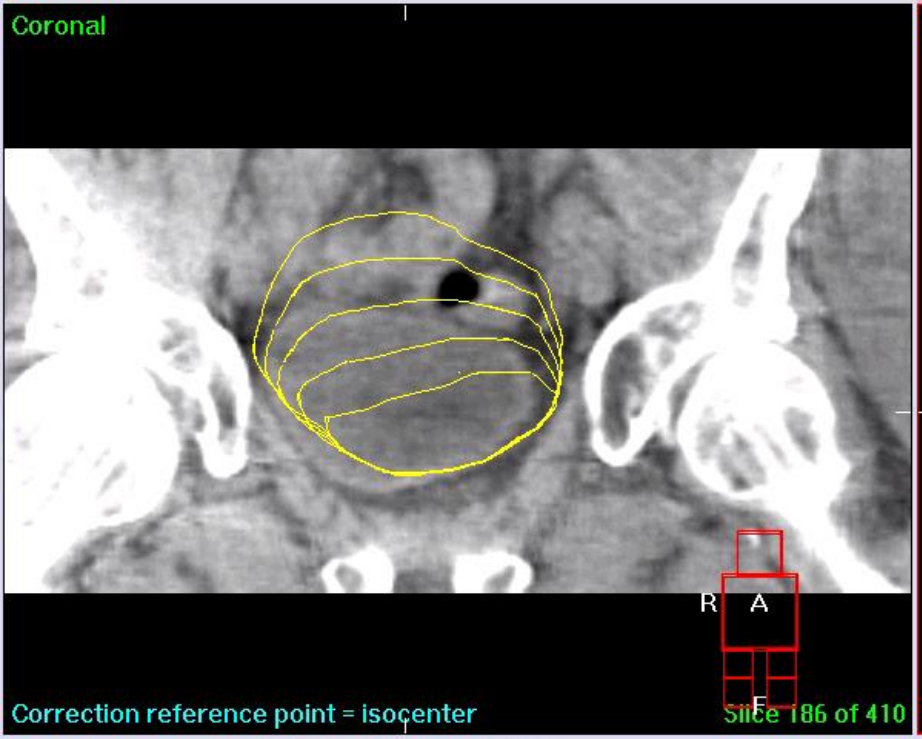
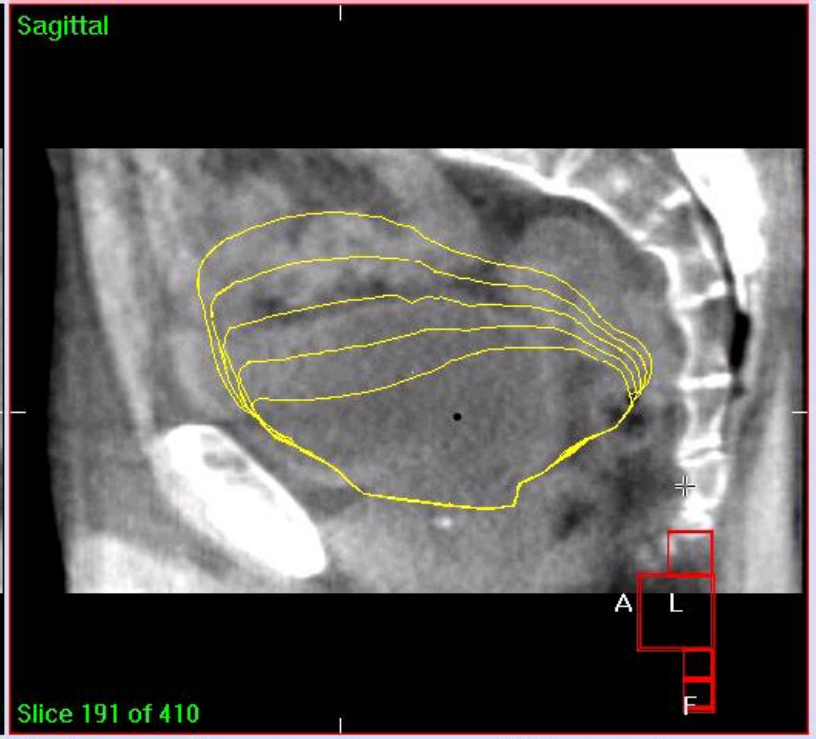






Image

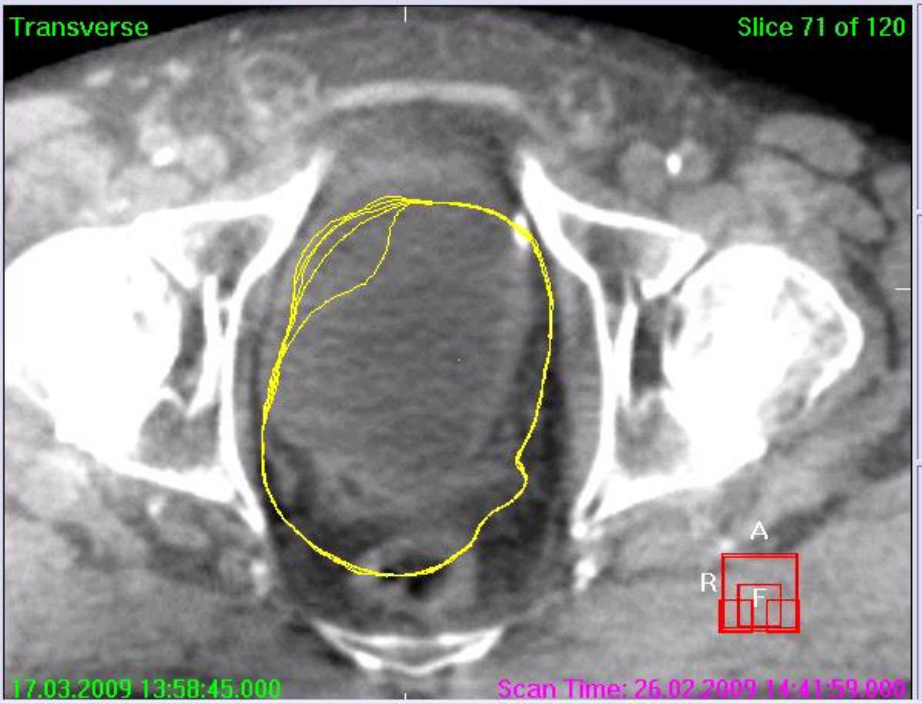
Slice Averaging

none

Display Mode

Localization on

GoTo ..



Reference Preset

Cor Ref Point ..

Scan

Alignment Clipbox

Structures ..

Alignment

Automatic

Bone

Reset

Convert To Correction

Position Error

Translation (cm)

X	0.00
Y	0.00
Z	0.00

Rotation (dg)

X	0.0
Y	0.0
Z	0.0

Table Correction

(cm)

Lateral -

Longitudinal -

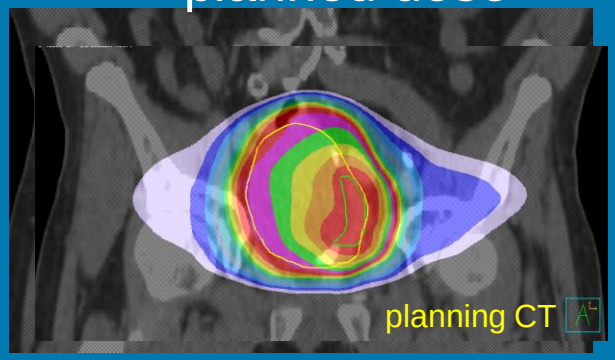
Vertical -

Dismiss

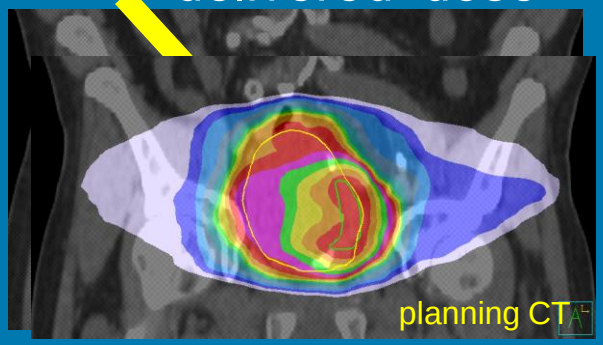
Accept

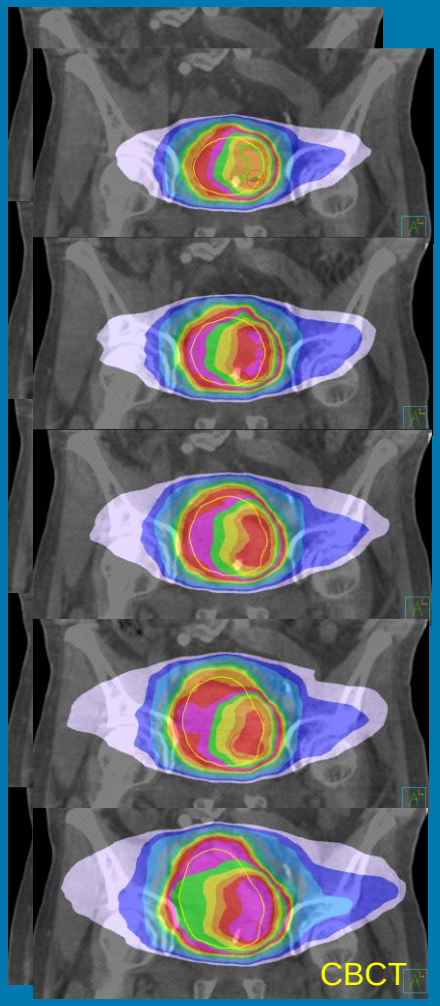
Dose warping of SCART procedure with Pinnacle 8.1x

planned dose



'delivered' dose





Conclusions

- Library planning delivery rarely implemented in the clinical routine
  - but ….
- Online plan adaptation helps us to steer the right dose to the right tissues in highly deforming target volumes

Acknowledgements:
Luiza Bondar from the Erasmus Medical Center Rotterdam
Anne Vestergaard from the Århus Universitetshospital
Simon van Kranen and Jasper Nijkamp from the Netherlands Cancer Institute

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)

Simplified PTV margin recipe for dose - probability

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

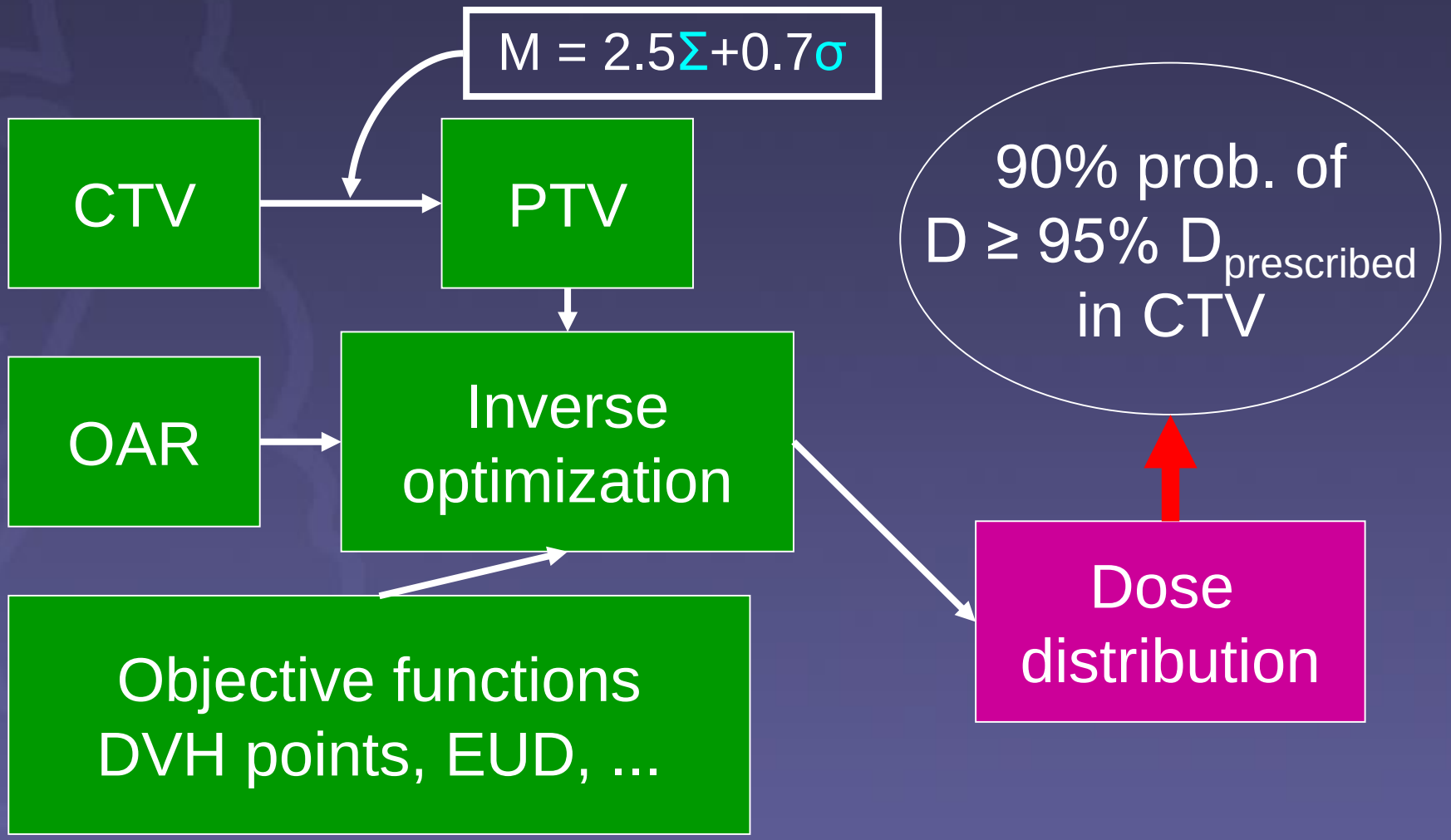
PTV margin = 2.5 Σ + 0.7 σ

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

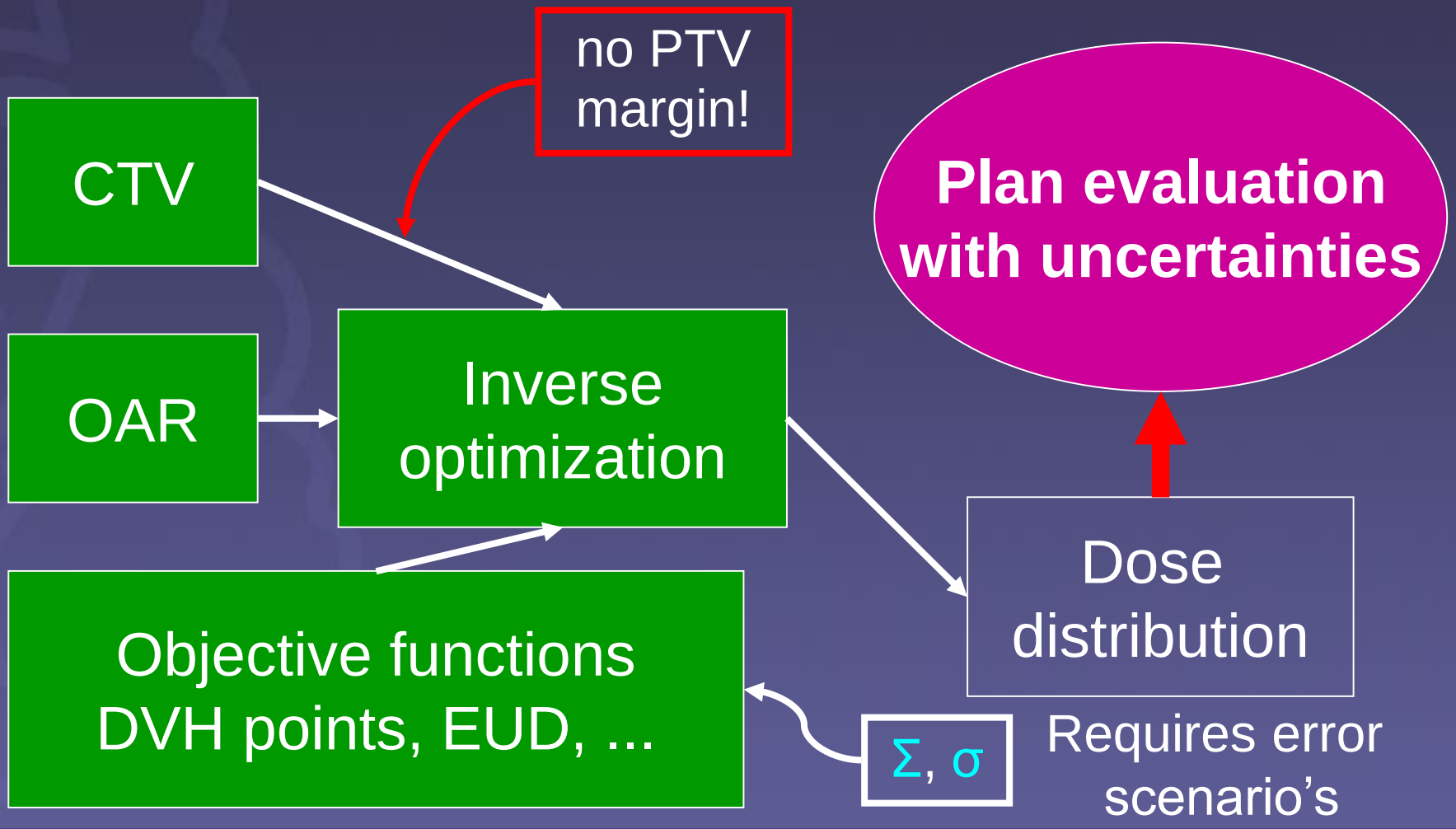
(van Herk et al, IJROBP 47: 1121-1135, 2000)

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

Uncertainty management: Conventional IMRT planning with margin

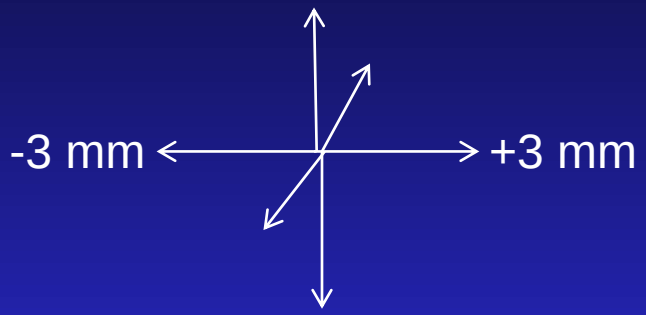


Uncertainty management: Probabilistic IMRT planning without margin



Robust vs probabilistic planning

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

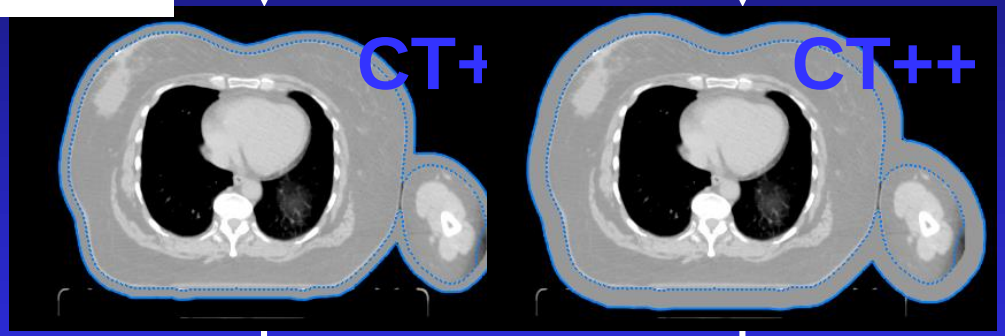


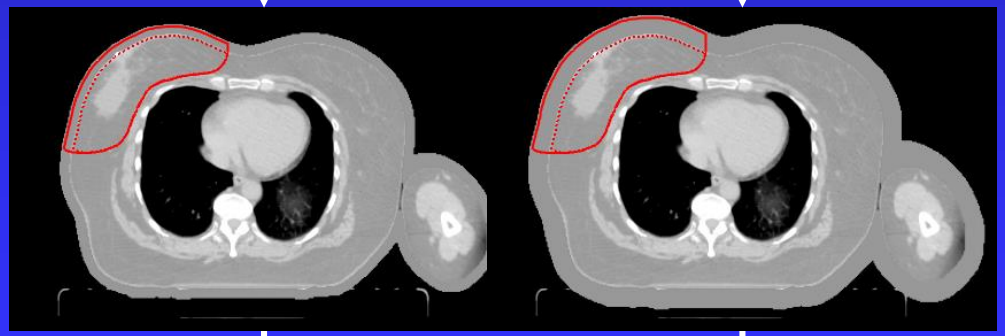
- Probabilistic planning
  - Hundreds of error scenarios
  - Include both random and systematic errors
  - Optimize on probability

Use of robust planning in photons

Planning CT and contours

1. Extend patient body
1 cm 2 cm





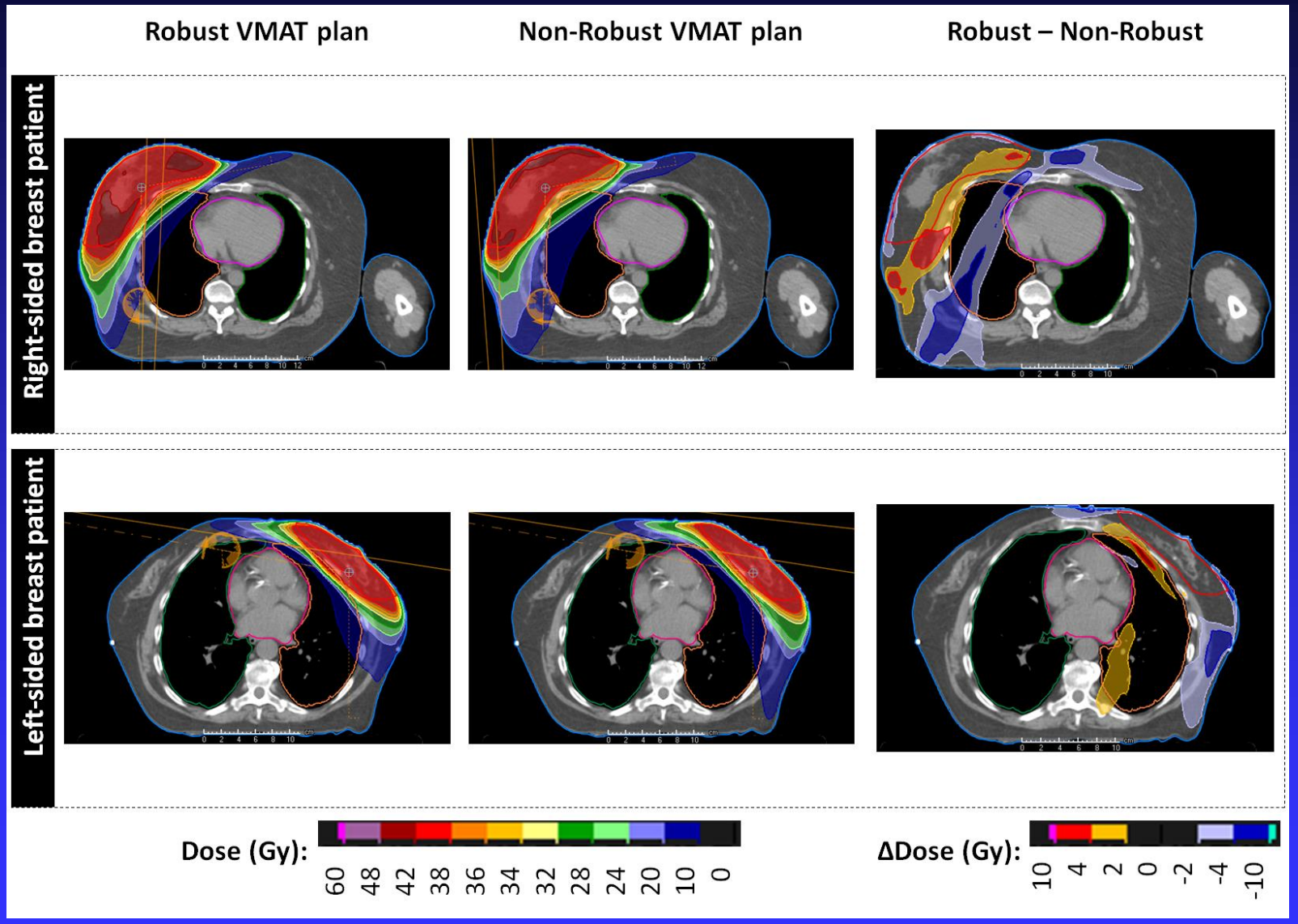
Robust planning

Optimise robust plan

- [Robust] Uniform dose of 40 Gy to Breast
- [Robust] Max DVH of 41.08 Gy to 15% of Breast
- [Robust] Max DVH of 42.16 Gy to 2% of Breast
- Max Dose of 42 Gy in External
- ..

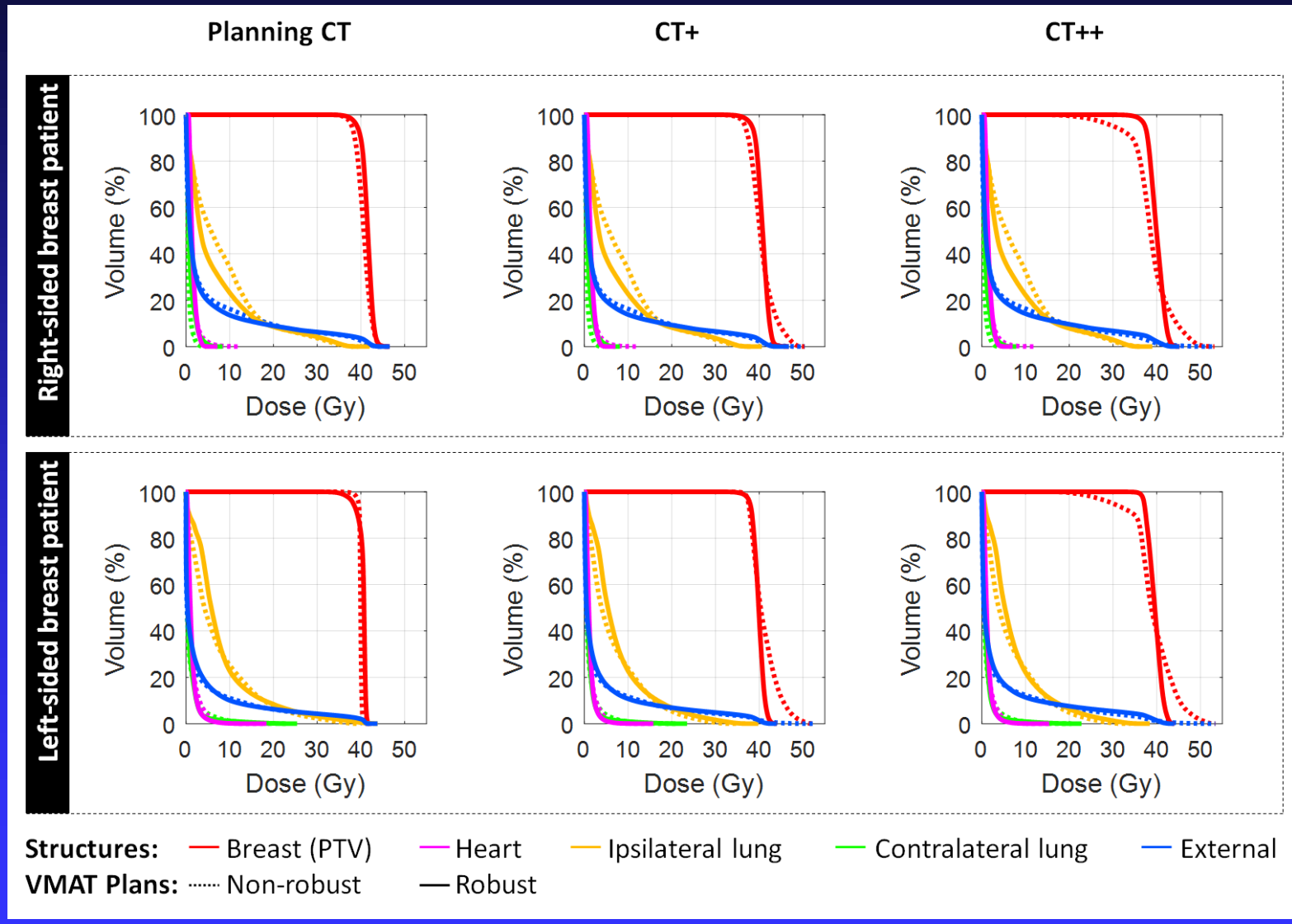
Vasquez Osorio ESTRO 2017

Plan comparison (nominal)



Vasquez Osorio ESTRO 2017

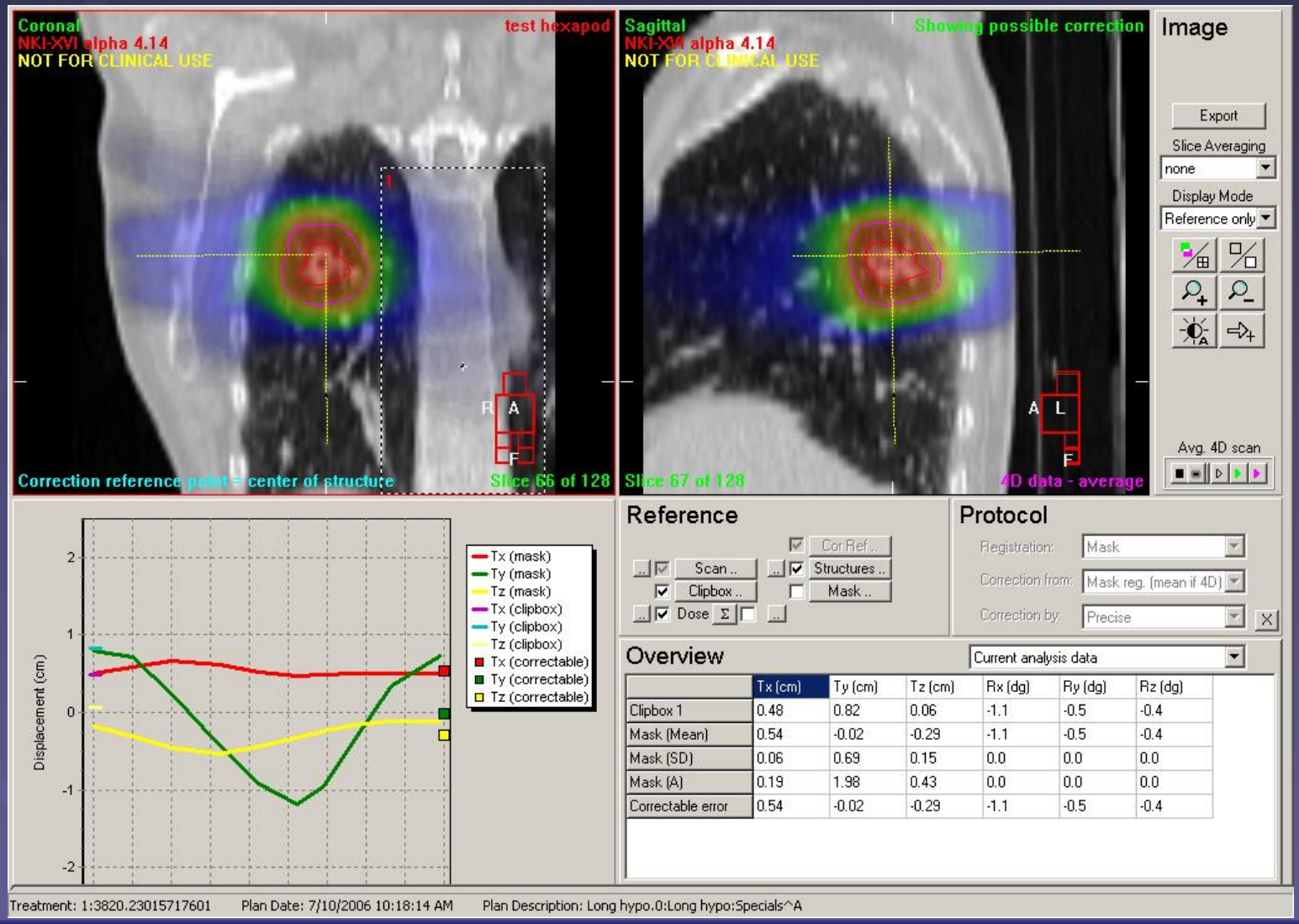
DVH comparison



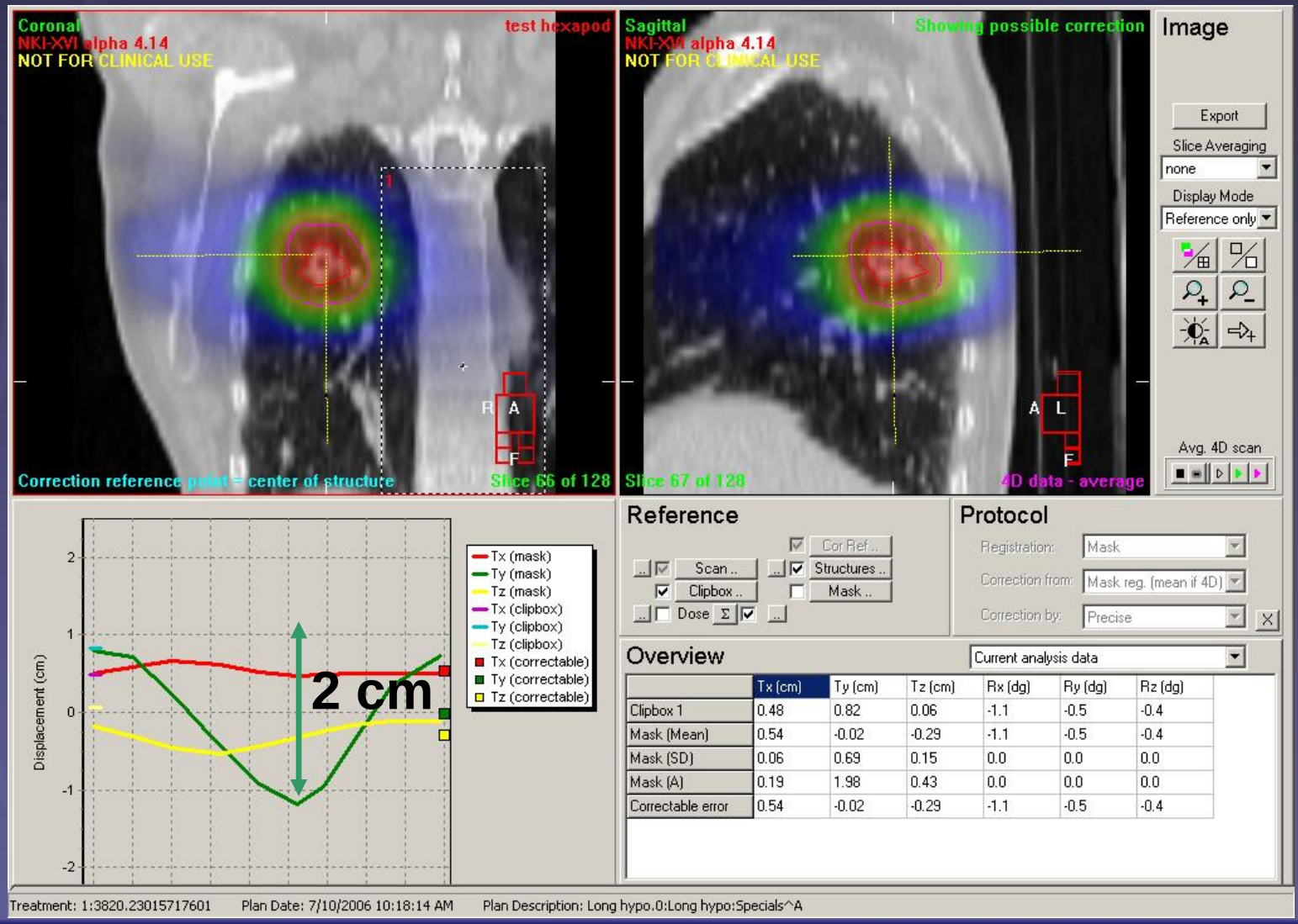
Vasquez Osorio ESTRO 2017

Random errors & breathing

Planned dose distribution: hypofractionated lung treatment 3x18 Gy



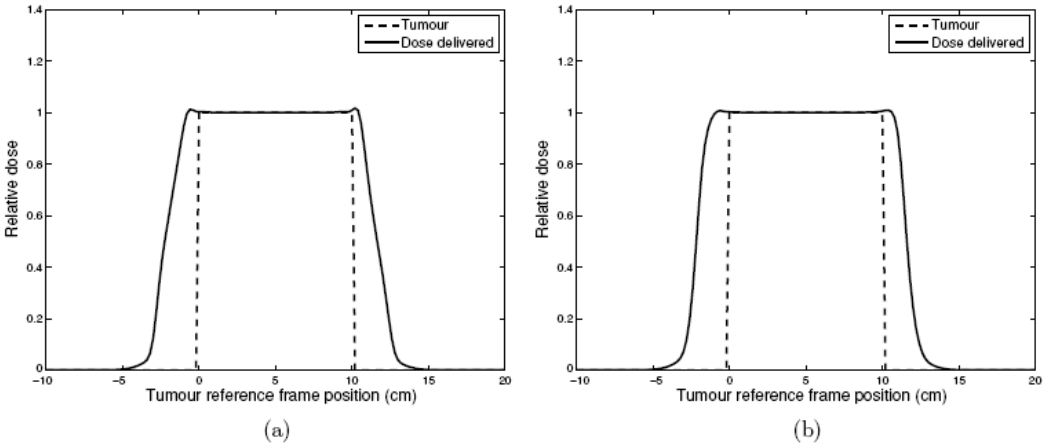
Realized dose distribution with daily IGRT on tumor (no gating)



Respiratory motion causes dose blurring – can it be deblurred ?

Variability in Motion Day-to-Day Revisited

Using Margins: Nominal plan

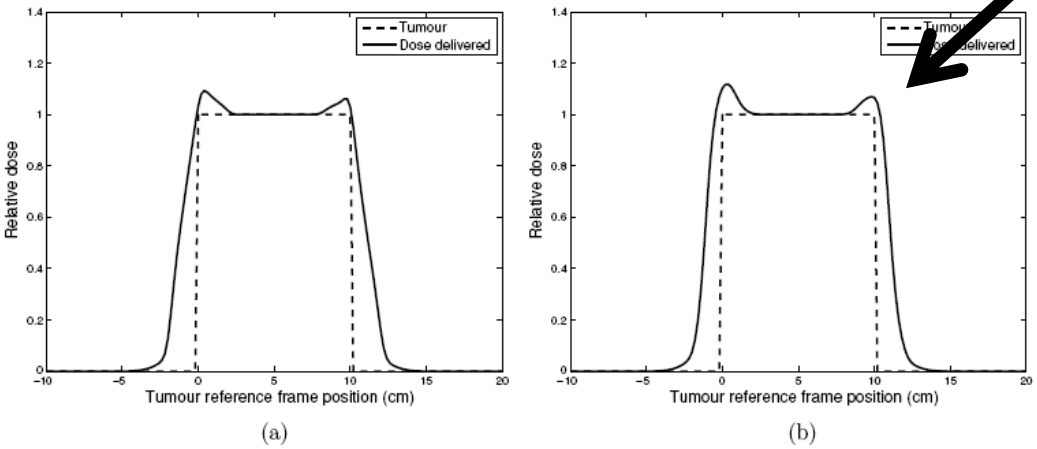


Using Margins: delivered

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

'horns' typically disappear

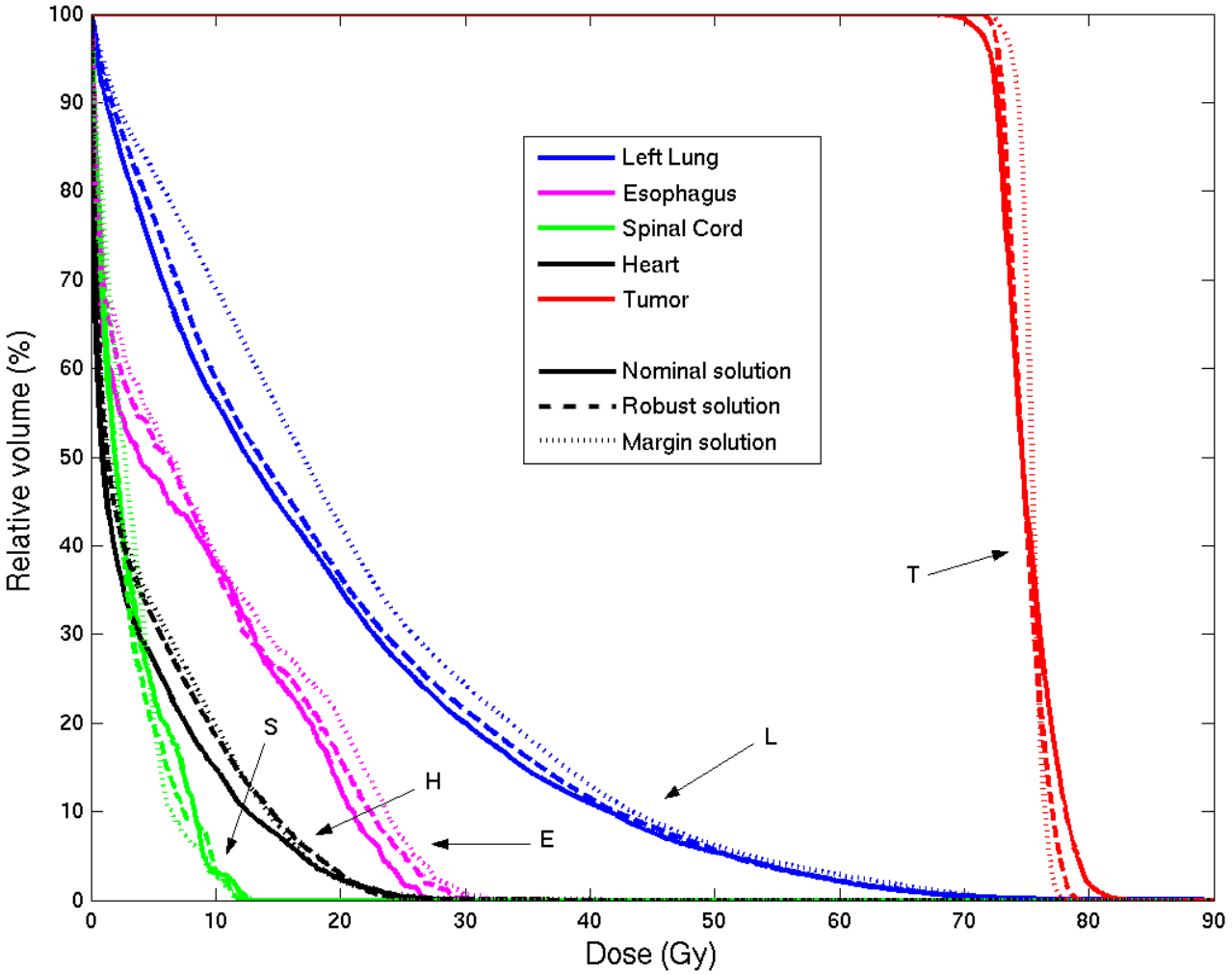
Motion modeling: Nominal plan



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.

Breathing: Margin vs Robust formulation



Courtesy of Tim Chan MIT/MGH

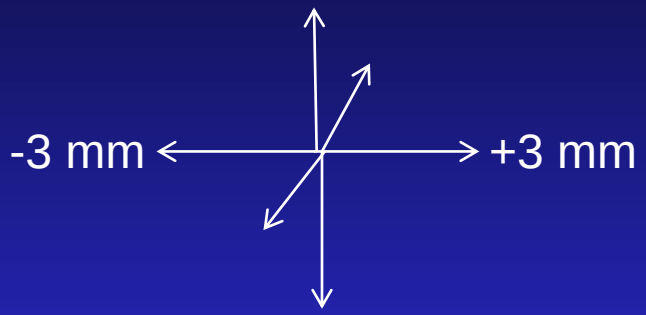
Small gain by taking ‘random’ motion into account in planning

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

Bohoslavsky et al. PMB 2013

Robust vs probabistic planning

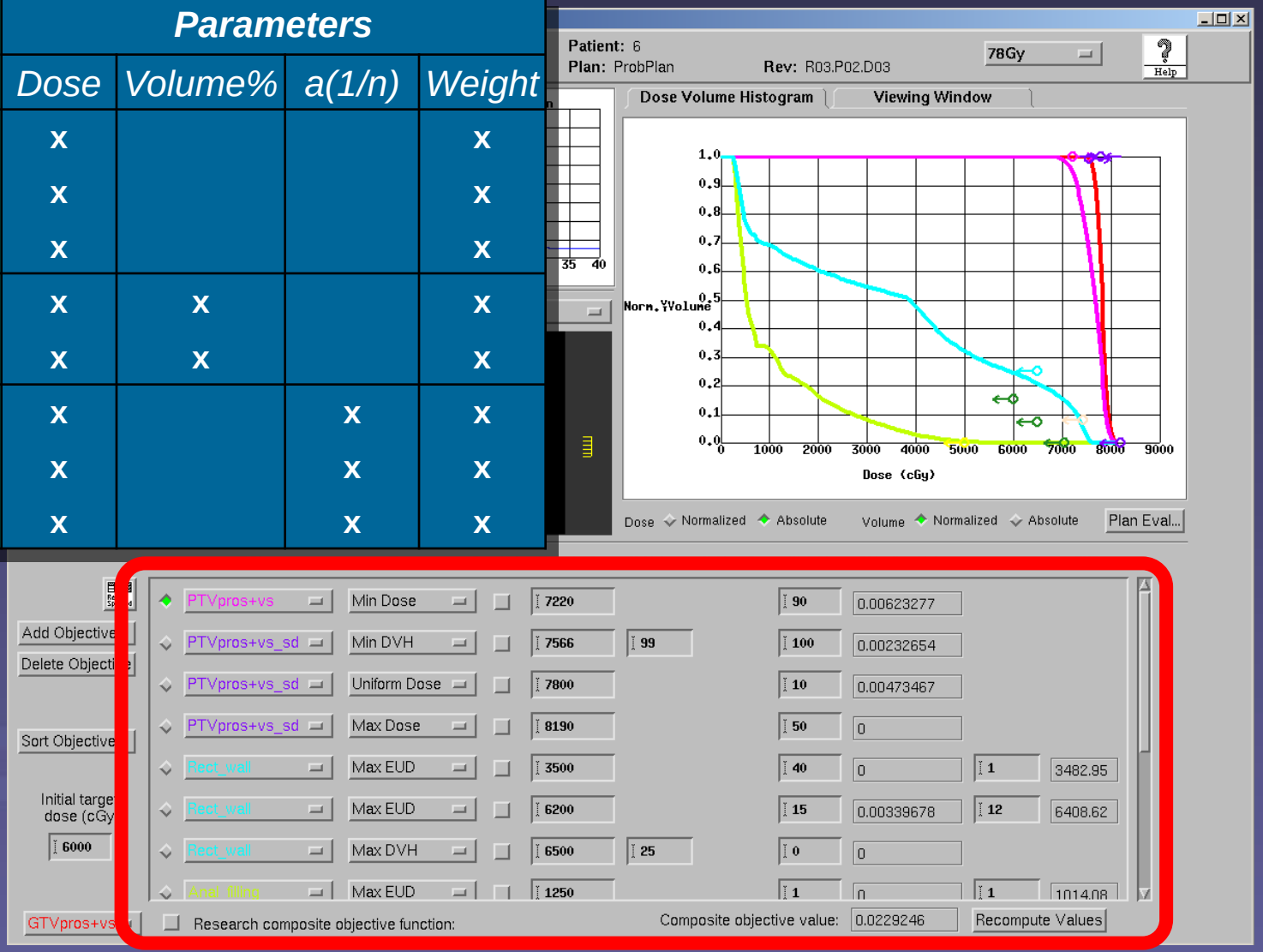
- Robust planning:
  - Few error scenarios
  - Worst case optimization
  - No differentiation random/systematic errors
  - Used mostly for protons



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

Regular planning objective functions

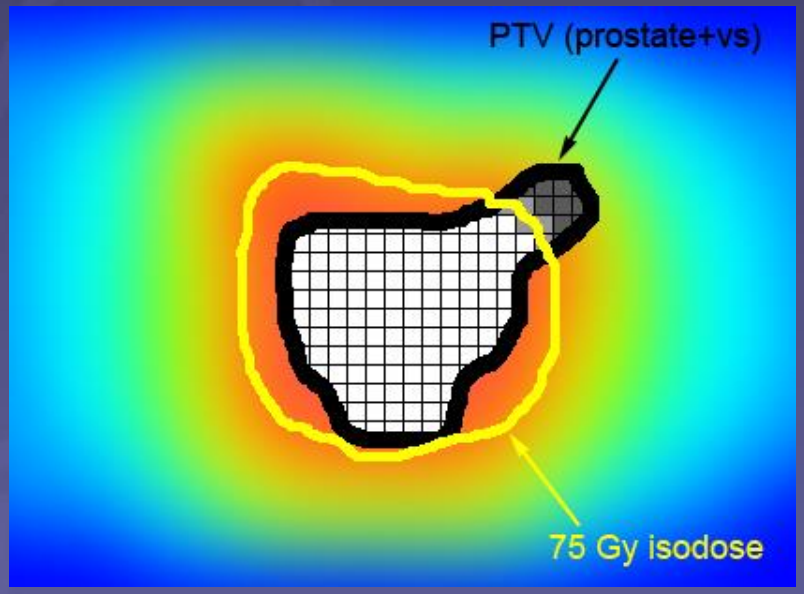
	Parameters			
	Dose	*Volume%*	*a(1/n)*	*Weight*
Minimum Dose	x			x
Maximum Dose	x			x
Uniform Dose	x			x
Minimum DVH	x	x		x
Maximum DVH	x	x		x
Target EUD	x		x	x
Minimum EUD	x		x	x
Maximum EUD	x		x	x

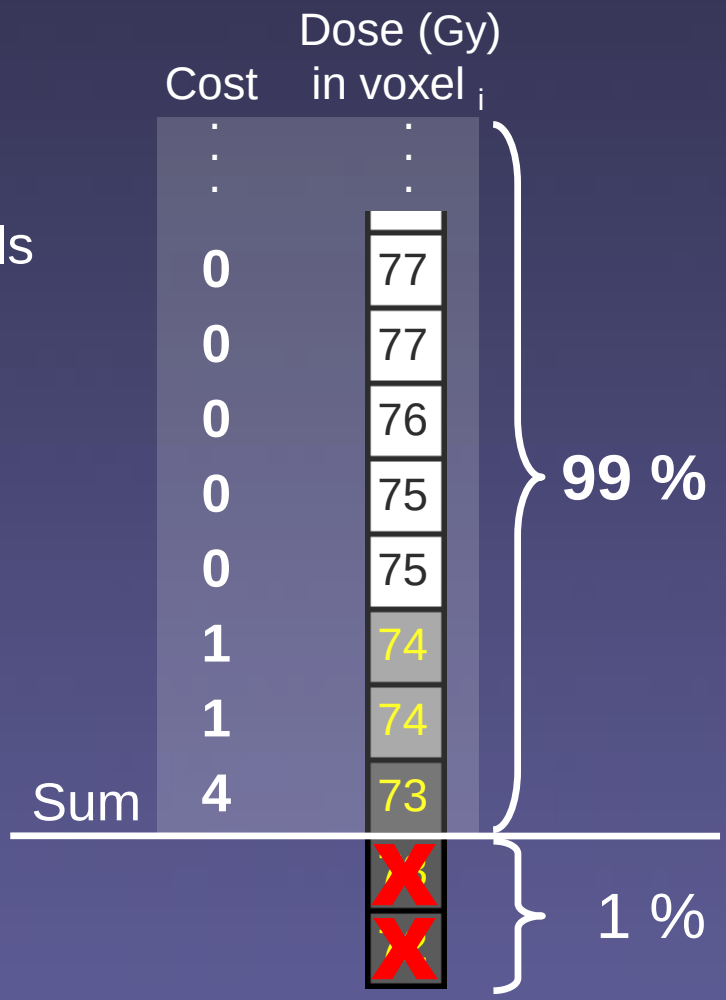


How DVH cost functions are calculated

PTV: MinDVH d=75Gy vol=99%

1. Sort voxels by dose
2. MinDVH: select highest 99% of voxels
3. Compute and add costs





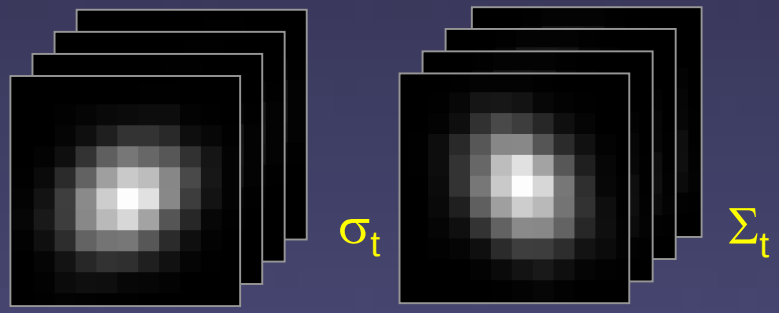
Probabilistic form of exactly the same cost functions

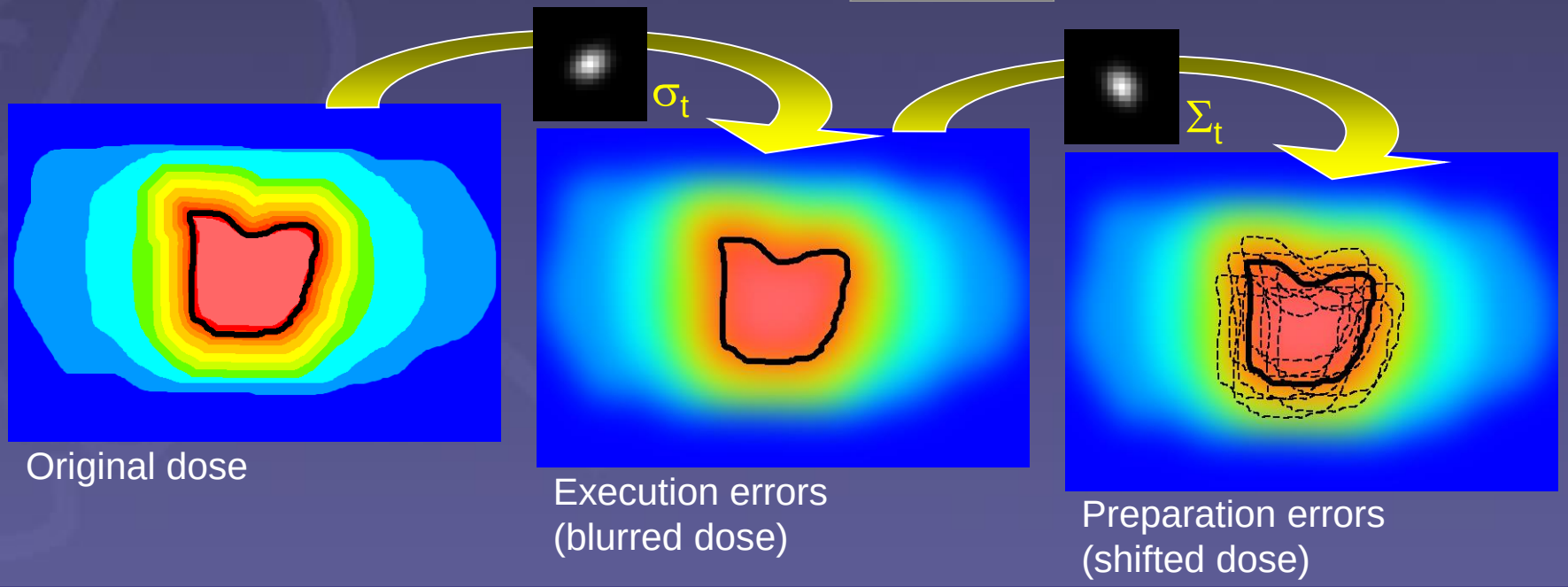
Pinnacle 8.1v research version

Inclusion of uncertainties in plan optimization

Translation errors

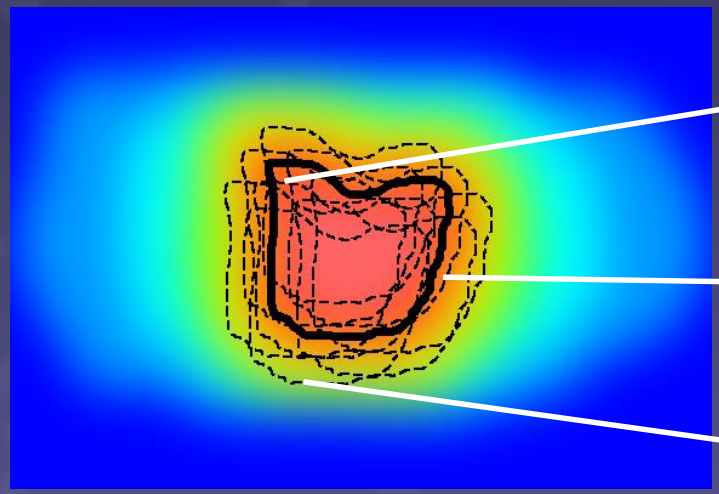
- Execution (random) errors → σ_t
- Preparation (systematic) errors → Σ_t



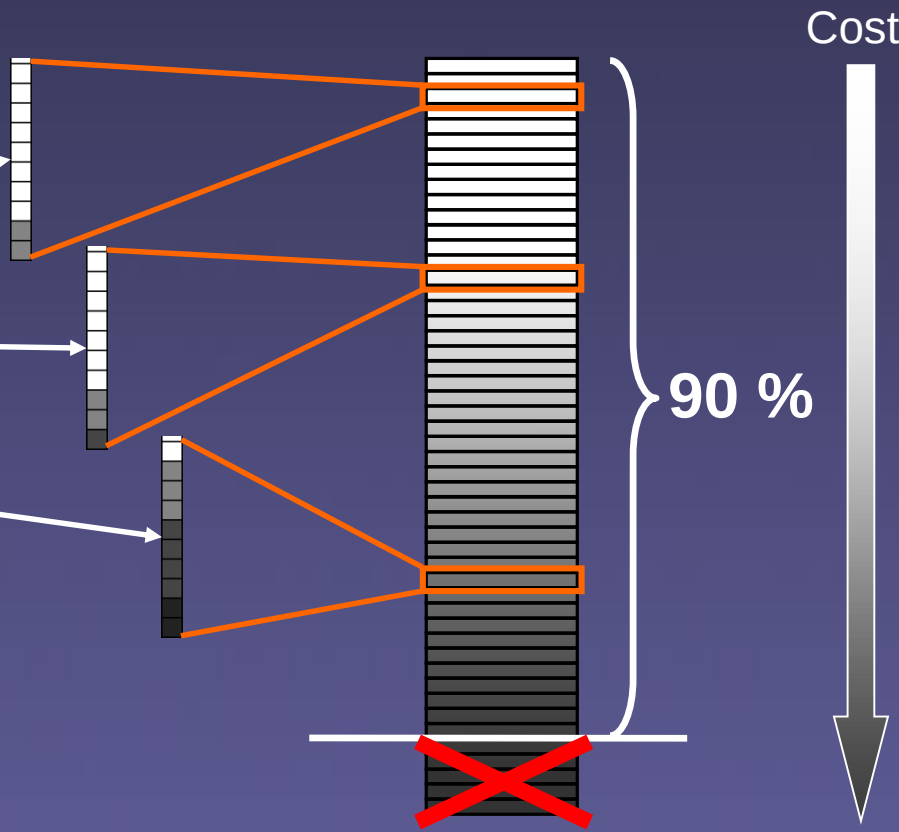


Confidence level of objective functions

1. Systematic error simulations are sorted by cost
2. The best (lowest cost) cases are selected



e.g.: MinDVH 75Gy for
90% of the population



Materials and Methods

Six prostate cases were replanned using probabilistic objective functions aiming for identical target coverage

All plans were evaluated using independent geometrical uncertainties simulation software (UNCERT)

- 10.000 patients x 39 fractions simulated per plan

Uncertainty values (1SD): setup errors + organ motion

Translation errors (mm)	LR	AP	SI
Preparation (systematic) Σ_k	2.6	3.5	2.4
Execution (random) σ_k	2.0	3.0	2.4

prostate
and
rectum

Objectives for treatment plans

Clinical plan objectives

ROI	Objective	Dose (cGy)	Vol (%)	a (1/n)	Weight
PTVpros+vs	Min Dose	7220			90
PTVpros+vs_sd	M				
PTVpros+vs_sd	U				
PTVpros+vs_sd	M				
Rect_wall	M				
Rect_wall	M				
Rect_wall	M				
Anal_filling	M				
PTV72min78	M				
PTVring	M				
PTVring	M				
PTVring	M				
Hip_R	M				
Hip_L	M				

Probabilistic planning objectives

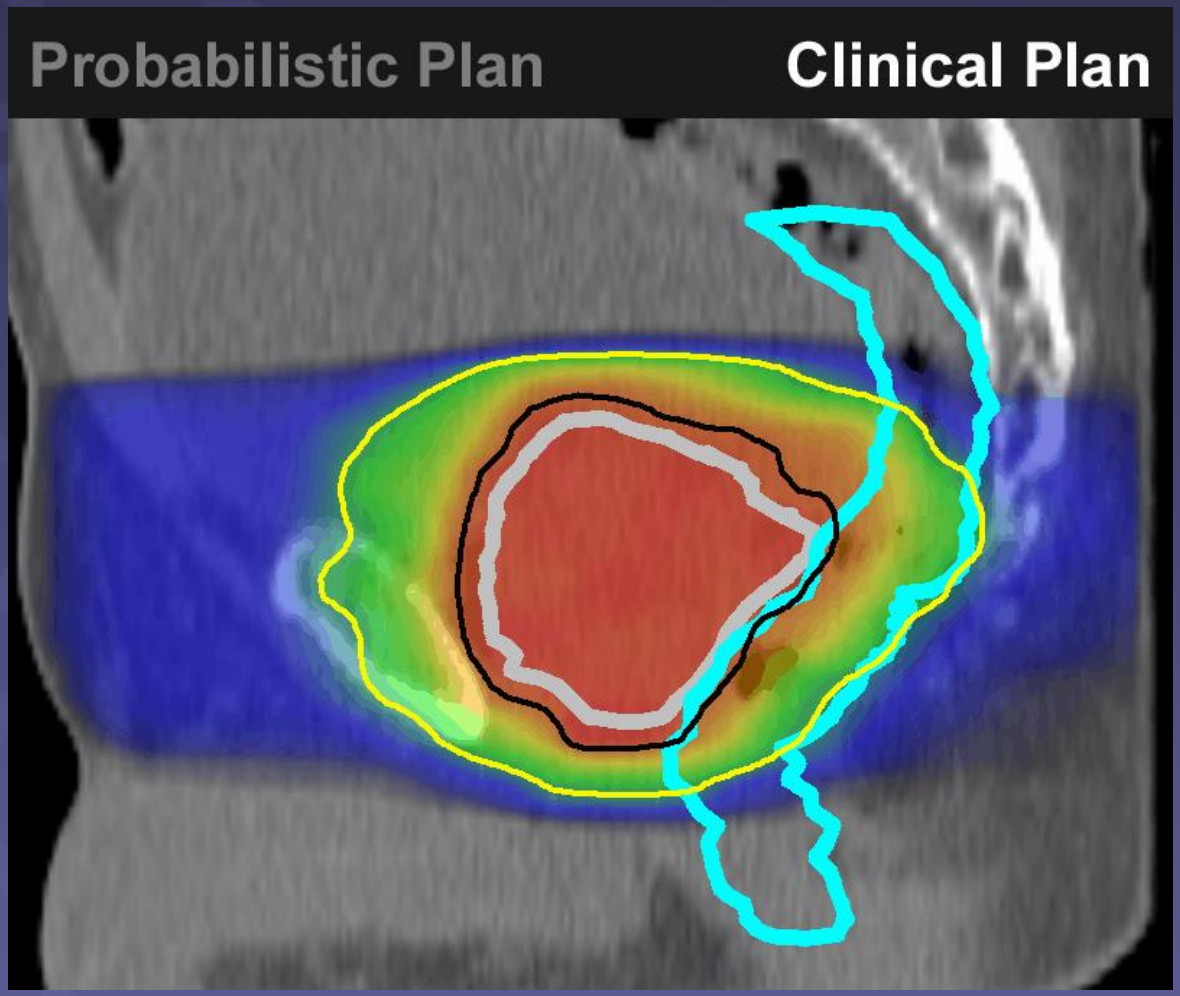
ROI	Objective	Dose (cGy)	Vol (%)	a (1/n)	Weight	Pop (%)	Kernel
GTVpros+vs	Min EUD	7820		1	100	92	sig
						92	sig
						92	sig
						--- (100)	env
						--- (100)	env
						92	sig
						92	sig
						92	sig
						--- (100)	---

GTV instead of PTV

No PTV boost

Less objectives

Effect of probabilistic planning



GTV

Rectum

95% isodose (74.1 Gy)

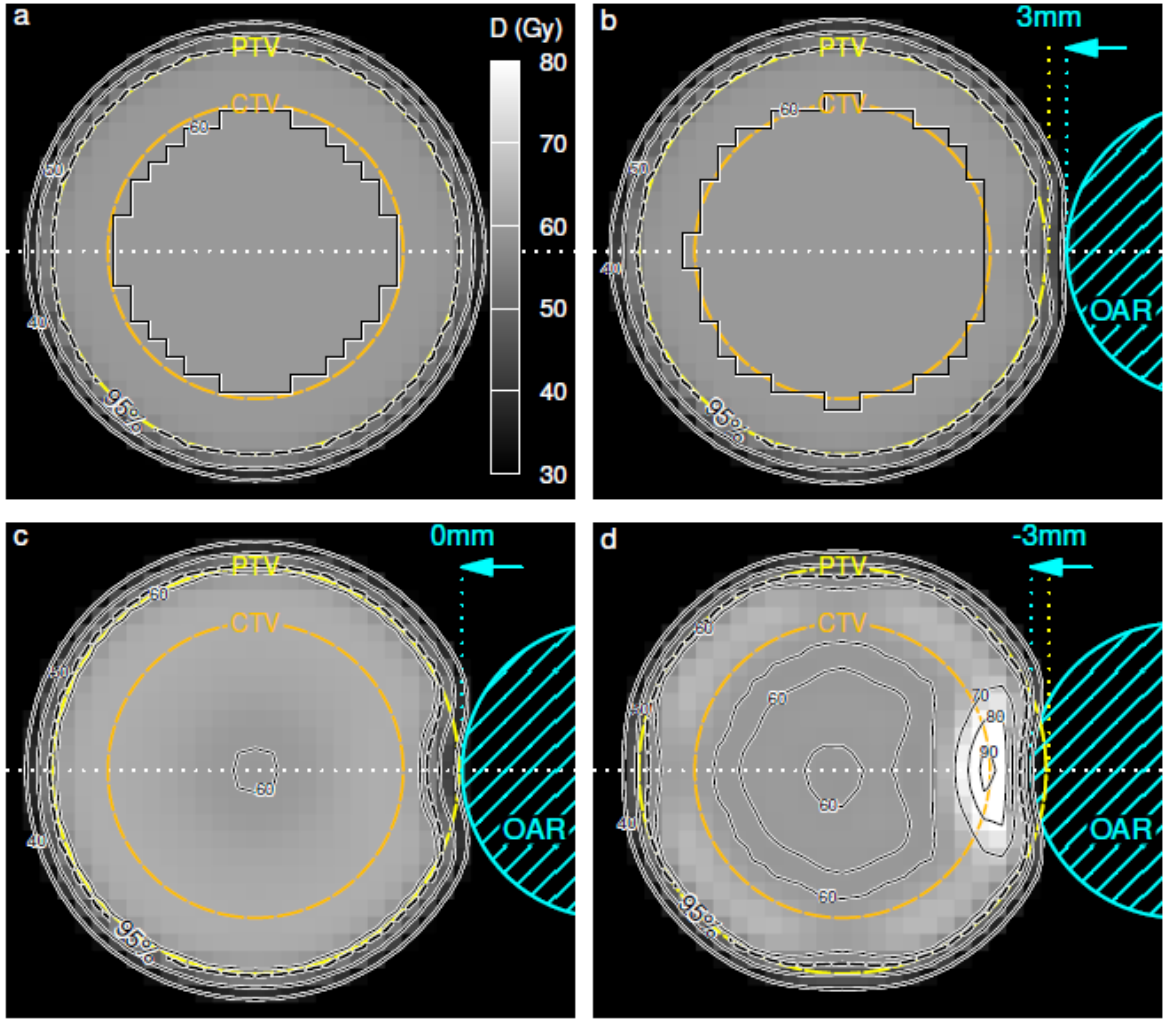
50% isodose (39.0 Gy)

Prescribed dose to the target: 78 Gy

PTV: a Paranoid Target Volume?

Marnix G. Witte[a], Jan-Jakob Sonke[a], Joseph O. Deasy[b], Marcel van Herk[a]

[a]*The Netherlands Cancer Institute, Amsterdam, The Netherlands*
[b]*Memorial Sloan-Kettering Cancer Center, New York, USA*



Conclusions

Small gain of including breathing motion in treatment optimization

- Off course, much 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
  Vendors, implement it!

Robust planning can solve issues with PTV outside body

Dose painted planning

Gert Meijer

ESTRO
European Society for Therapeutic Radiology and Oncology

Wilfried De Neve (2008):

The vision is clear

- Tumors are heterogeneous
- CTV is more heterogeneous
- PTV is even more heterogeneous
- Homogeneous PTV dose distributions
  - Planning goal
  - Dogmatic
  - Stupid?

ELSEVIER

Int. J. Radiation Oncology Biol. Phys., Vol. 47, No. 3, pp. 551–560, 2000

0360-3016/00/$–see front matter

PII S0360-3016(00)00467-3

CRITICAL REVIEW

TOWARDS MULTIDIMENSIONAL RADIOTHERAPY (MD-CRT): BIOLOGICAL IMAGING AND BIOLOGICAL CONFORMALITY

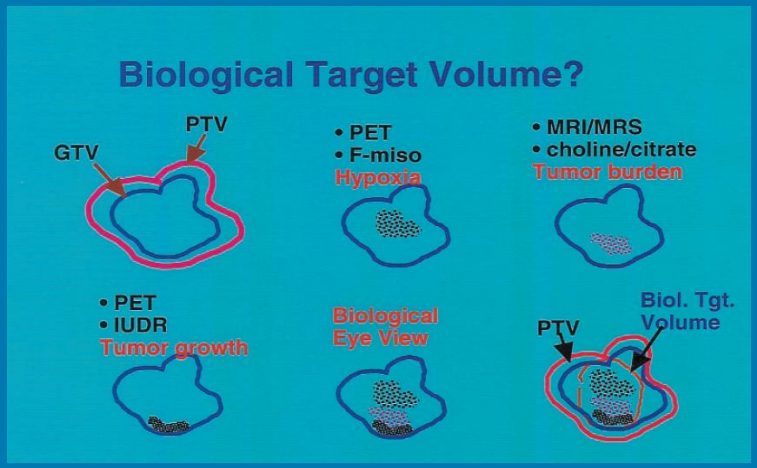
C. Clifton Ling, Ph.D.,* John Humm, Ph.D.,* Steven Larson, M.D.,† Howard Amols, Ph.D.,* Zvi Fuks, M.D.,‡ Steven Leibel, M.D.,‡ and Jason A. Koutcher, M.D., Ph.D.*

Departments of *Medical Physics, †Radiology, and ‡Radiation Oncology, Memorial Sloan Kettering Cancer Center, New York, NY

An engineering approach to cancer treatment?

- Radiation therapy was developed in the heyday of "modern" physics – and, arguably, the greatest progress in the last century has been in physics and technology
- Most of the disease concepts applied in radiotherapy today date back to the 1920's
- Characteristically, we treat VOLUMES rather than DISEASE PROCESSES

UNIVERSITY OF WISCONSIN SCHOOL OF MEDICINE AND PUBLIC HEALTH



Søren Bentzen (ESTRO 2010)

ESTRO
European Society for Therapeutic Radiology and Oncology

Dose painting is the prescription of a non-uniform radiation dose distribution to the target volume based on functional or molecular images shown to indicate the local risk of relapse

Hypothesis 1:
Local recurrence is related to resistant areas not eradicated by currently precribed and delivered uniform doses

Hypothesis 2:
Non-invasive functional and molecular imaging allows mapping the target in terms of radioresistance

biological caveats

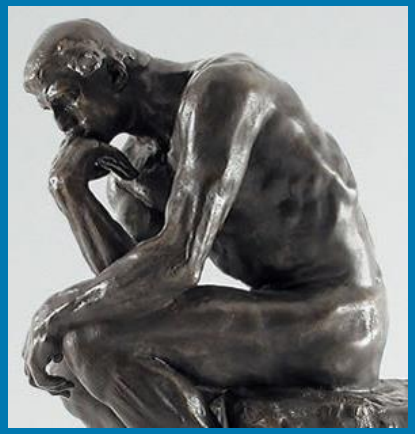
what parameters?

sensitivity/ specificity?

intensity to dose?

3D fractionation?

4D heterogeneity?



physical caveats

image resolution?

delivery resolution?

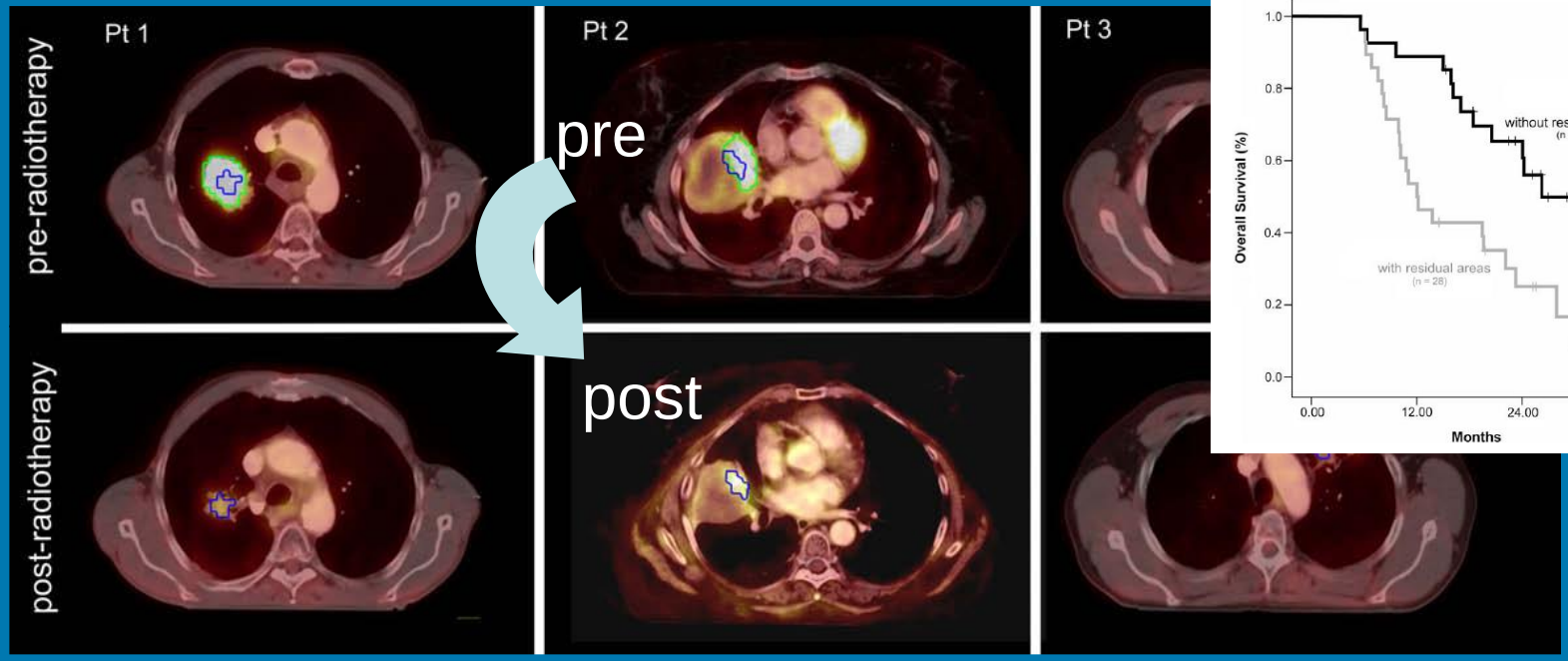
planning?

plan evaluation?

tumour movements?

image guidance?

phenomenological relationships do matter !!



Aerts *et al.* R&O 2009

confirmed by the Dresden group and PMH

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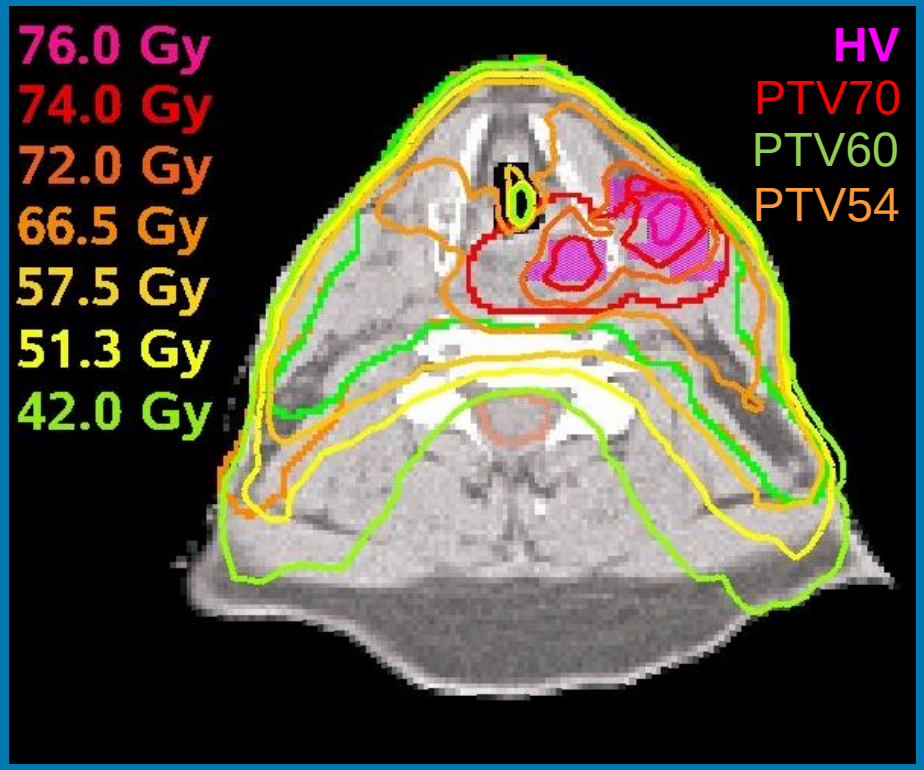
Hypoxia Dose Painting Trail in Tübingen, Germany

- Definition of hypoxic volume (HV) according to [^{18}F]-FMISO PET/CT
- Dose escalation of 10% (77Gy) in the HV inside the PTV70 in the experimental treatment arm
- Isotoxic approach!
- So far n=26 patients included.



IMRT plan for patient #3 in the HDP trial.

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Table 3 Summary of the ongoing phase-III trials in radiotherapy "dose painting" for Head and Neck squamous cell carcinoma.

Acronym/investigator (NCT #)	Tumor location	HPV status	Tumor stage	Molecular imaging	Phase	Study design		Completion date
						Standard arm	Experimental arm	
Xuzhou Medical College, China (NCT# 02089204)	NPC	Not relevant	III-IVa	FDG-PET FMISO-PET	III	IMRT + cddp + docetaxel	(1) IMRT + cddp + docetaxel + boost dose on FDG (2) IMRT + cddp + docetaxel + boost dose on FMISO	December 2015?
De Neve (NCT# 01341535)	Oro, Hyp, Cav, Lar	HPV–	III-IV	FDG-PET	rand. II	69.12/56 Gy in 6.5w + weekly cddp	84/40 Gy in 6w + weekly cddp	Q1 2018
Eisbruch (NCT# 02031250)	Oro, Hyp, Lar, Cav, NPC	HPV–HPV+ high risk	III-IV	DCE-MRI	rand. II	70 Gy in 7w + cddp/carbo	80 Gy in 7w+ cddp/carbo	December 2020
INTELHOPE (NCT# 0275722)	Oro, Hyp, Lar	n.a.	III-IV	FDG-PET	rand. II	66/54 Gy in 6w + concomitant cddp	73.5/63/54 Gy in 6 weeks + cddp	December 2020
Zips (NCT# 02352792)	Oro, Hyp, Cav, Lar	n.a.	III-IV	FMISO-PET	Rand. II	70 Gy in 7w + 5Fu + mitomycin C or cddp	77 Gy in 7w + 5Fu + mitomycin C or cddp	December 2022
ESCALOX (NCT # 01212354)	Oro, Hyp, Cav	n.a.	n.a.	FMISO-PET	III	70/56 Gy in 7w (SIB-IMRT) + concomitant cddp	80.5/70/56 Gy in 7w (SIB-IMRT) + concomitant cddp	January 2025

DCE, dynamic contrast-enhanced; Oro, oropharynx; Hyp, hypopharynx; Cav, oral cavity; Lar, larynx; NPC, nasopharynx; CH, chemotherapy; n.a., non available; rand., randomized.

Gregoire *et al.*, Sem in Radiat.Onc.2018

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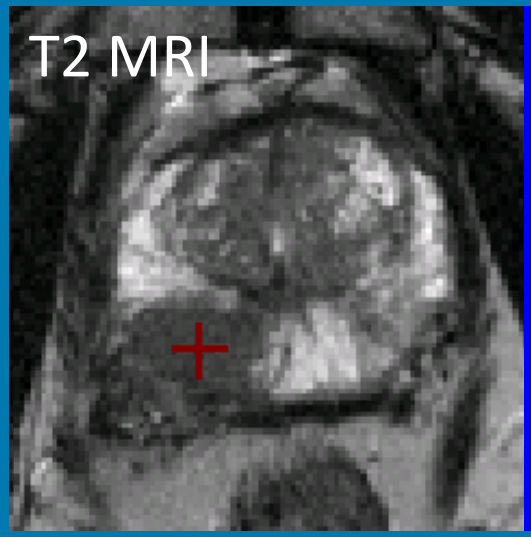
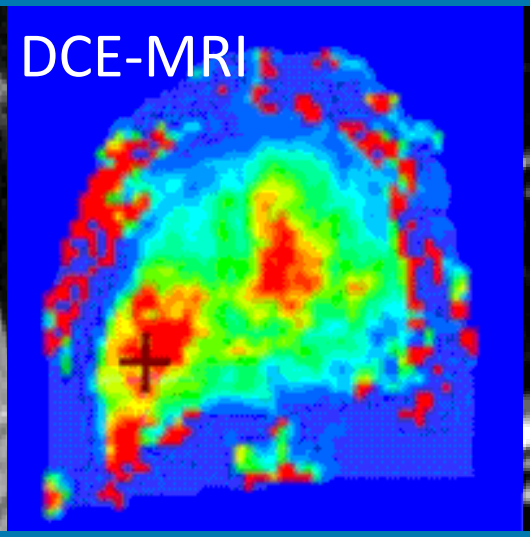
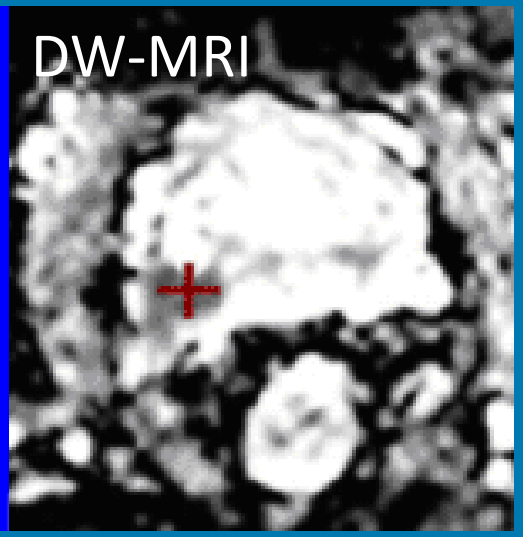
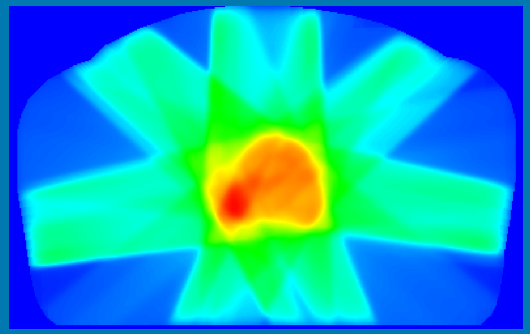
the FLAME trial: Focal Lesion Ablative Microboost







FLAME



the FLAME trial: Focal Lesion Ablative Microboost

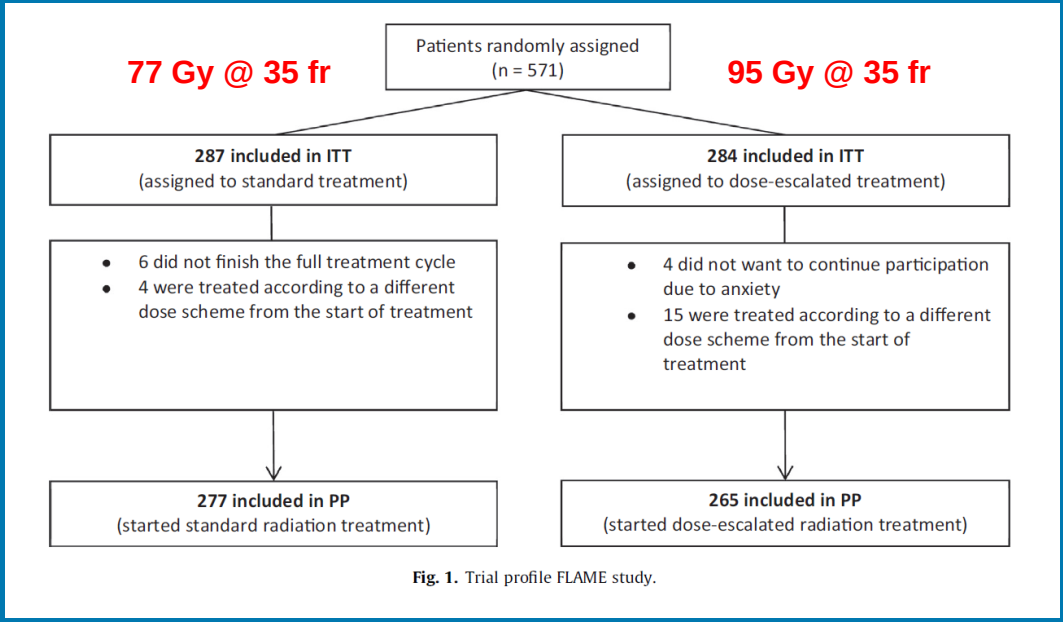
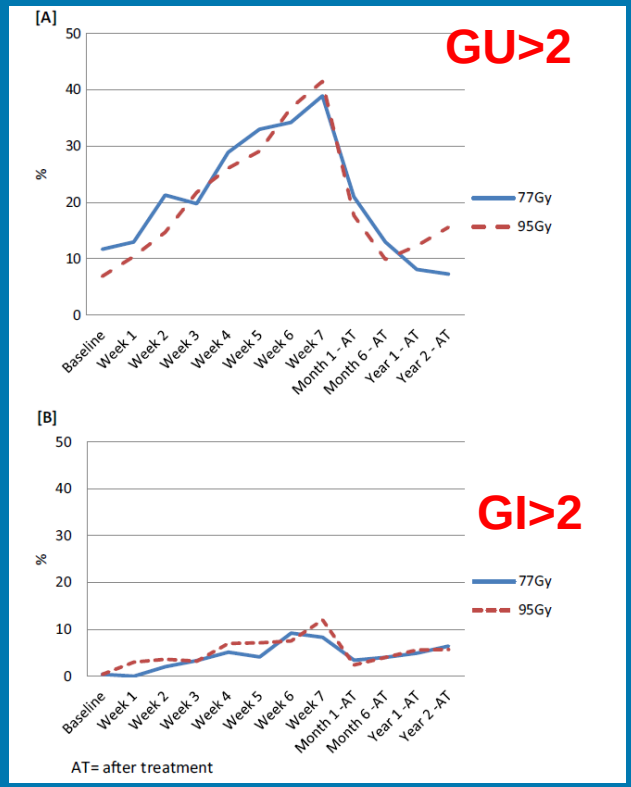


Fig. 1. Trial profile FLAME study.

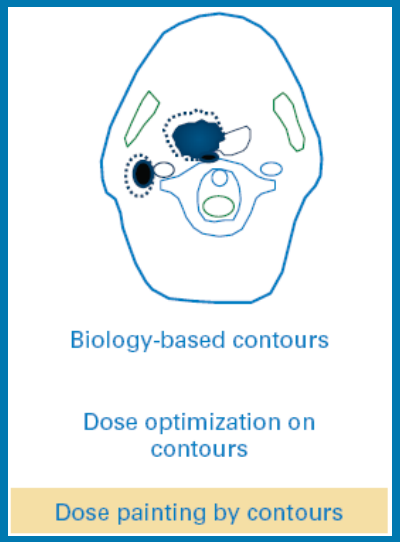


Commercial planning systems do not support dose painting

- objectives based on DVH parameters
  - max dose
  - min dose
  - max DVH
  - EUD
  - NTCP
  - TCP

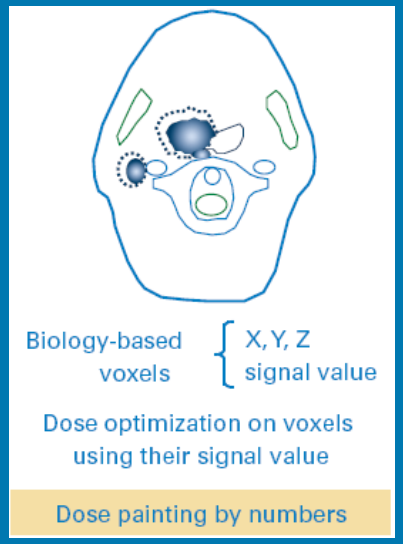
How?

dose painting by contours



Xing (PMB 2002), Chao (IJROBP 2001)
Madani (IJROBP 2007), De Ruysscher (R&O 2006)

dose painting by numbers



Bentzen (Lancet Oncol 2005), Thorwarth (IJROBP 2007)
Vanderstraeten (PMB 2006)

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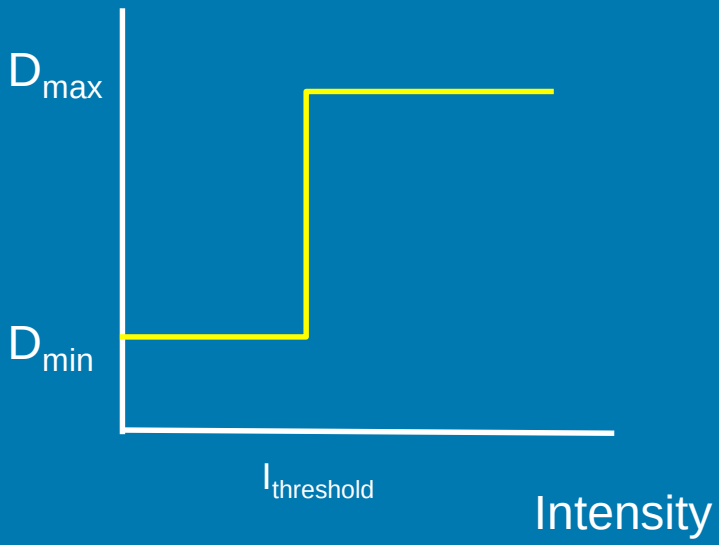
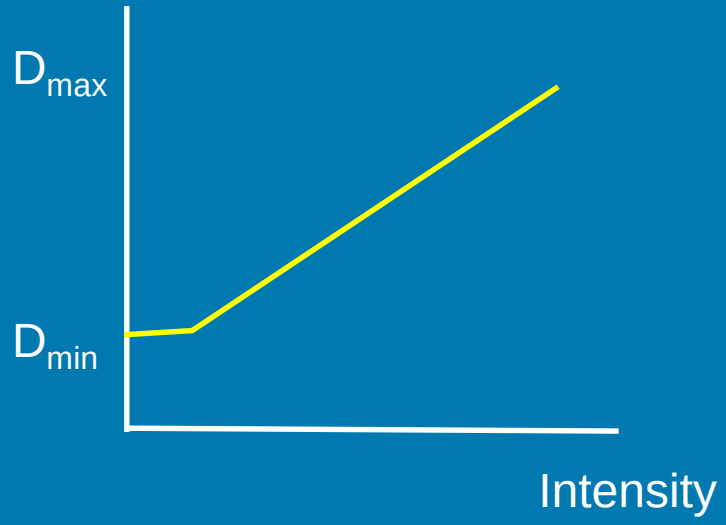
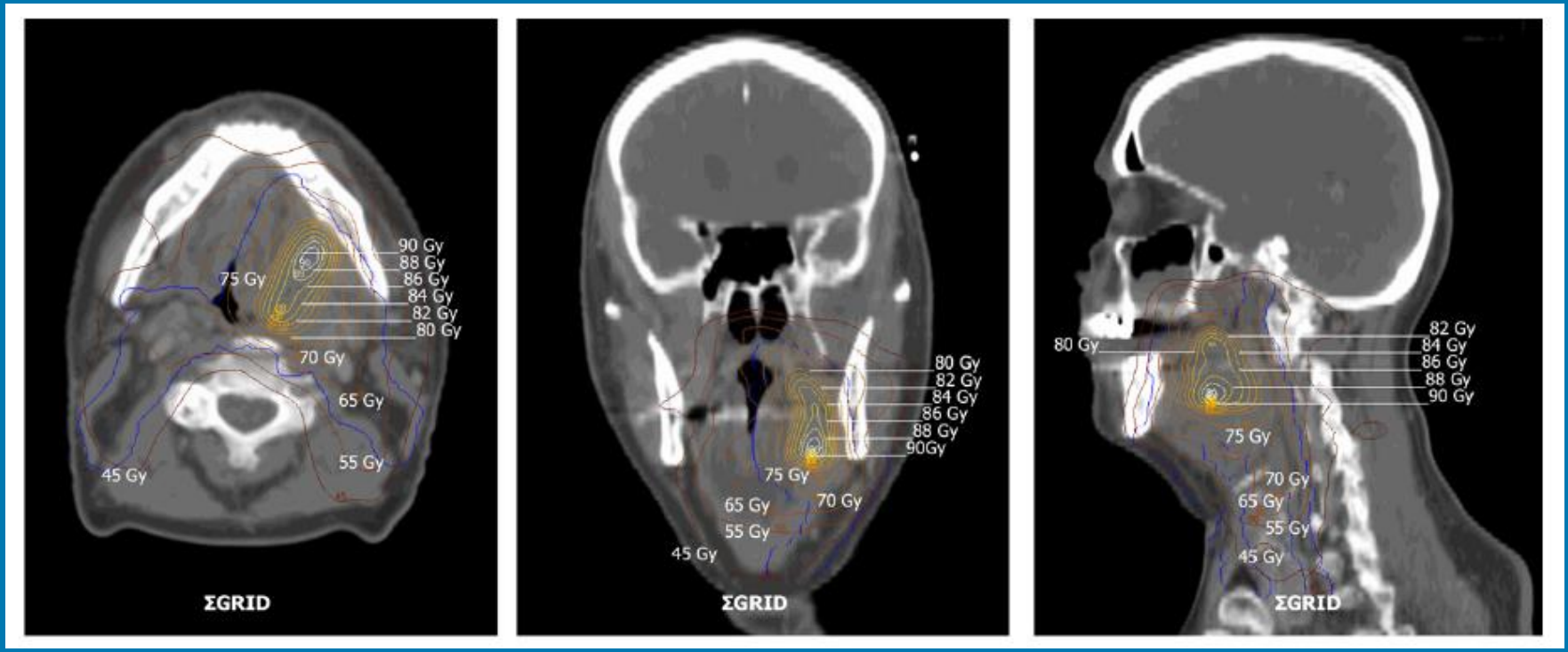
How?

dose painting by contours



dose painting by numbers





Frederic Duprez *et al.* (IJROBP 2010)

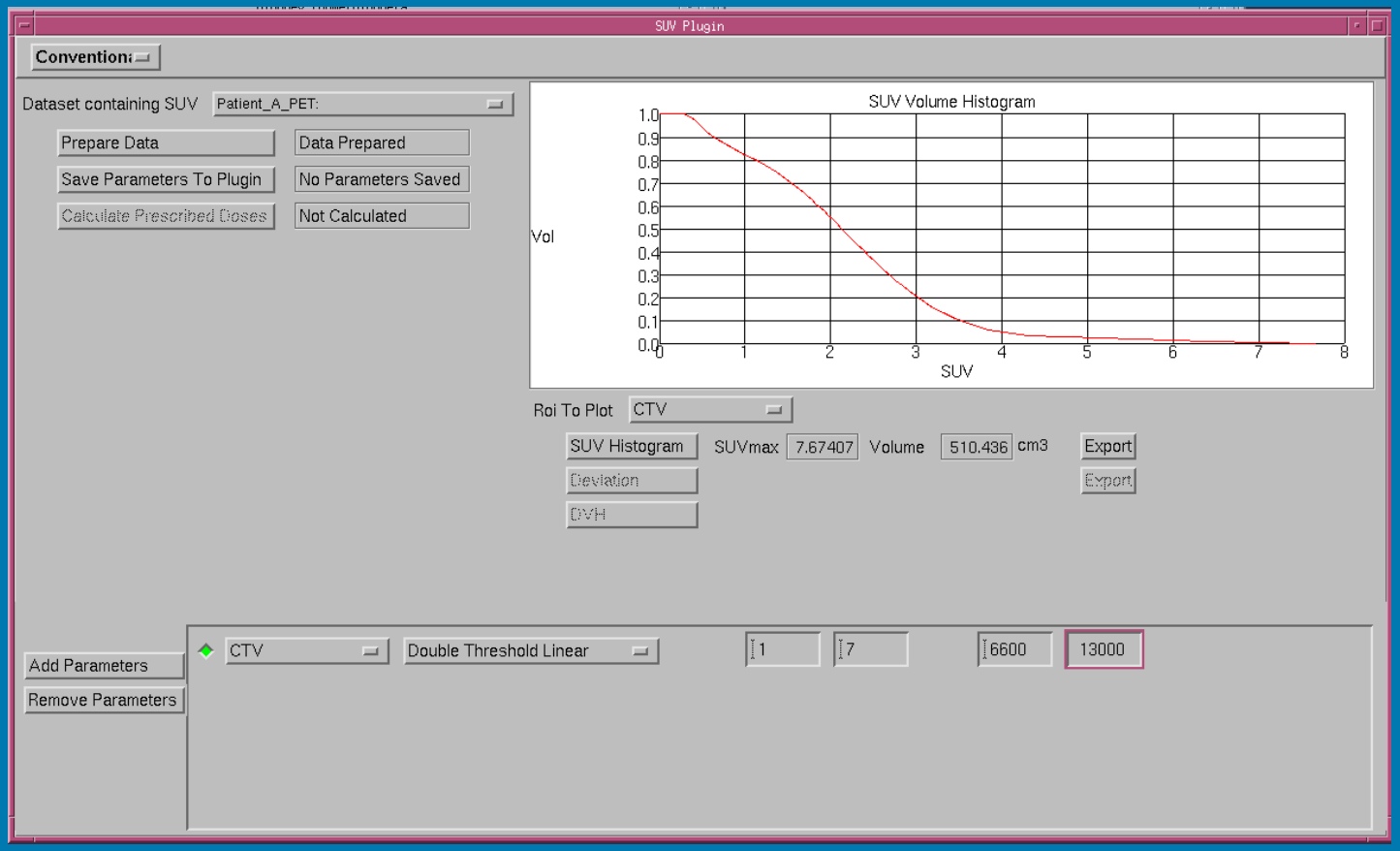
How?

dose painting by contours

- standard software
- allows for margin expansion
- based on thresholding
- evaluation based on DVHs

dose painting by numbers

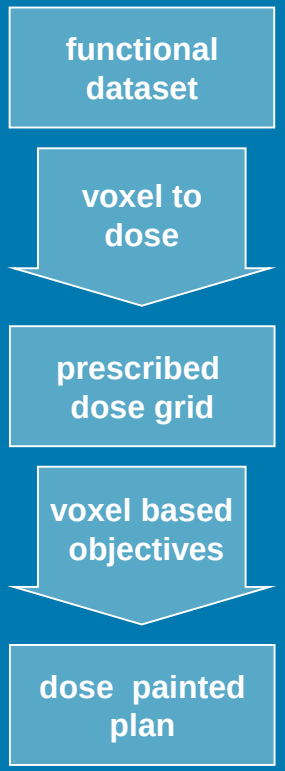
- research software
- no margins
- ‘no’ thresholding
- evaluation based on new descriptors



How?

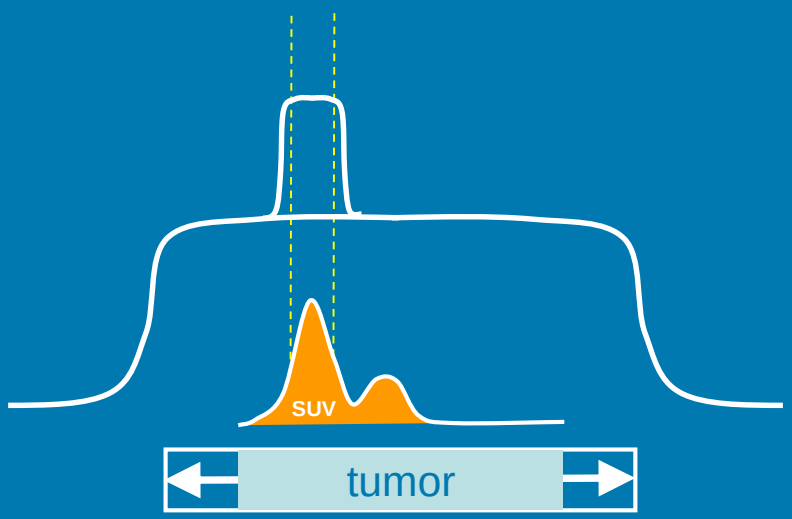
dose painting by contours

dose painting by numbers

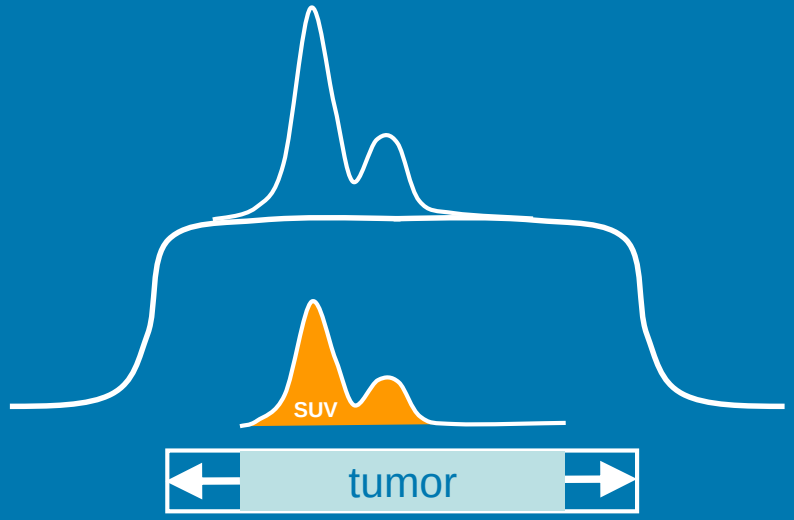


How?

dose painting by contours



dose painting by numbers



How?

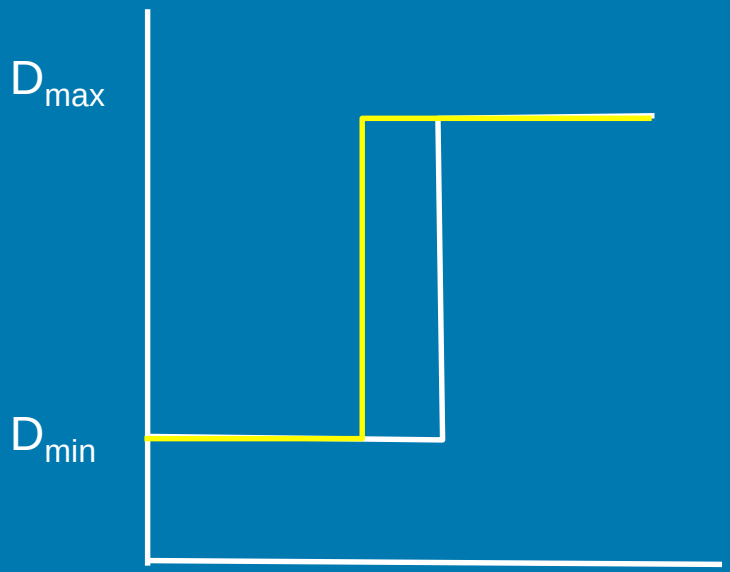
dose painting by contours

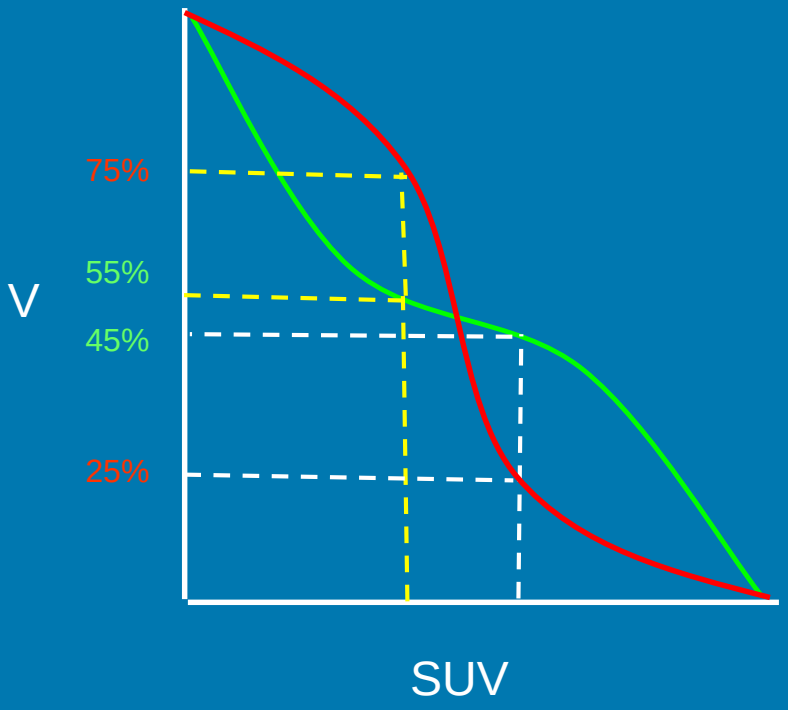
- standard software
- allows for margin expansion
- based on thresholding
- evaluation based on DVHs

dose painting by numbers

- research software
- no margins
- ‘no’ thresholding
- evaluation based on new descriptors

thresholding might be tricky





How?

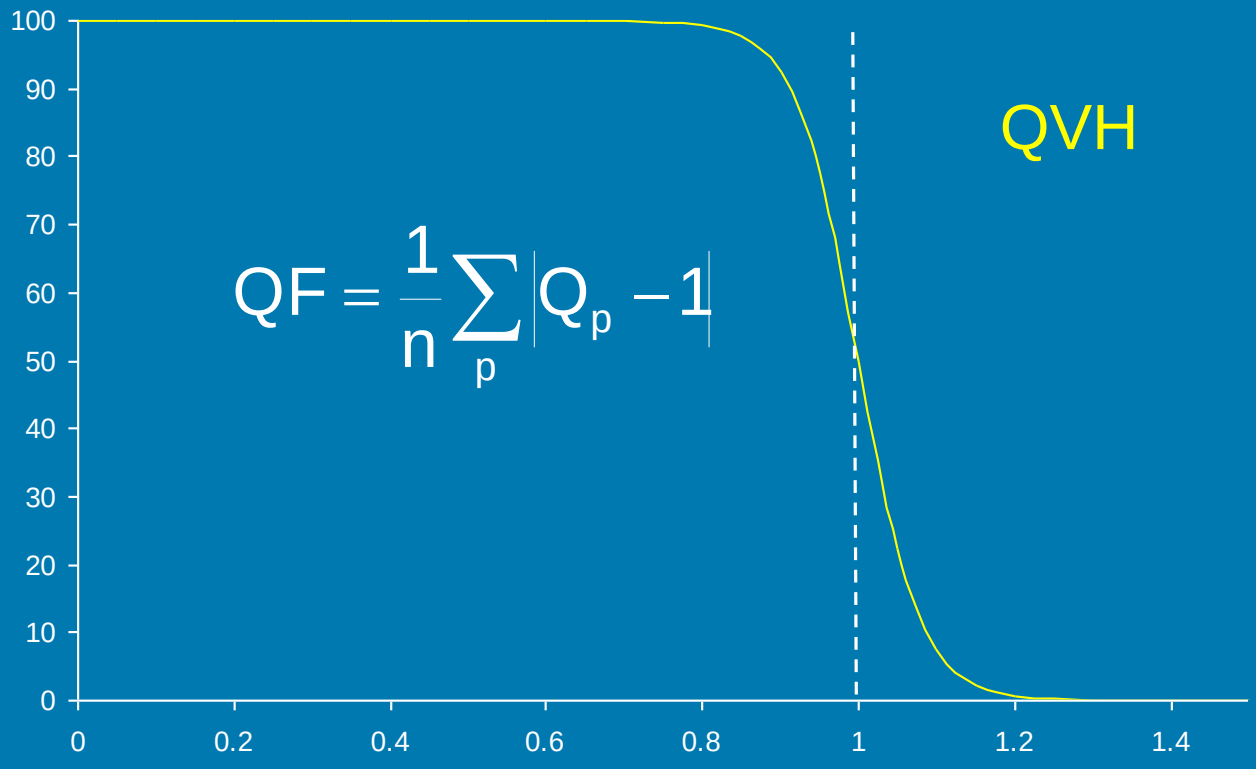
dose painting by contours

- standard software
- allows for margin expansion
- based on thresholding
- evaluation based on DVHs

dose painting by numbers

- research software
- no margins
- ‘no’ thresholding
- evaluation based on new descriptors

Treatment plan evaluation



Barbara Vanderstraeten *et al* (PMB 2006)

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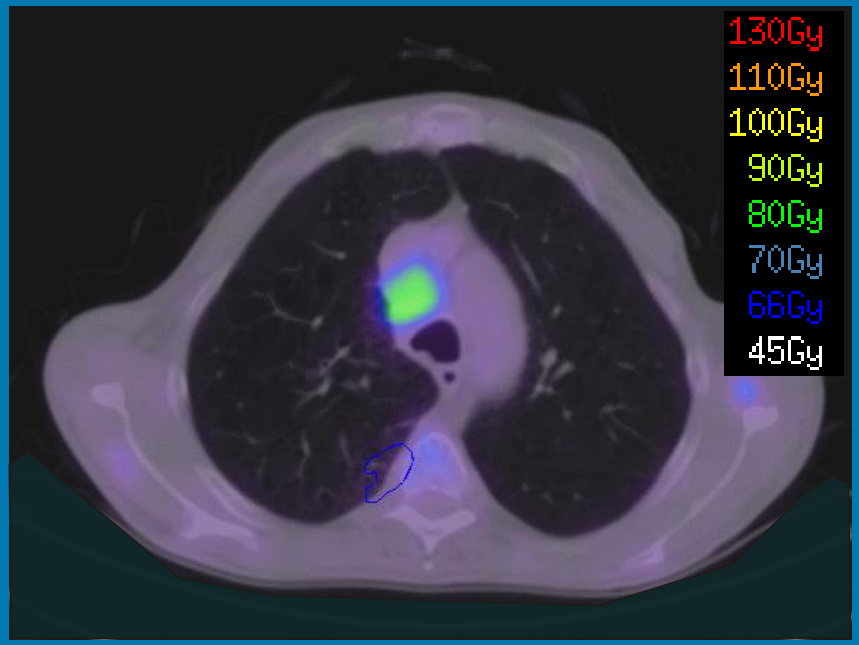
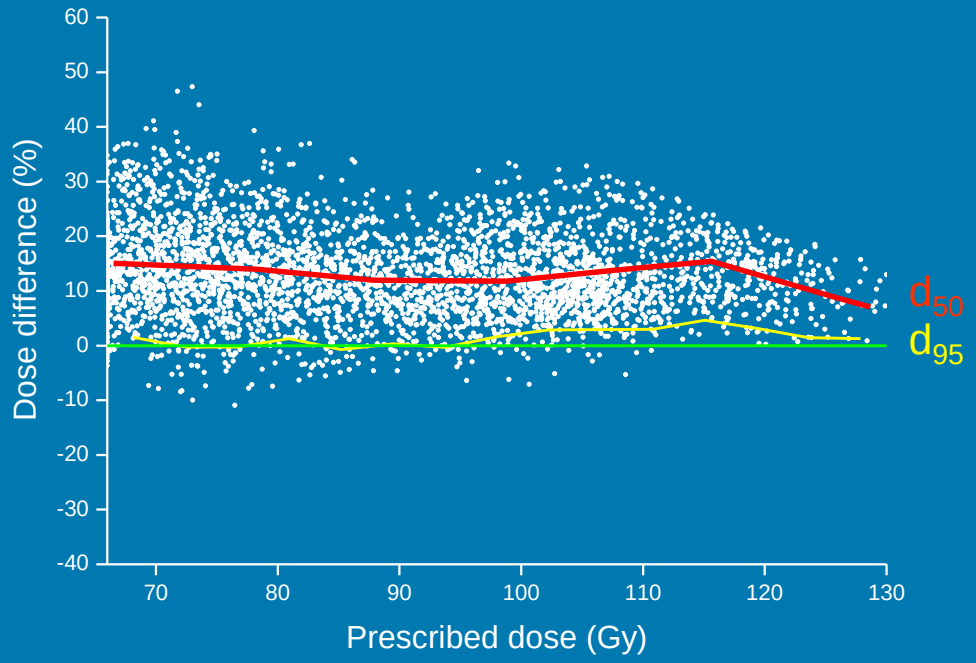
Treatment plan evaluation





7 beams 60 segments

biological gradients match the dose gradients reasonably well

Zwanenburg *et al.* ICCR 2010

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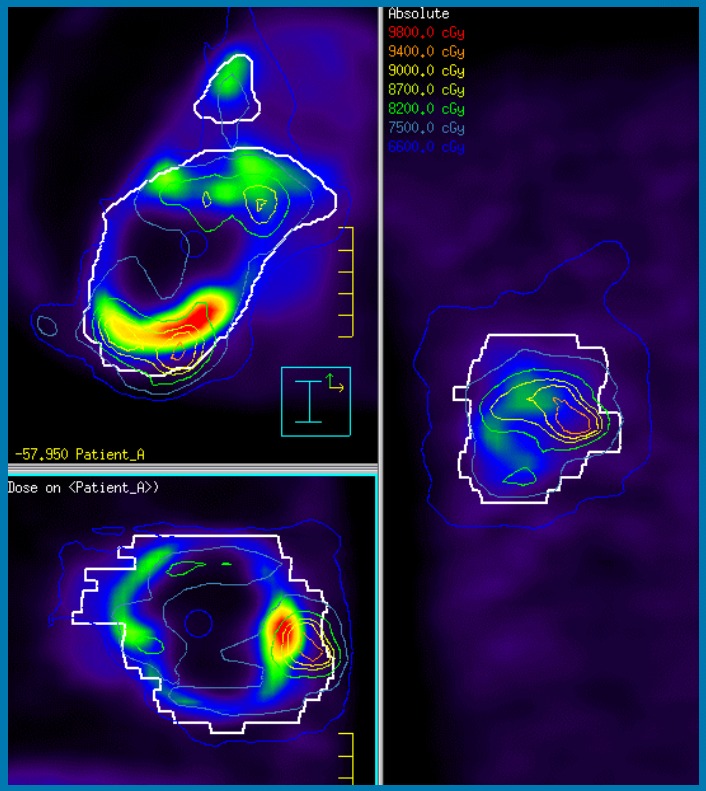
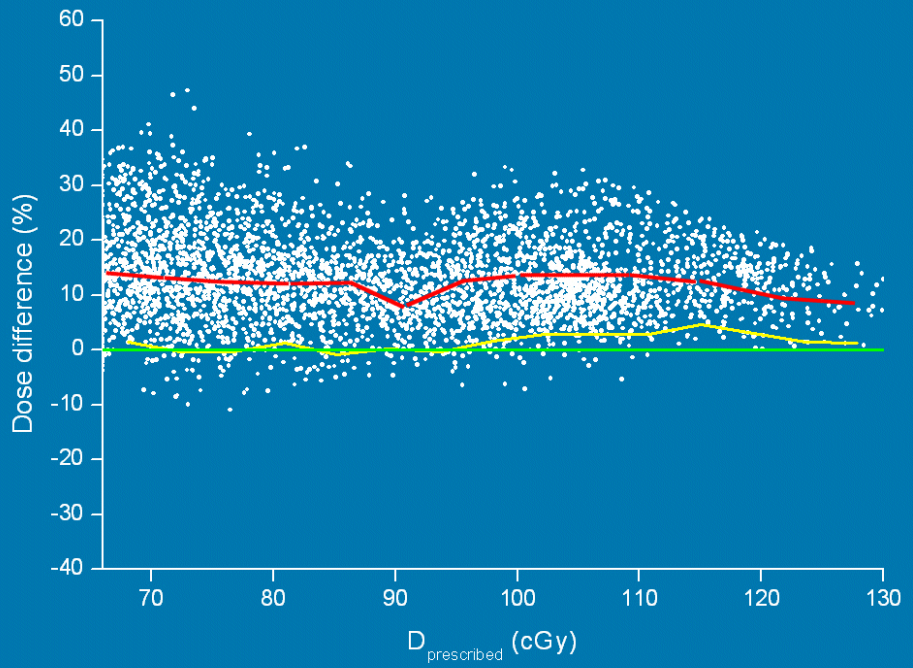
Treatment plan evaluation





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Conclusions

- dose painting is feasible
  - highly conformal delivery technique
  - functional imaging (robust in time and geometry)
  - a sensible relationship between image intensity and high-risk tumor characteristics

- clinical results of large multicenter trials are to be awaited

Rigid and deformable registration

Marcel van Herk

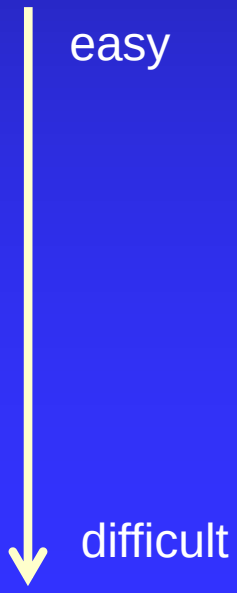
on behalf of the imaging group

Institute of Cancer Sciences,
University of Manchester / The Christie

With slides from:
Netherlands Cancer Institute
Academic Medical Center

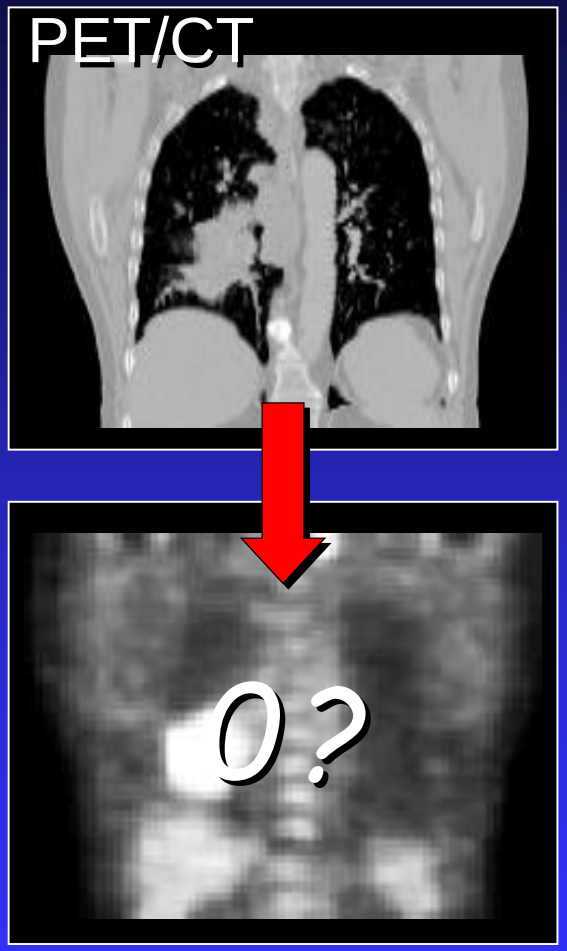
Image registration

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

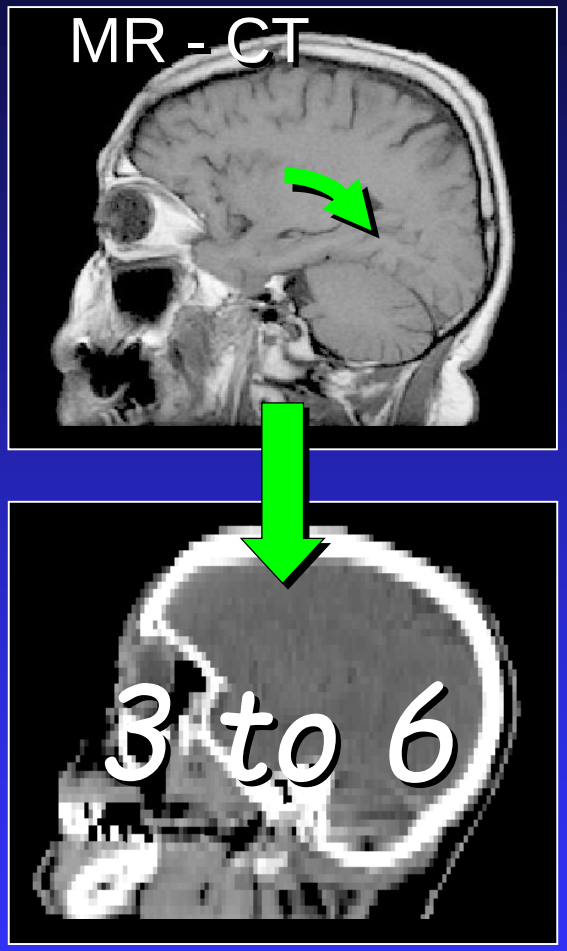


Marc Kessler / UM

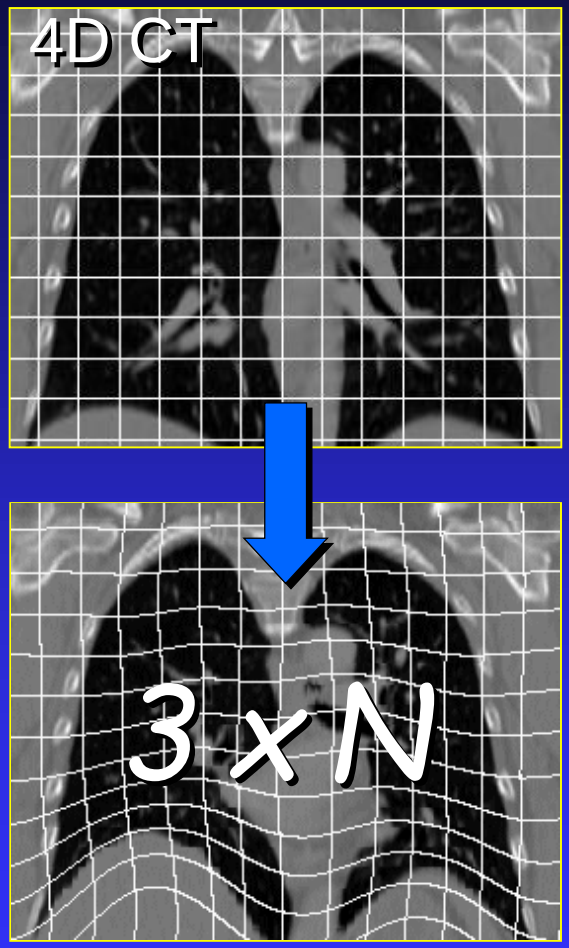
Degrees of Freedom



None ?



Few

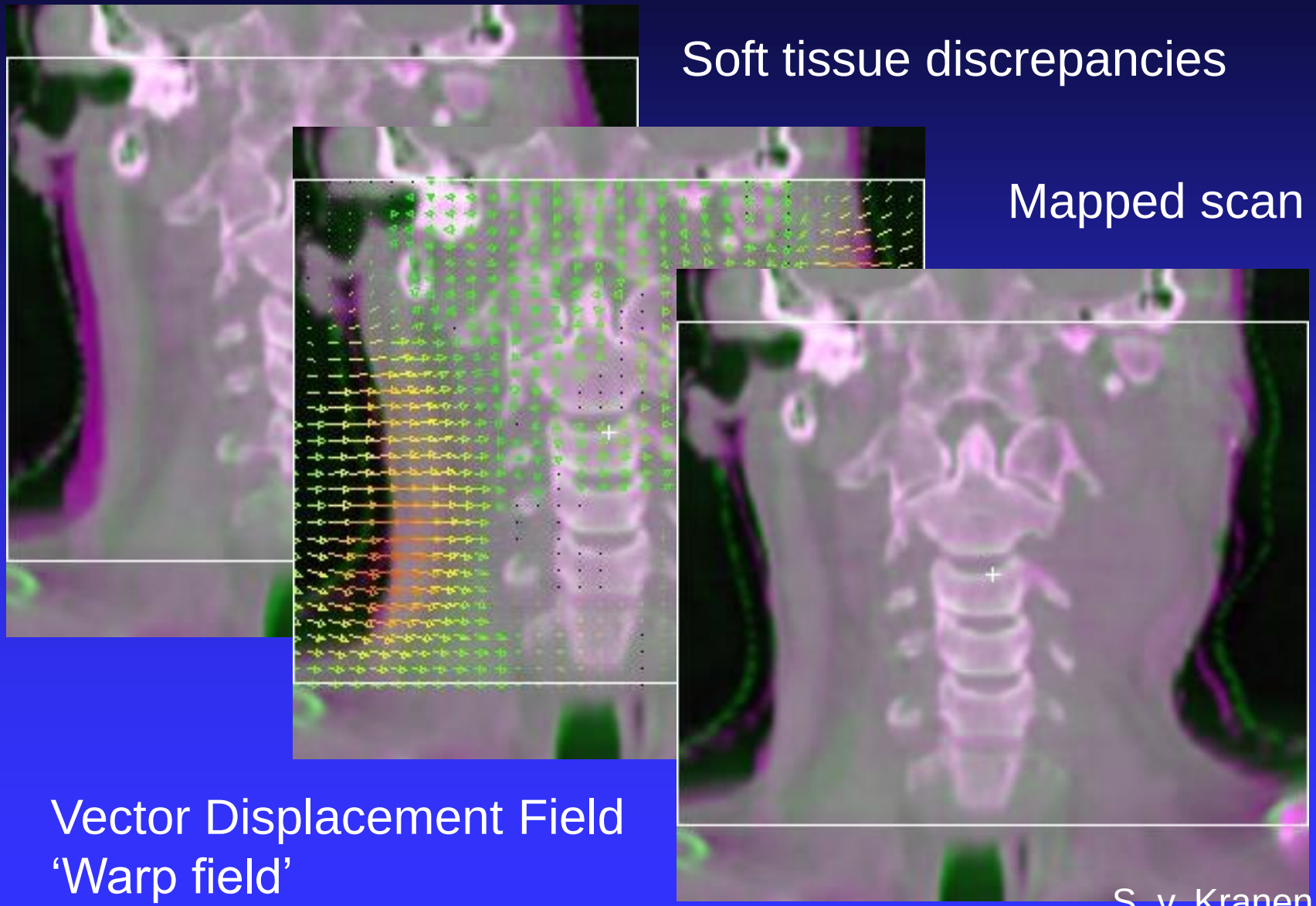


Many

By enforcing smoothness the optimization becomes tractable

Demo rigid registration

Deformation vector fields



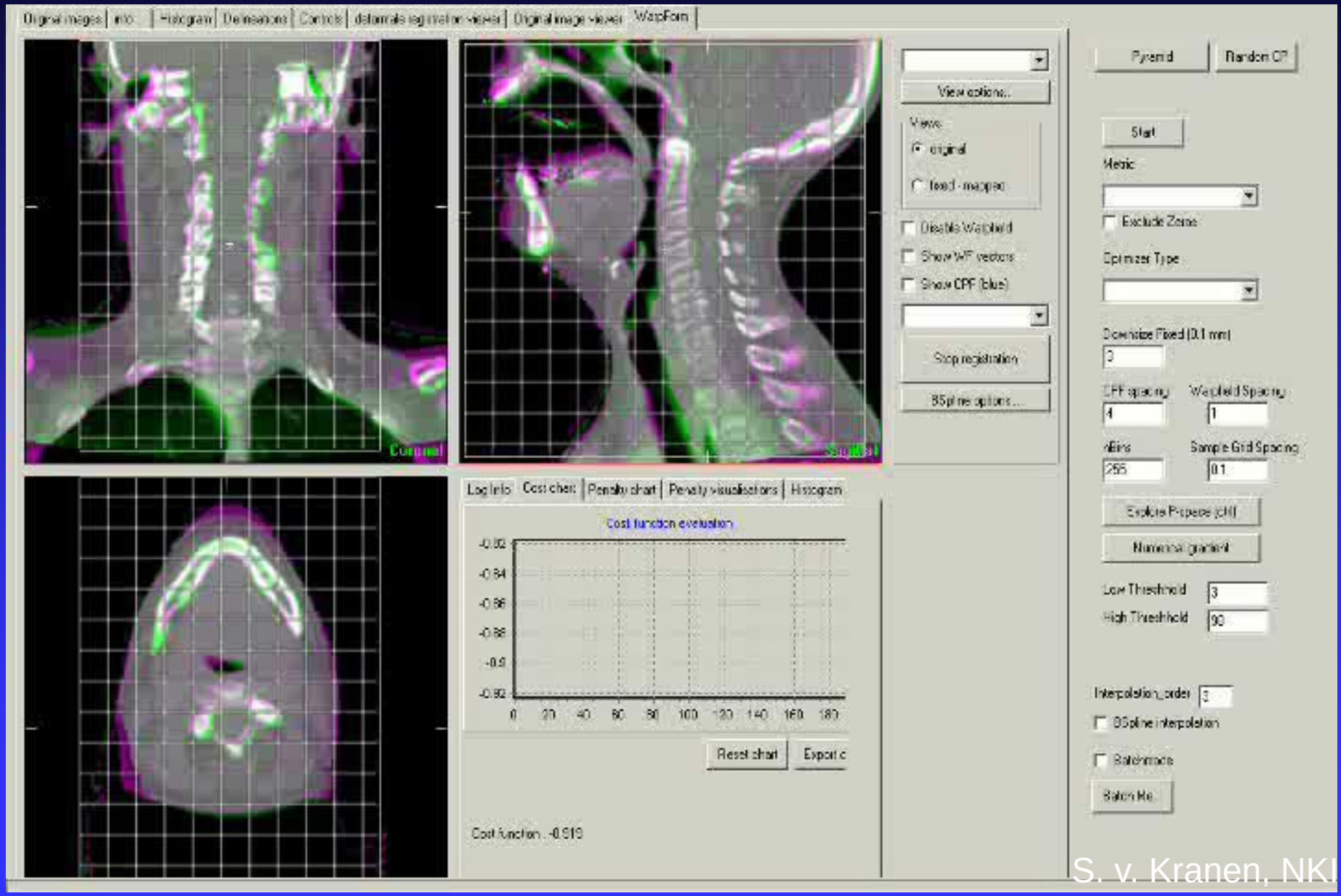
Soft tissue discrepancies

Mapped scan

Vector Displacement Field
‘Warp field’

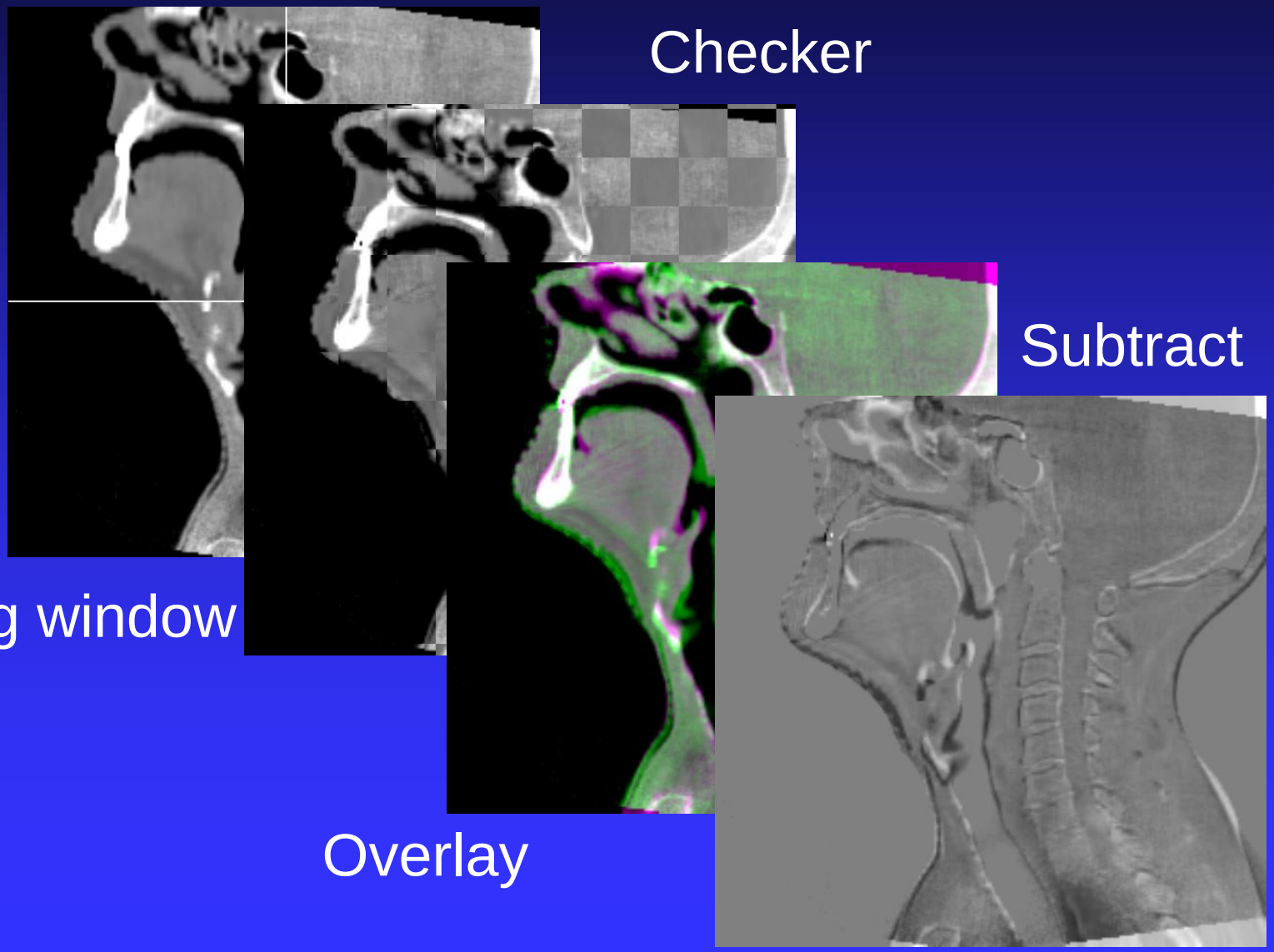
S. v. Kranen, NKI

Deformable registration example

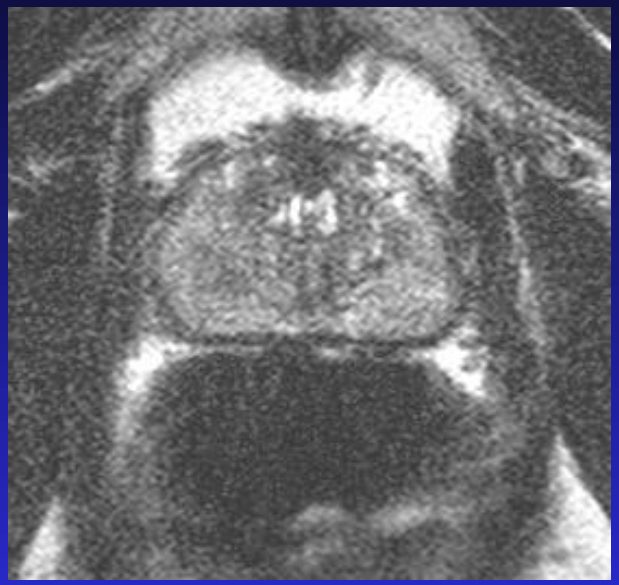


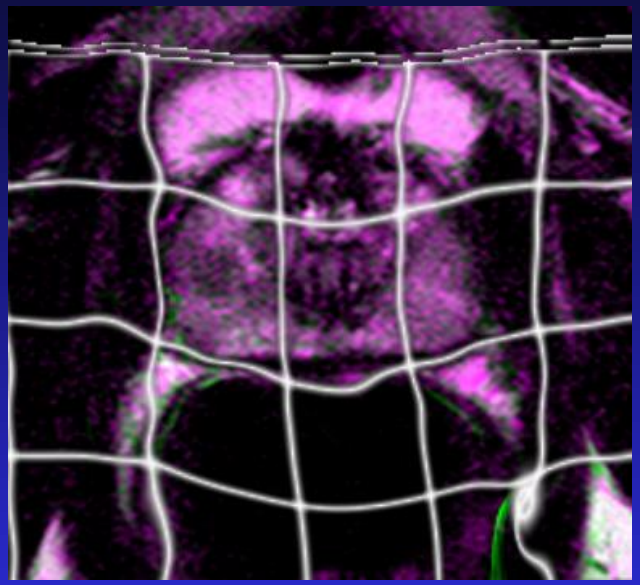
S. v. Kranen, NKI

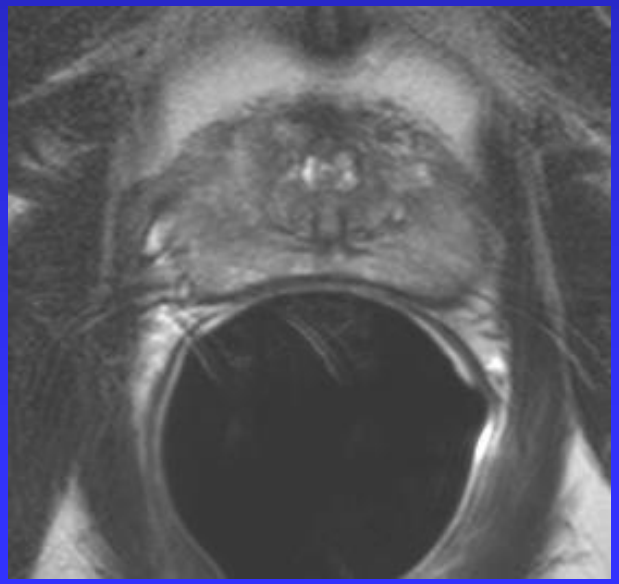
Visual verification

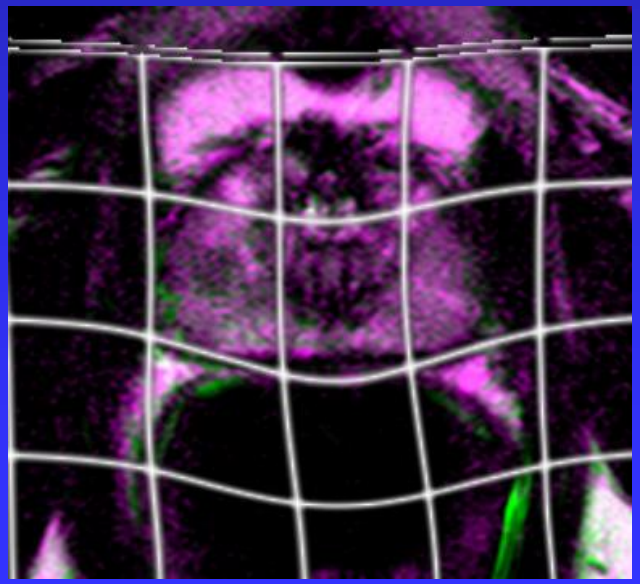


Prostate MRI w/wo Endo Rectal Coil









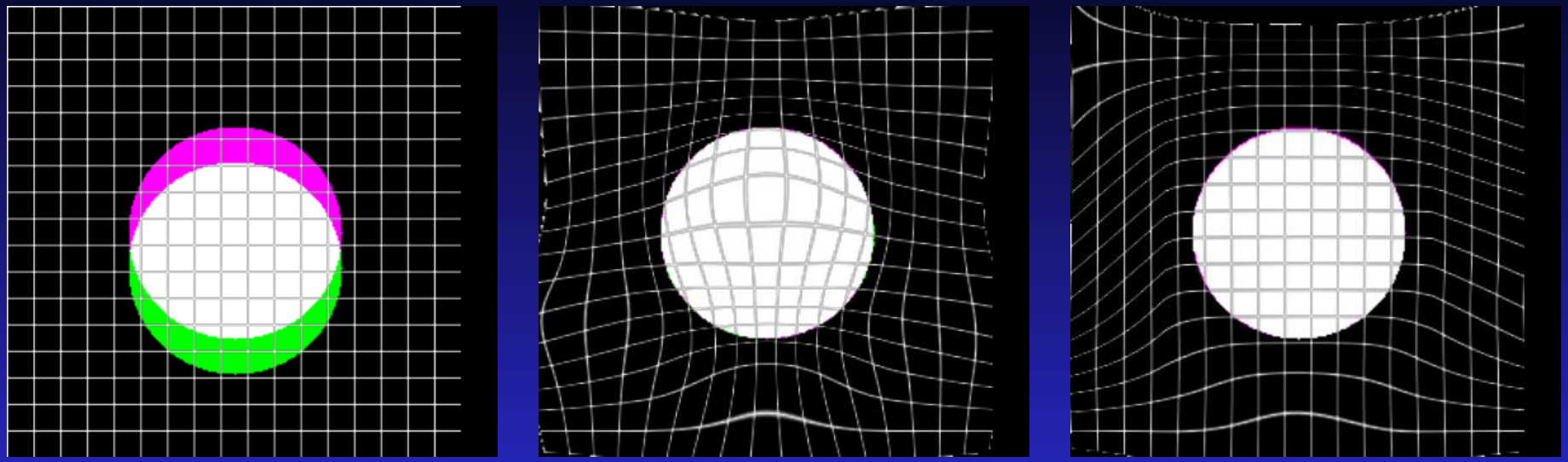
Large effect of parameters on deformable registration

Both solutions are visually correct

Which answer is right?

S van Kranen,
C Kamerling, NKI

Deformable registration classes



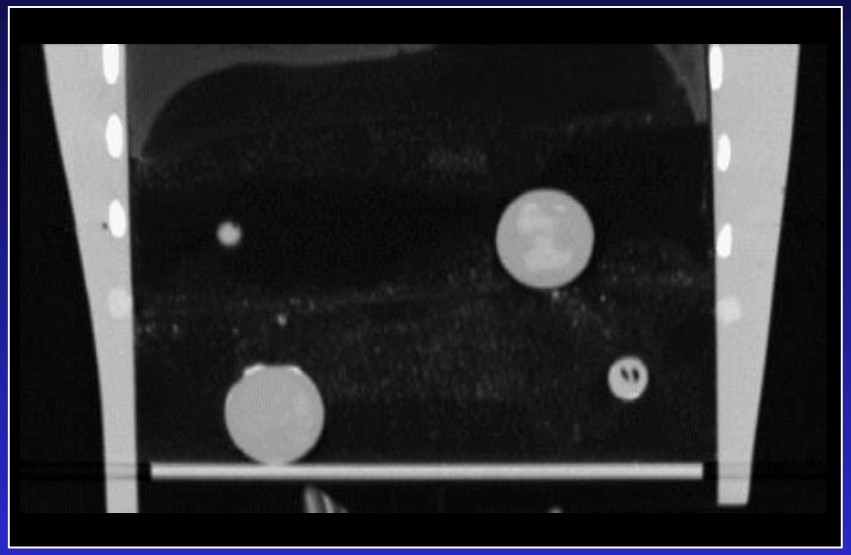
Different DVF provide same visual registration result

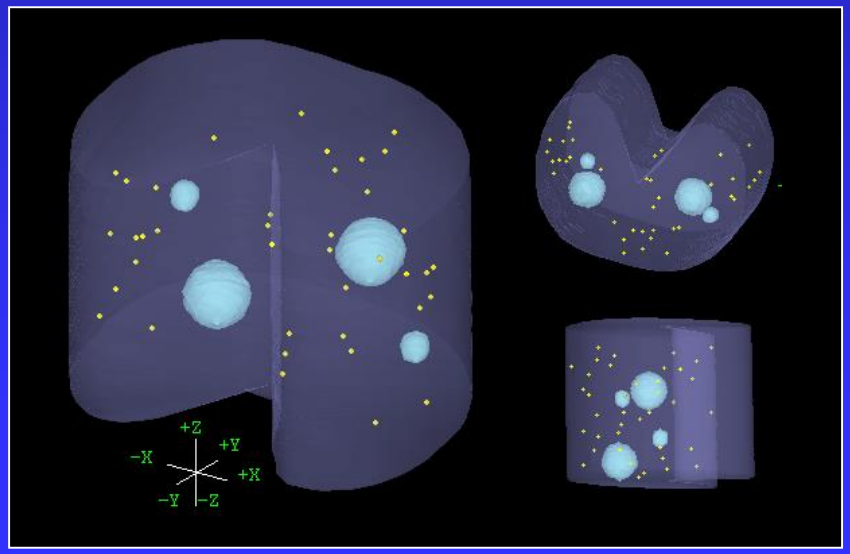
- Descriptive: it must look good
  - e.g. contour propagation
- Quantitative: it must be an anatomically correct, also inside and at surface of homogeneous organ
  - e.g. dose accumulation

QA methods

- The algorithm works technically
  - Use phantom or simulated data
- The program works in general
  - Best: use patients with implanted markers (data scarce)
  - Second: compare with human observers
- The program works for this patient
  - Visual verification
  - Consistency, plausibility

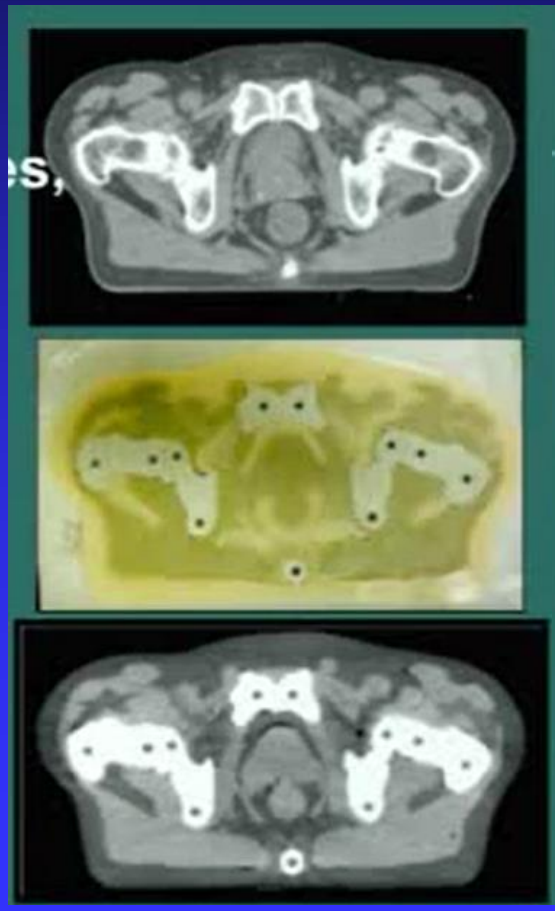
4D Phantoms





		RL[a] (cm)	AP[b] (cm)	SI[c] (cm)	3-D distance (cm)
Affine	Average	−0.01	0.00	0.05	0.38
	Stdev[d]	0.04	0.04	0.44	0.22
	Max[e]	−0.12	−0.13	0.90	0.90
B-splines	Average	−0.02	−0.01	0.05	0.18
	Stdev[d]	0.08	0.06	0.22	0.16
	Max[e]	−0.42	0.19	0.67	0.81
Thin-plate splines	Average	−0.07	−0.15	−0.14	0.37
	Stdev[d]	0.12	0.19	0.28	0.19
	Max[e]	−0.56	−0.58	−0.74	0.75

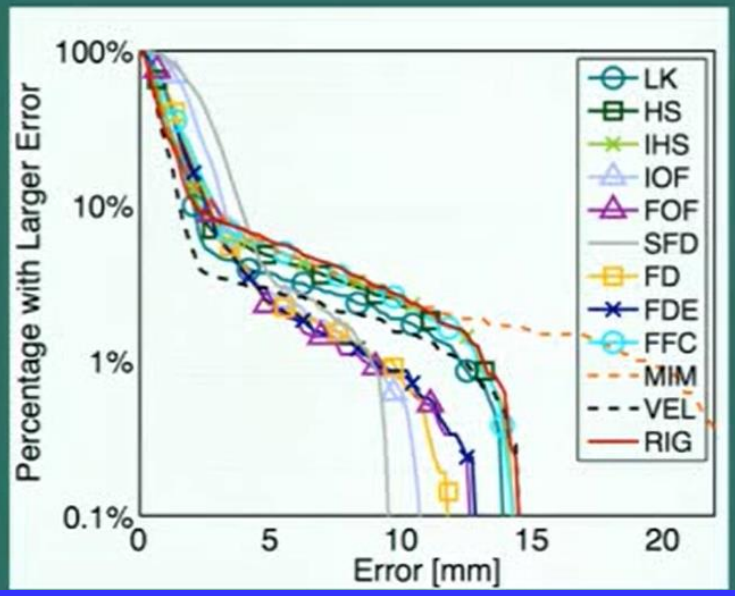
Registration of anatomically realistic phantom in pelvis



UCSF University of California San Francisco

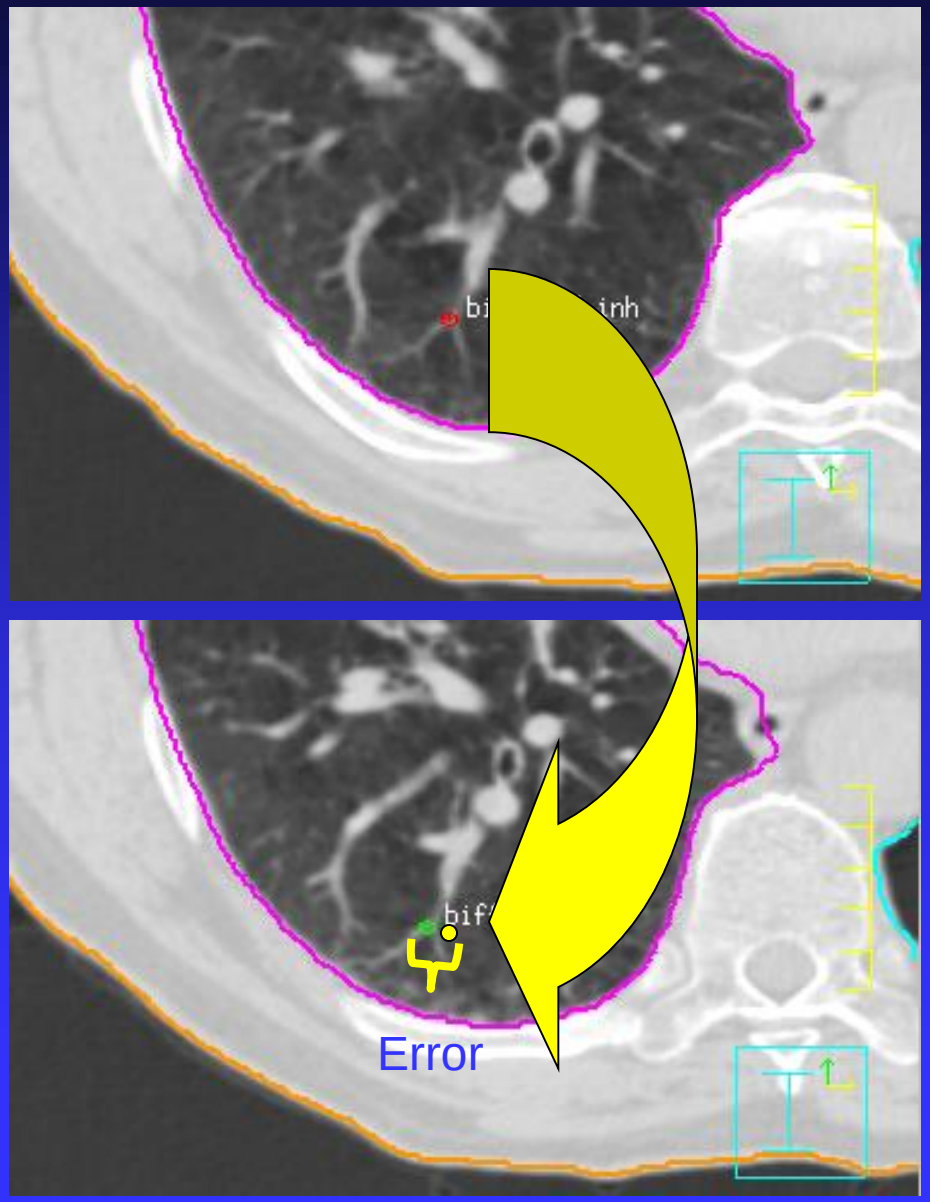
DIR Error Distribution

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

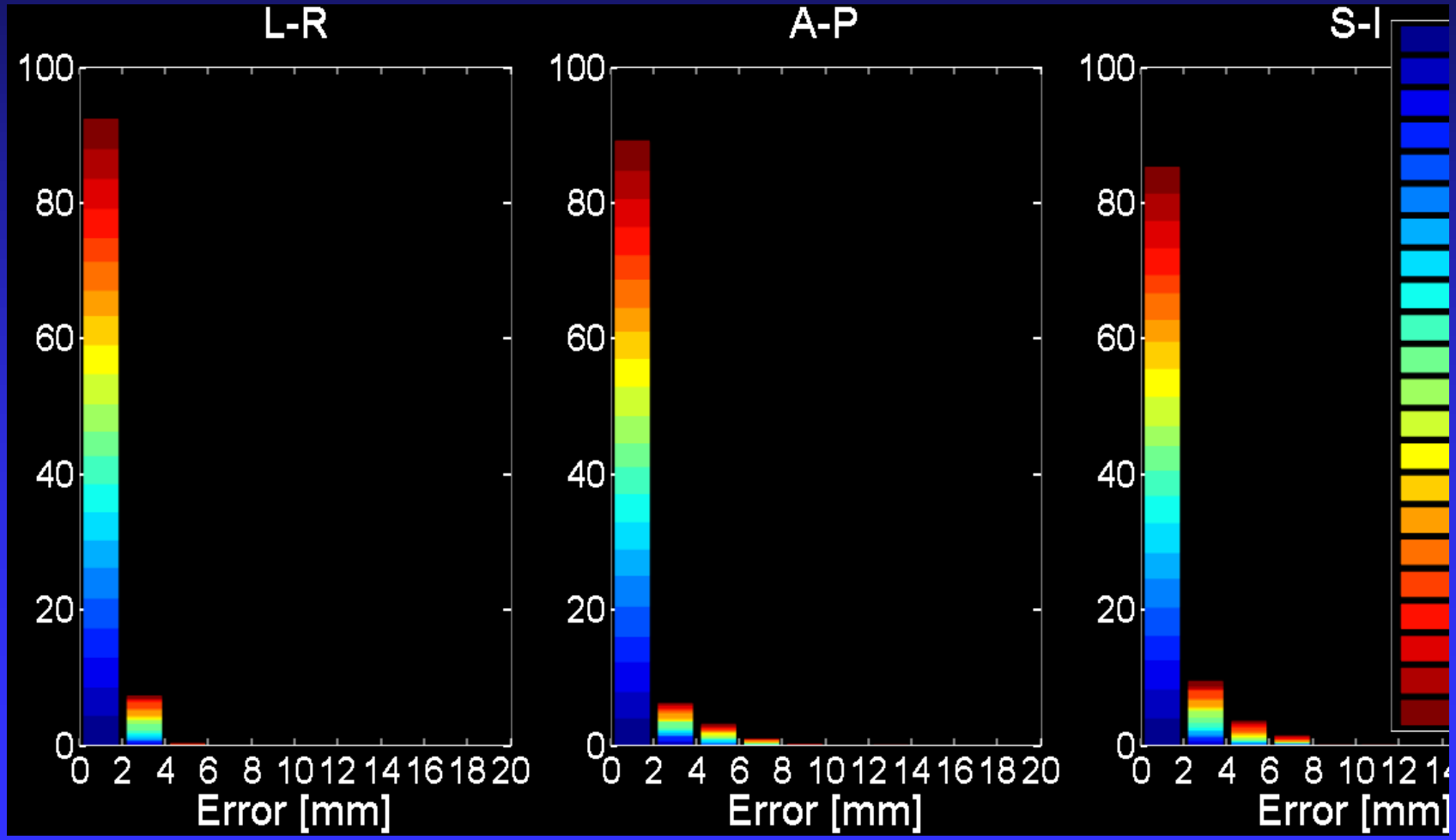


J Pouliot, UCSF

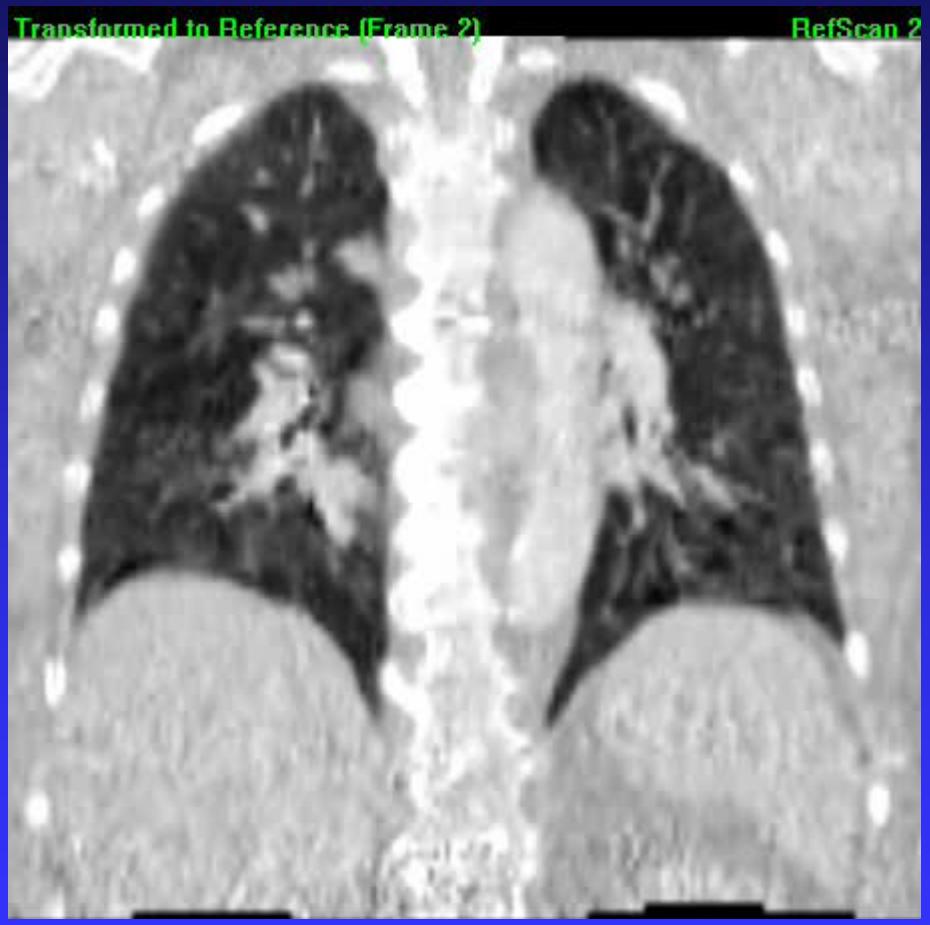
Natural Fiducials



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

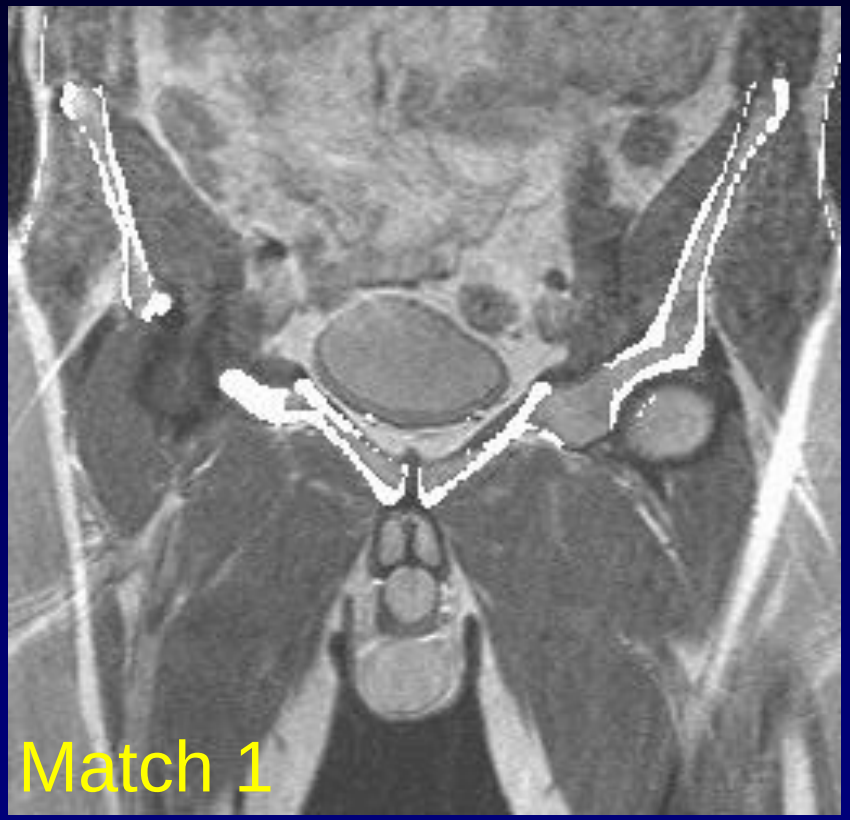


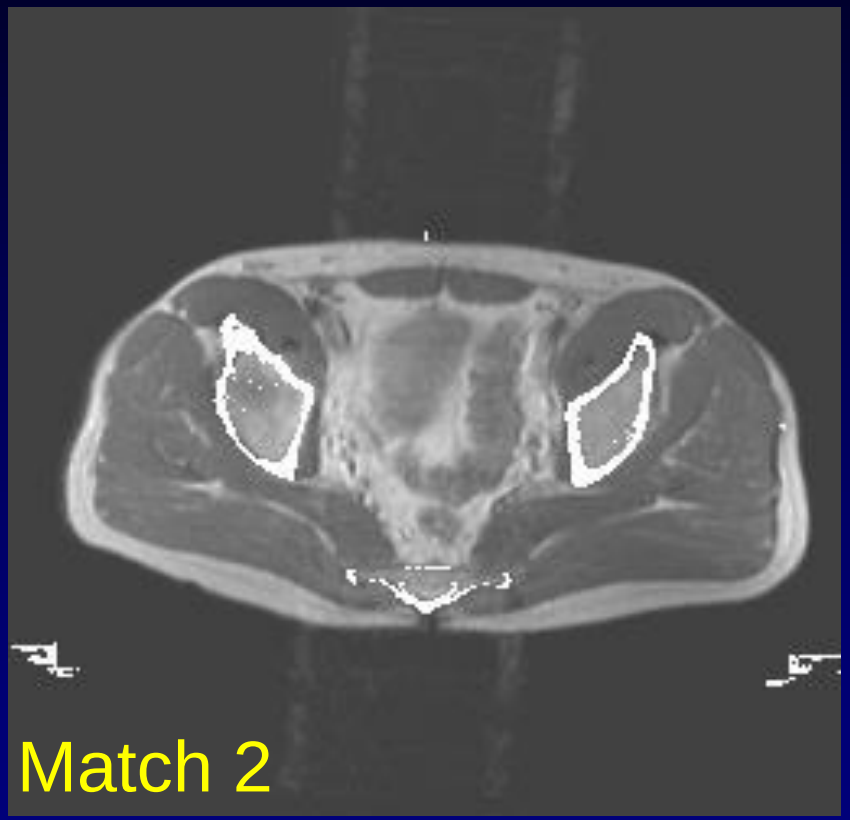
Lung deformable registration easy ?



J Wolthaus, NKI

Consistency check as QA tool



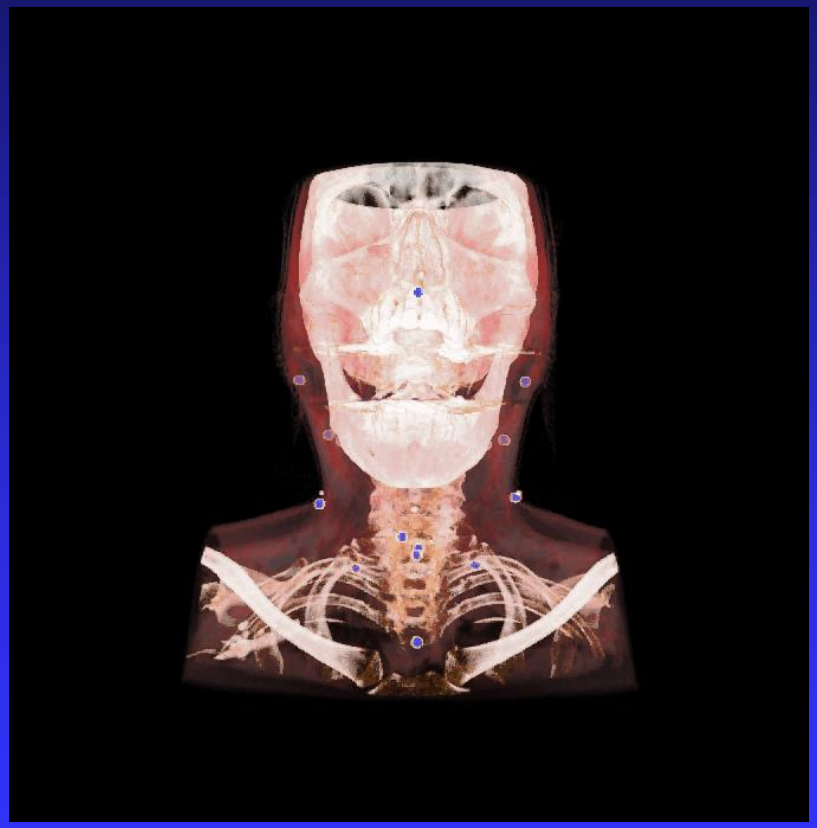


Deviation	Δ x (L-R)	Δ y (A-P)	Δ z (C-C)	Δ rx (L-R)	Δ ry (A-P)	Δ rz (C-C)
between match 1 and 2	-0.5 mm	2.0 mm	-1.6 mm	-0.9 dg	-0.8 dg	-0.7 dg

Van Herk et al, 1998

Landmark QA, analysis of variance

- Landmark validation
- 7 patients, 7 - 8 fractions
- 23 landmarks per CBCT, two human observers
- B-spline deformable registration for landmark propagation
- Use of ANOVA method to correct for observer variation



A. Mencarelli, NKI

Analysis of variance

Observer places O_1, Observer places O_2
Computer places O_3

Measure distances for many scans and landmarks

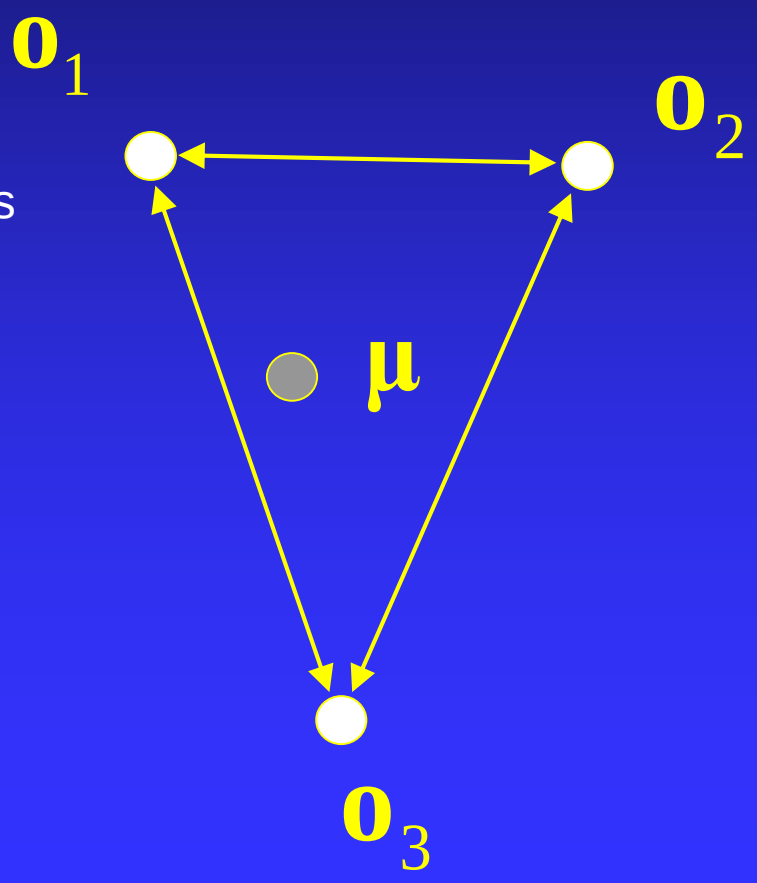
Compute standard deviations of differences

Solve for standard deviation of individual observers

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

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

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

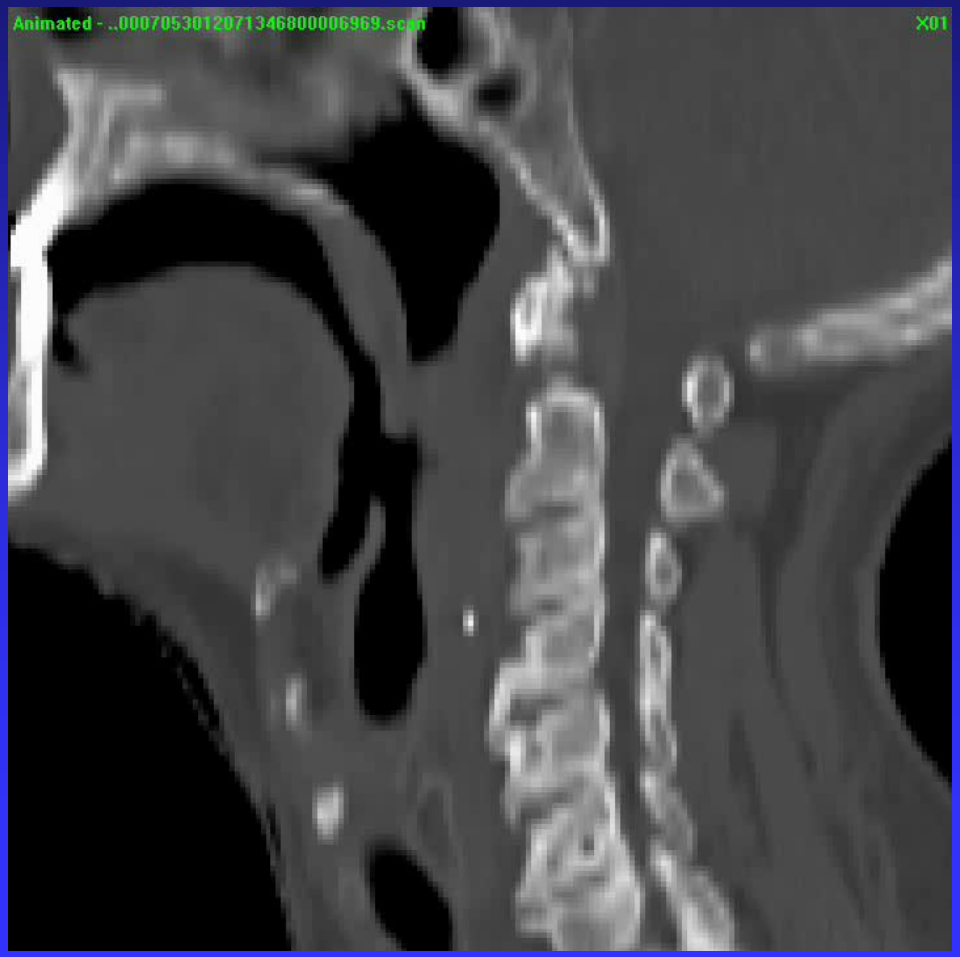


Results: head and neck CT-CBCT

Method	Accuracy (1SD mm)		
	SD_{LR}	SD_{CC}	SD_{AP}
Rigid registration	**1.8**	**2.0**	**1.7**
B-spline *No penalties*	**1.4**	**1.5**	**1.1**
B-spline + *penalties*	**0.9**	**1.0**	**0.9**

A. Mencarelli, NKI

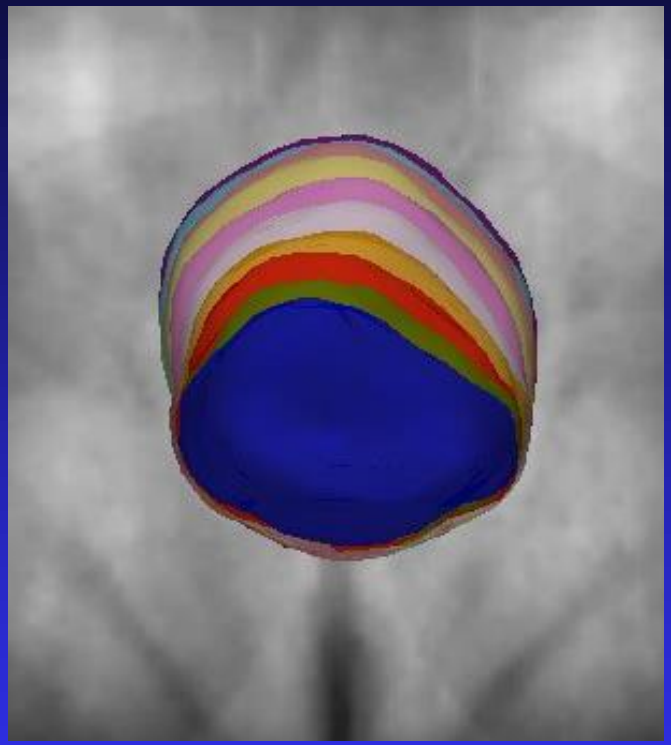
Can you see all anatomical changes ?

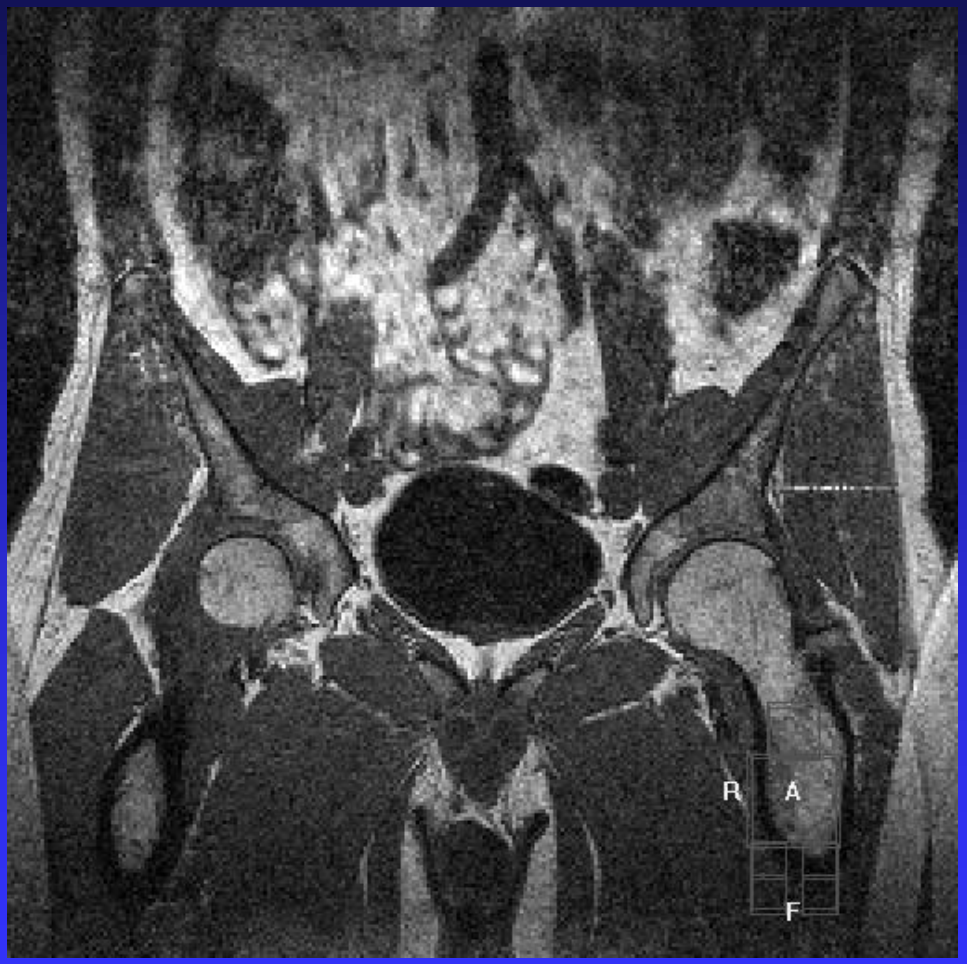


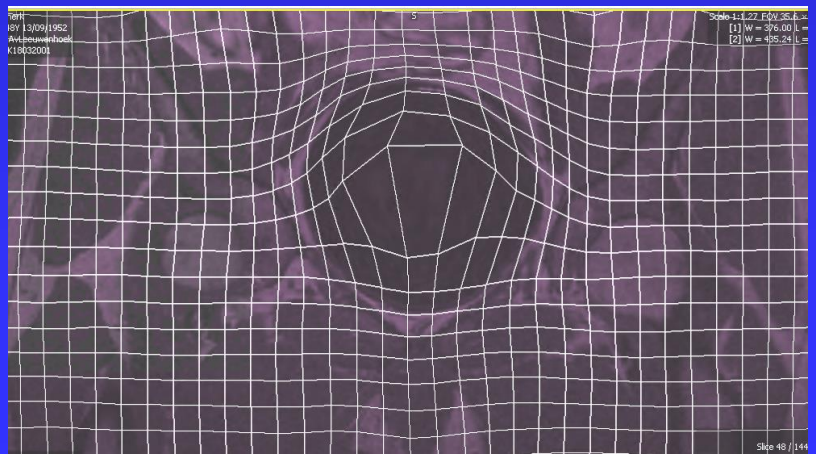
Deformable registration will not pick up motion parallel to interfaces

O Hamming, NKI

Easy deformable registration of the bladder?

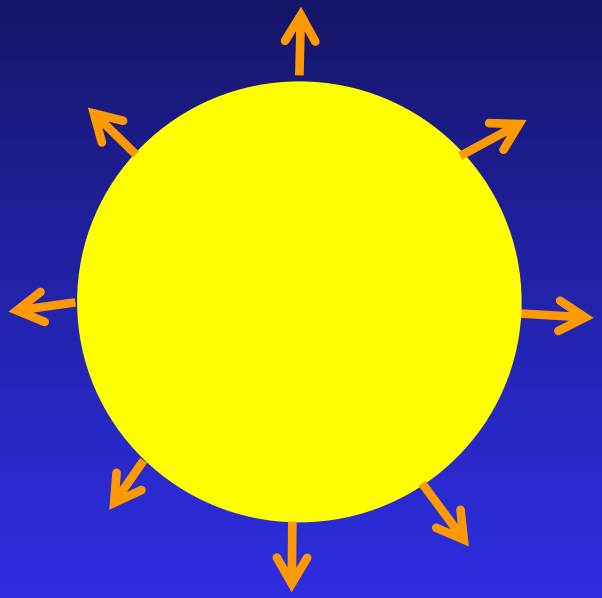


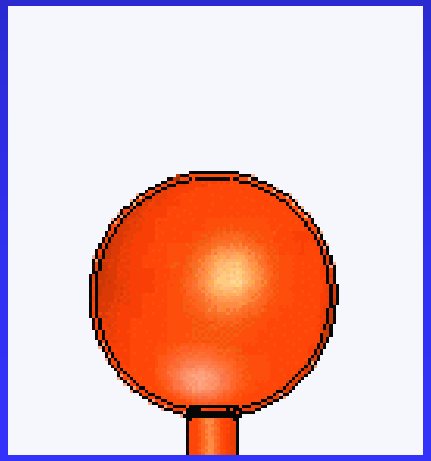


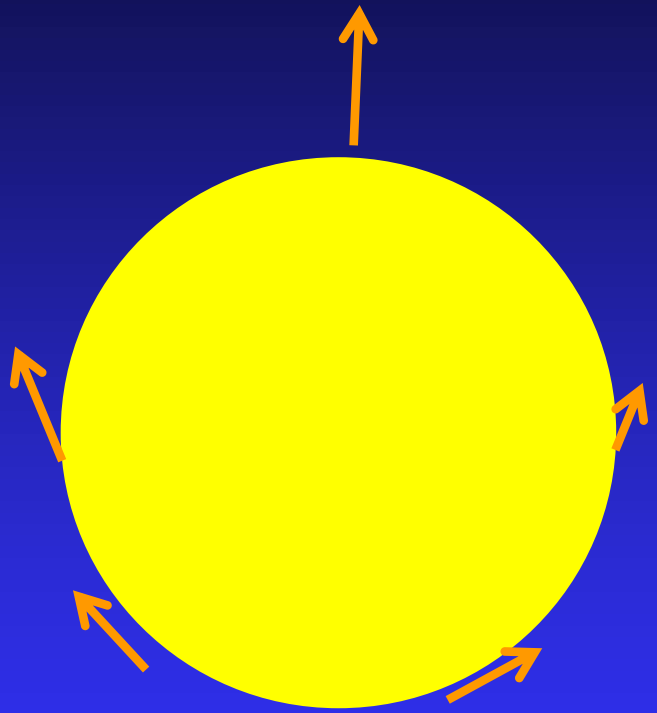


Very high contrast but does software ‘understand’ the anatomy ?

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

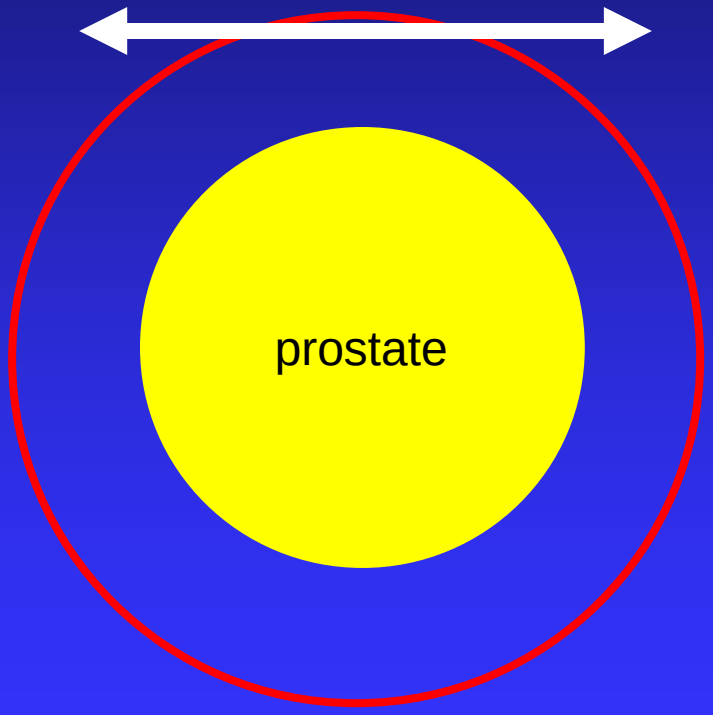




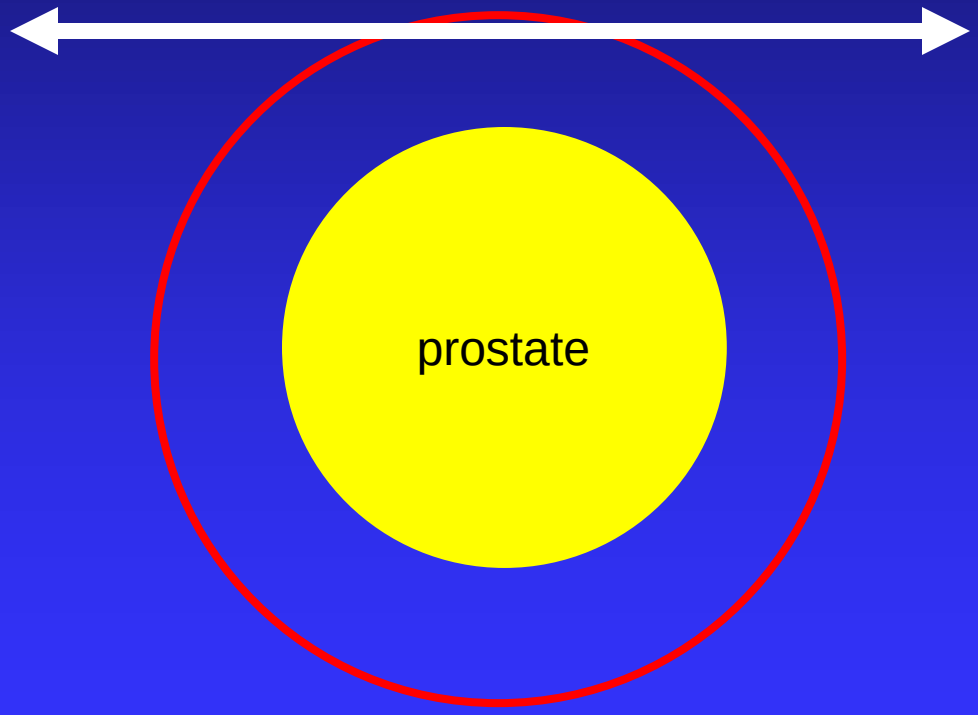


You get the contours right, but not the tissue cells → danger for dose accumulation

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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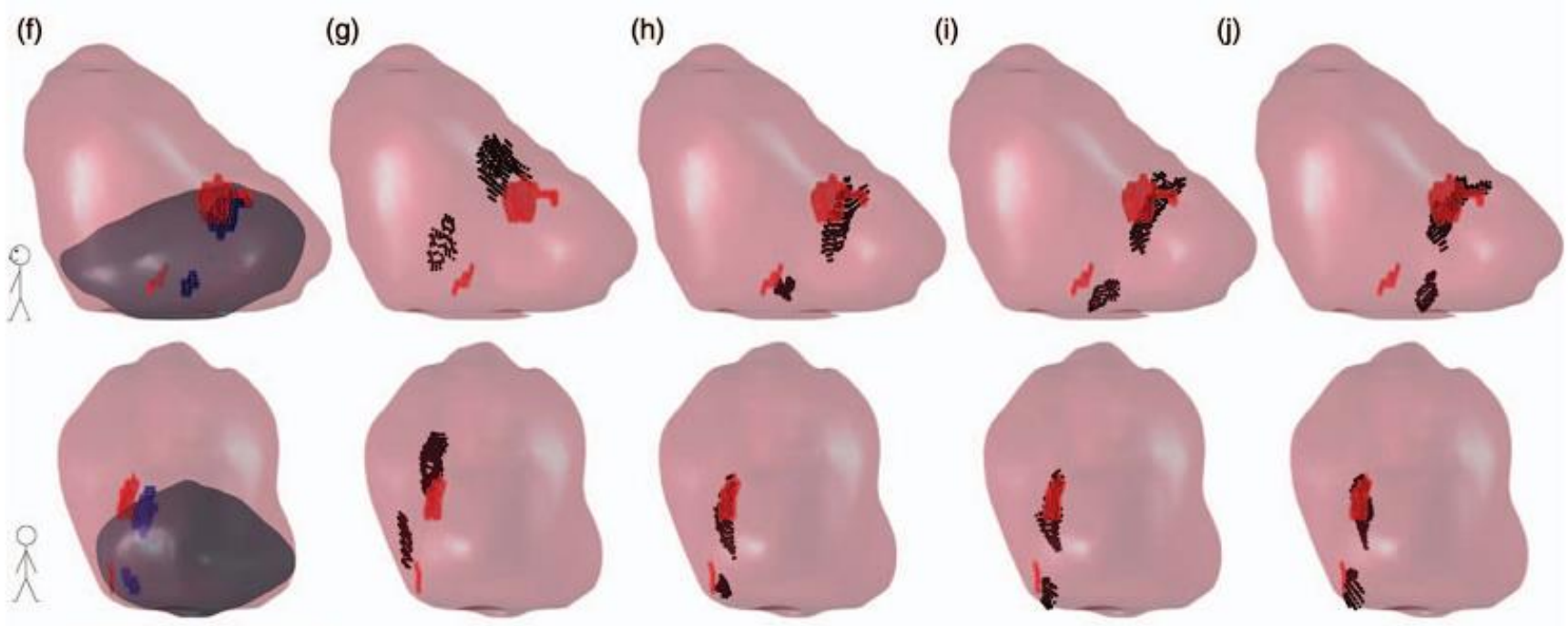
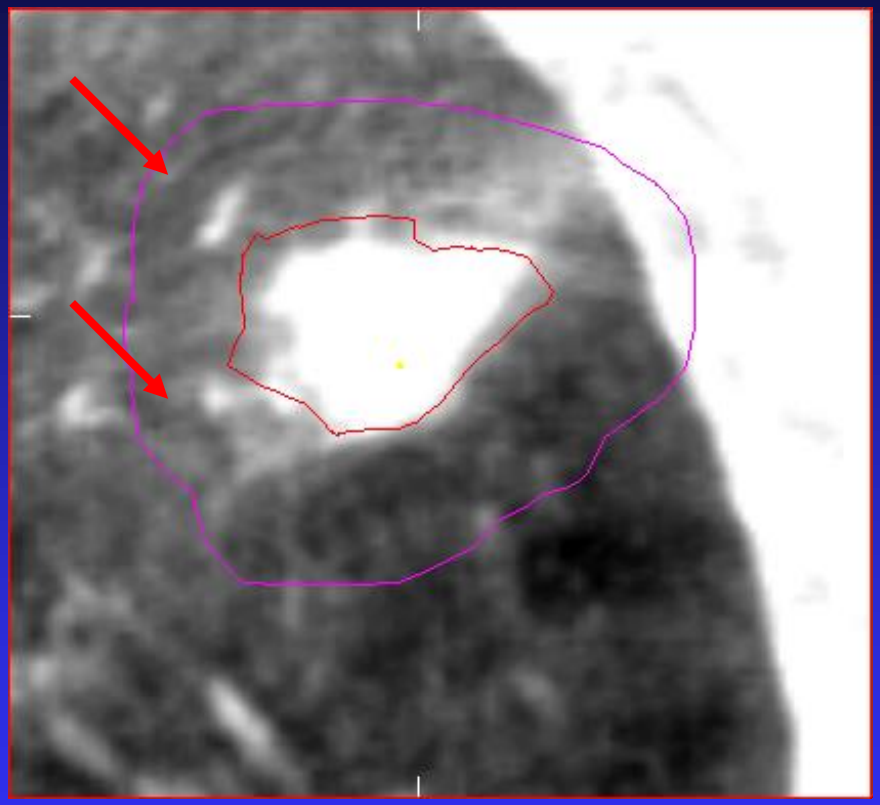


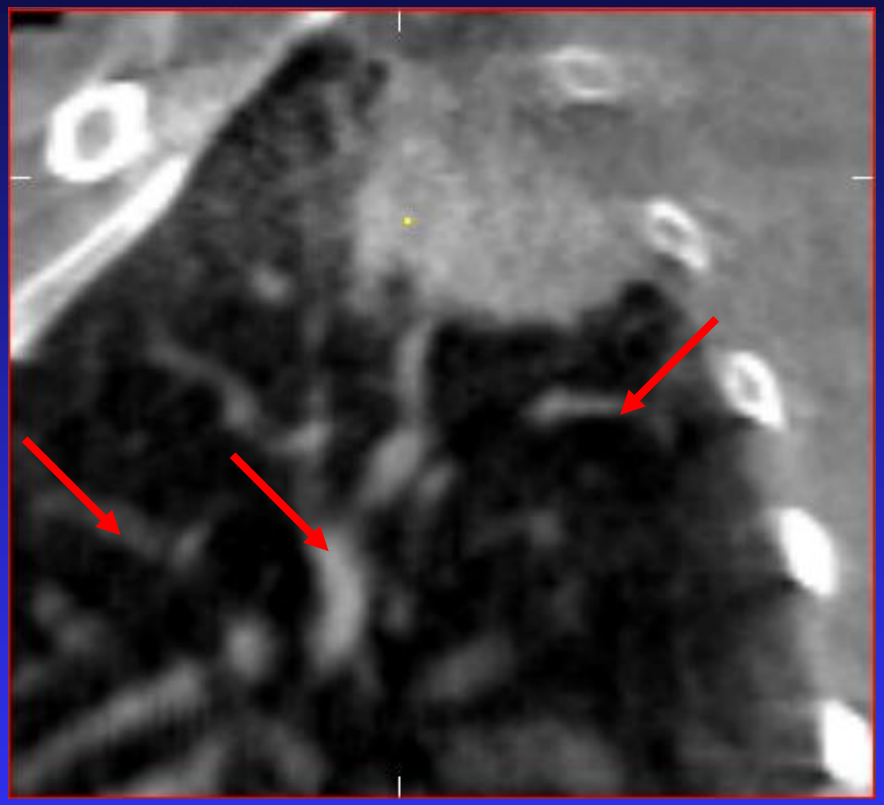
RDE lipiodol (mm)

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

Use of deformable registration for data mining

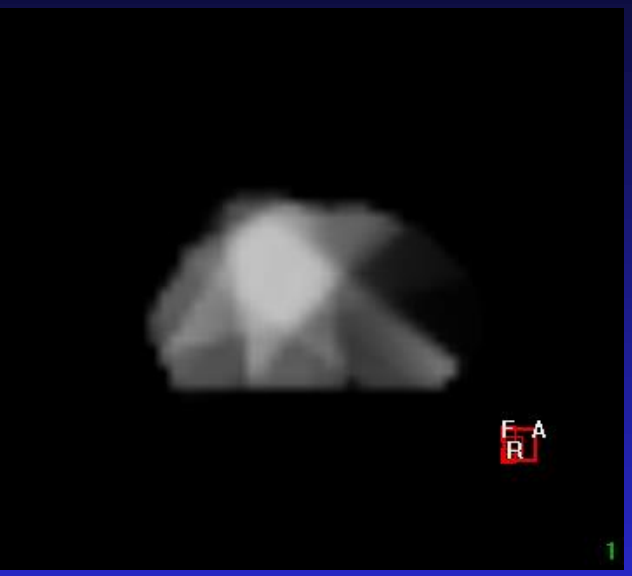
- Map all patients to reference scan
- Split patients according to outcome
- Average dose for
  - Dead @ 12 months
  - Alive @ 12 months
- Is there a difference ?

The Christie treats loads of patients

- **1101 patients**
  - NSCLC
  - Curative intent
  - 55Gy 20 fractions

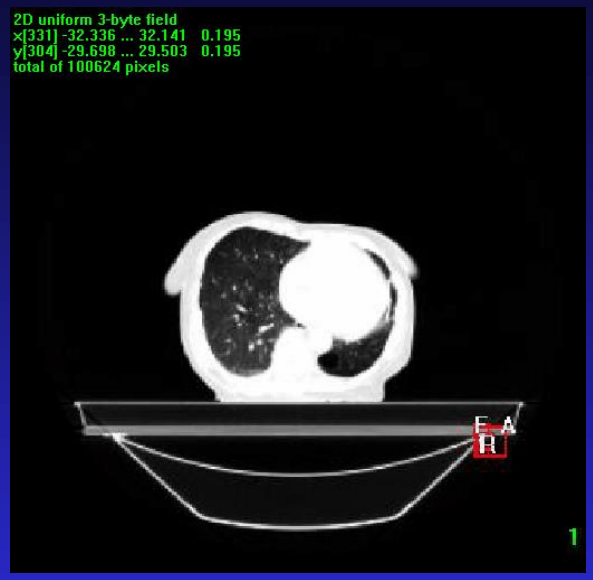
Variable	Sub-variable	Sub-total	Total in group
Gender	Male	593	1101
	Female	508	
Age (median)		73 (38-95)	
Smoking history	Current Ex-smoker	153 197	359
	Life-long non smoker	8	
T Stage	T1	159	1000
	T2	434	
	T3	238	
	T4	169	
N stage	N0	546	1006
	N1	137	
	N2	257	
	N3	66	
M stage	M0	1018	1068
	M1	50	
Induction chemo	Yes No	266 835	1101

Is dose related to 12M survival ?



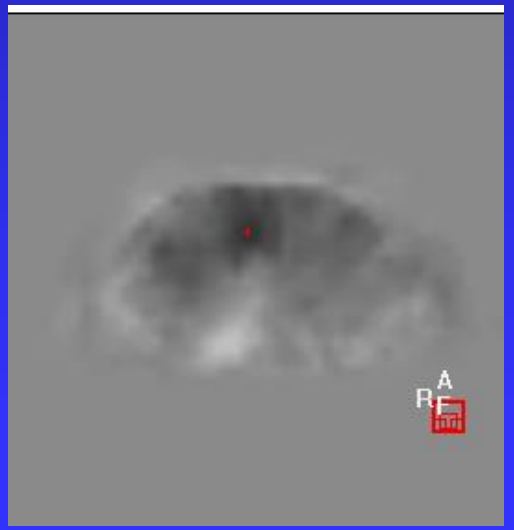
Alive

Dead



Registered CT

Average



Difference

Significance– dose difference @ 12 months

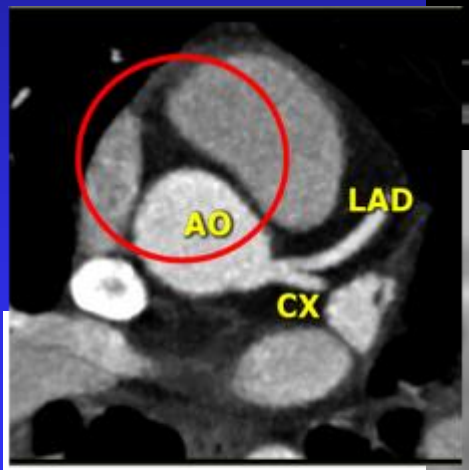
t - statistics

---- -5.7

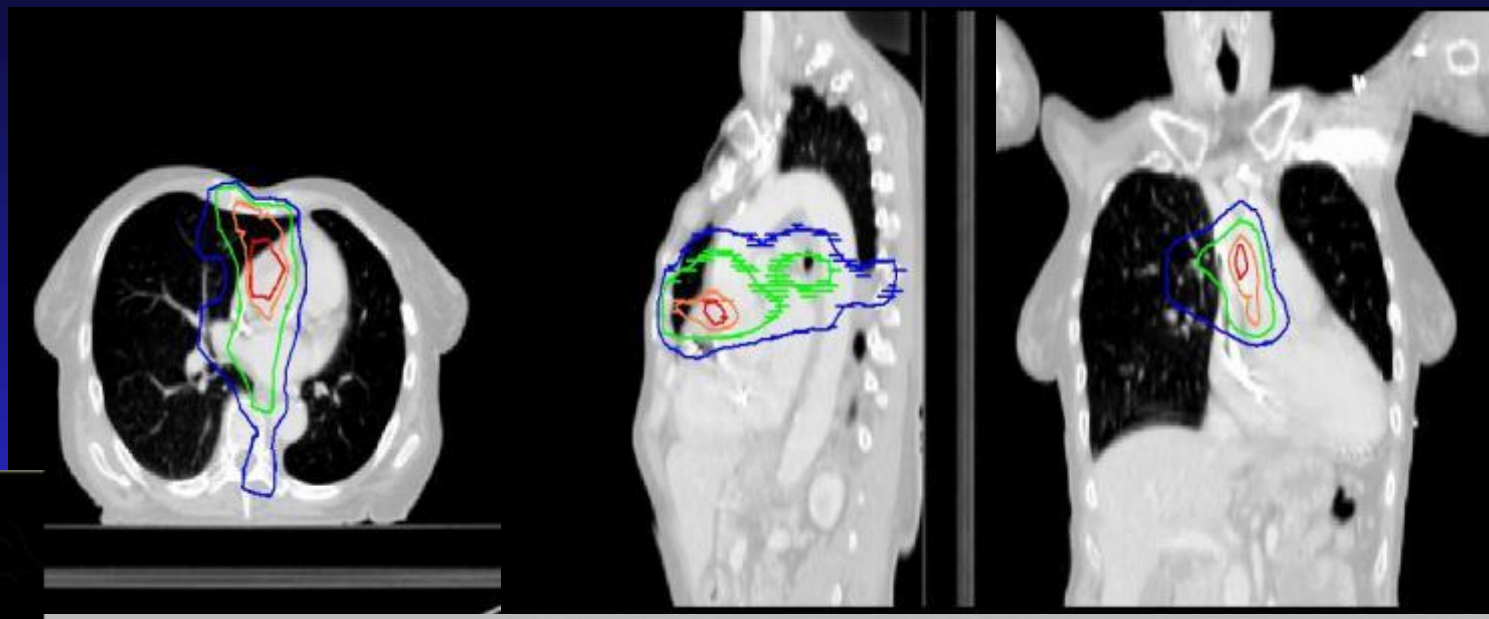
---- -5.5

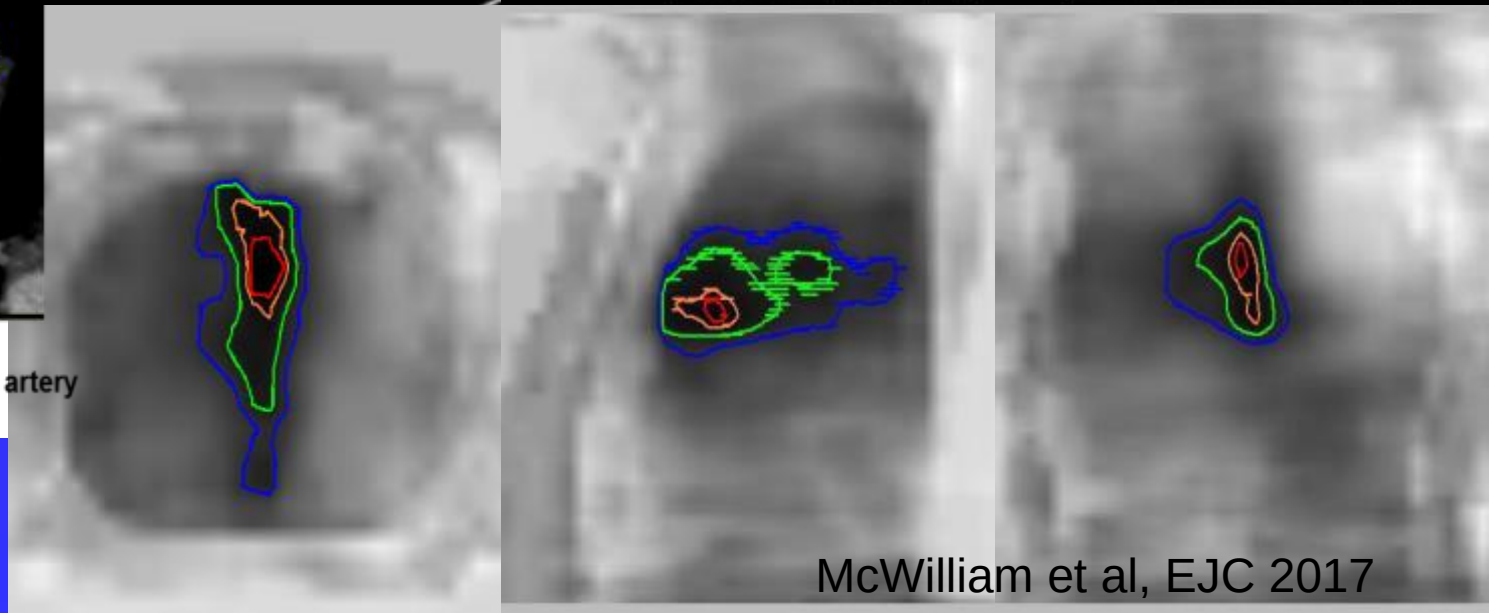
---- -5.0

---- -4.5



AO = Aorta
LAD = Left-Anterior Descending artery
CX = Circumflex artery



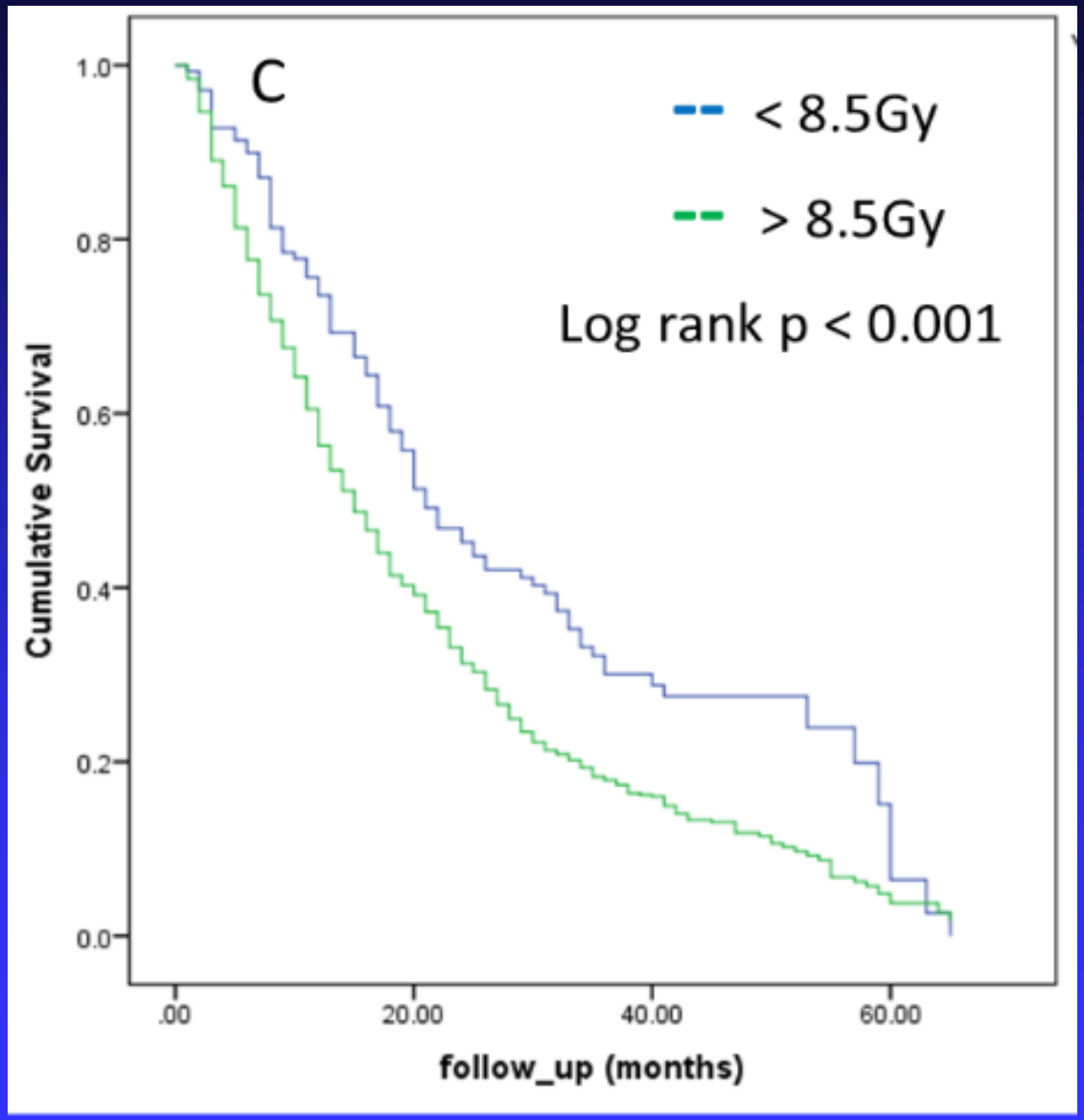


McWilliam et al, EJC 2017

MANCHESTER 1824
The University of Manchester

Cox-regression survival analysis

- **Controlling for: Age + tumour size**
- **Split on first quartile dose to region**
  - **8.5 Gy**
- **Hazard ratio between curves**
  - **~1.2**



McWilliam et al, ASTRO 2016

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 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
- Data mining gives more insight into organs at risk

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WWW.ESTRO.ORG/SCHOOL

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

Introduction to Case 4: Bilateral Oropharynx

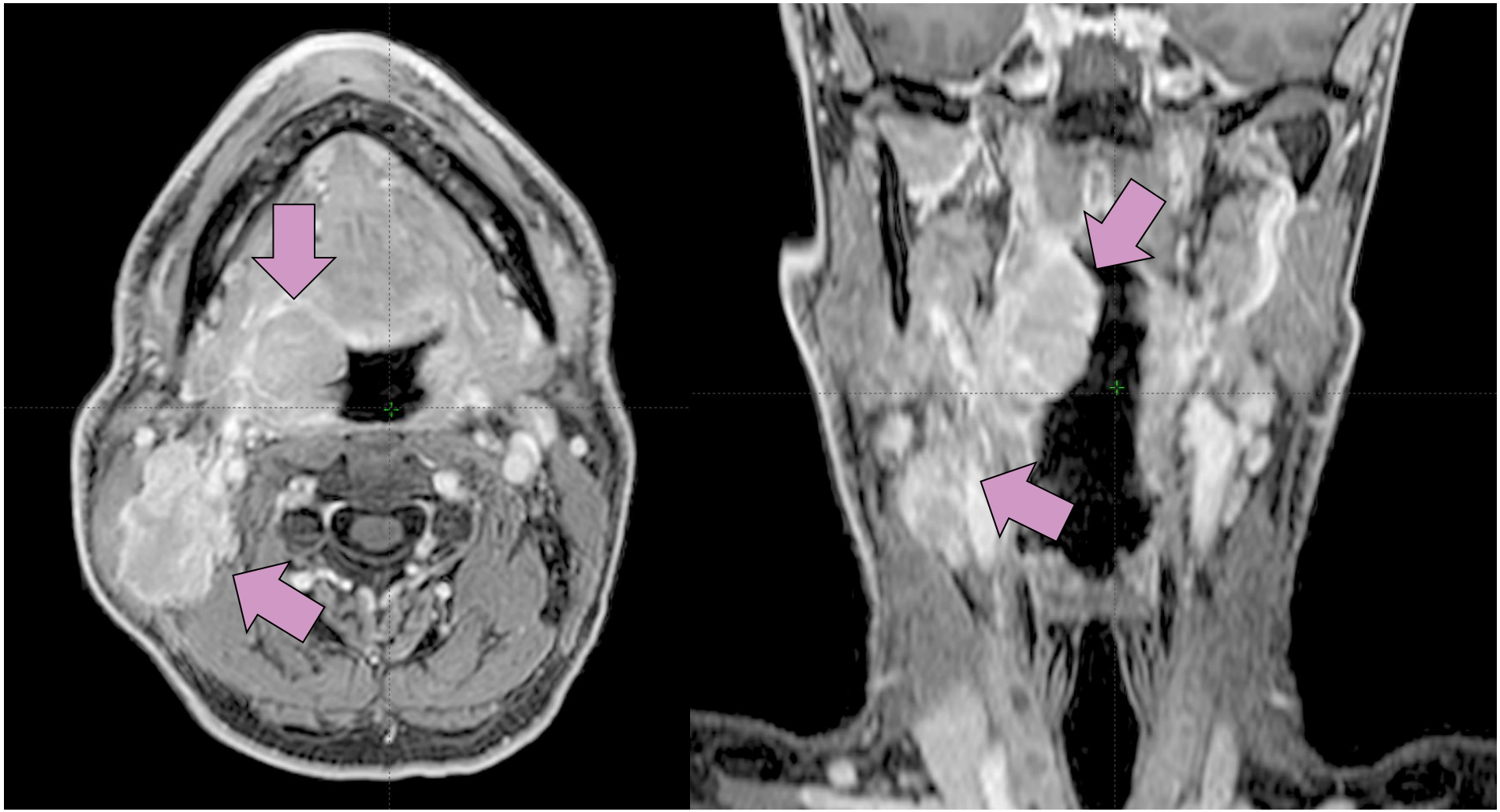
N. Dinapoli

Staging

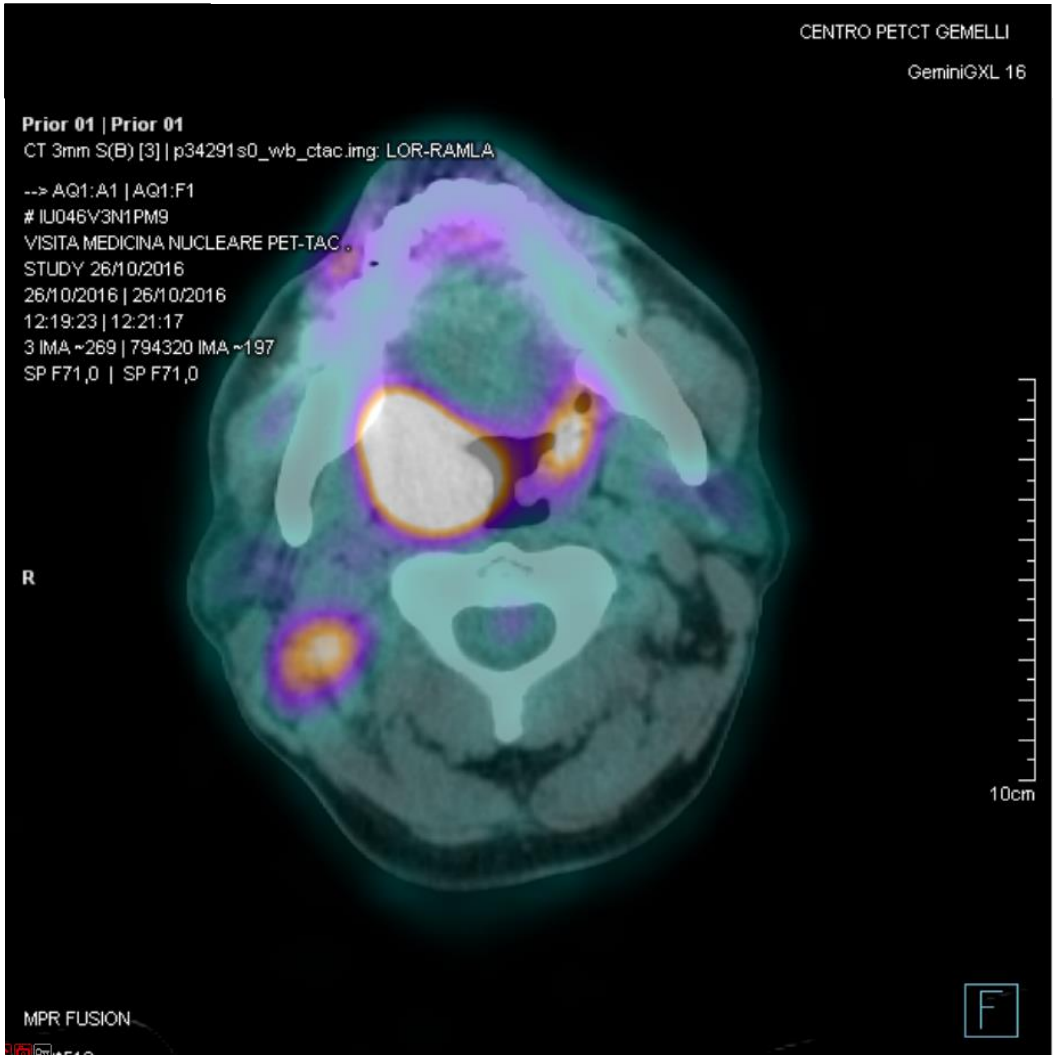
- Male patient, 56 years old
- Stage: T3 (T ≥ 4.1 cm) N3b* M0 (stage IVa)
- Primary starts from the right tonsil, spreads down to the glosso-epiglottic fold, soft palate involvement
- Positive nodes in the same side of the tumor (levels 2, 3 and 5)

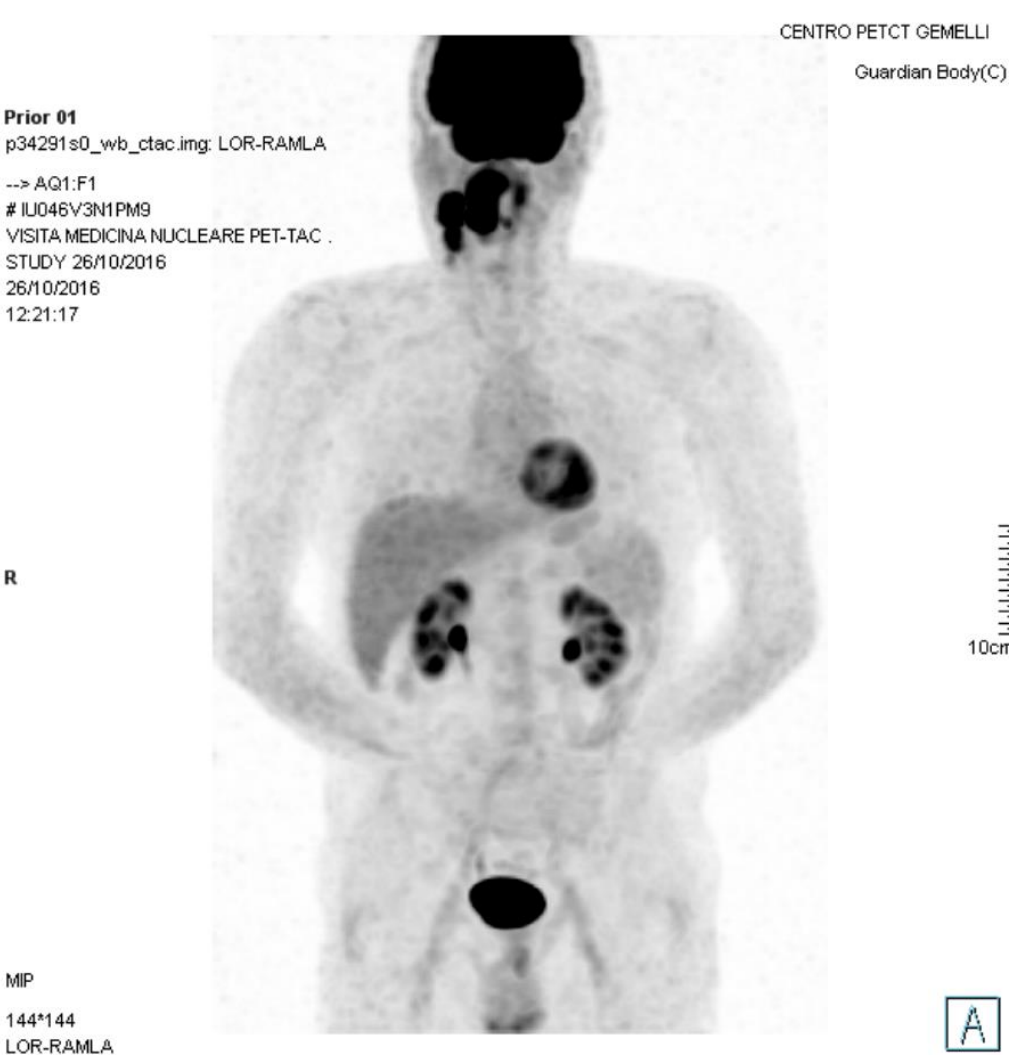
- *8th ed TNM with update for HPV positive Oropharynx tumors, in our case involvement of neck muscles

MR Staging



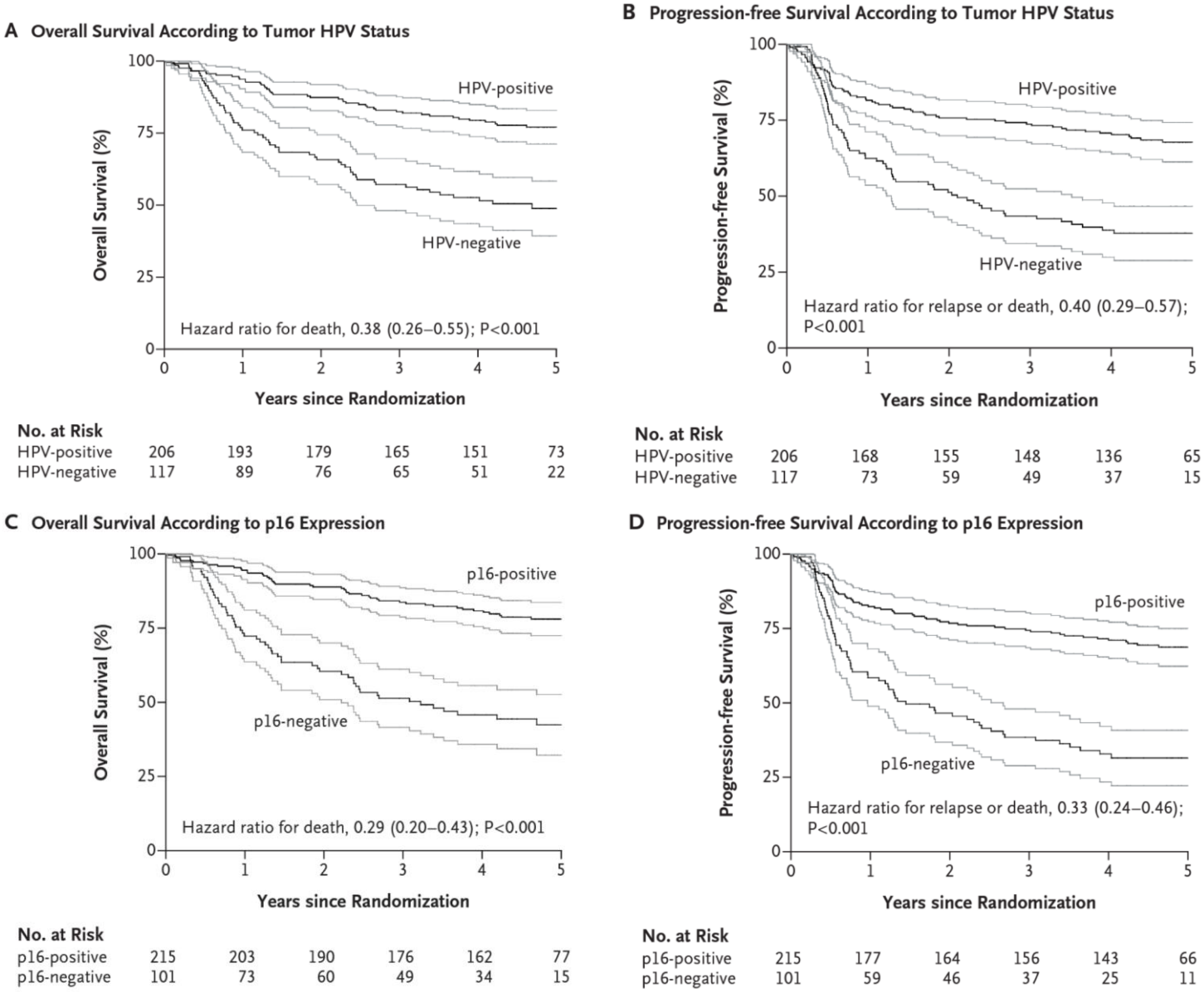
PET-CT Staging





HPV status: positive

HPV status (needed for prognosis)



Ang KK et al. Human Papillomavirus and Survival of Patients with Oropharyngeal Cancer. N Engl J Med 2010;363:24-35.

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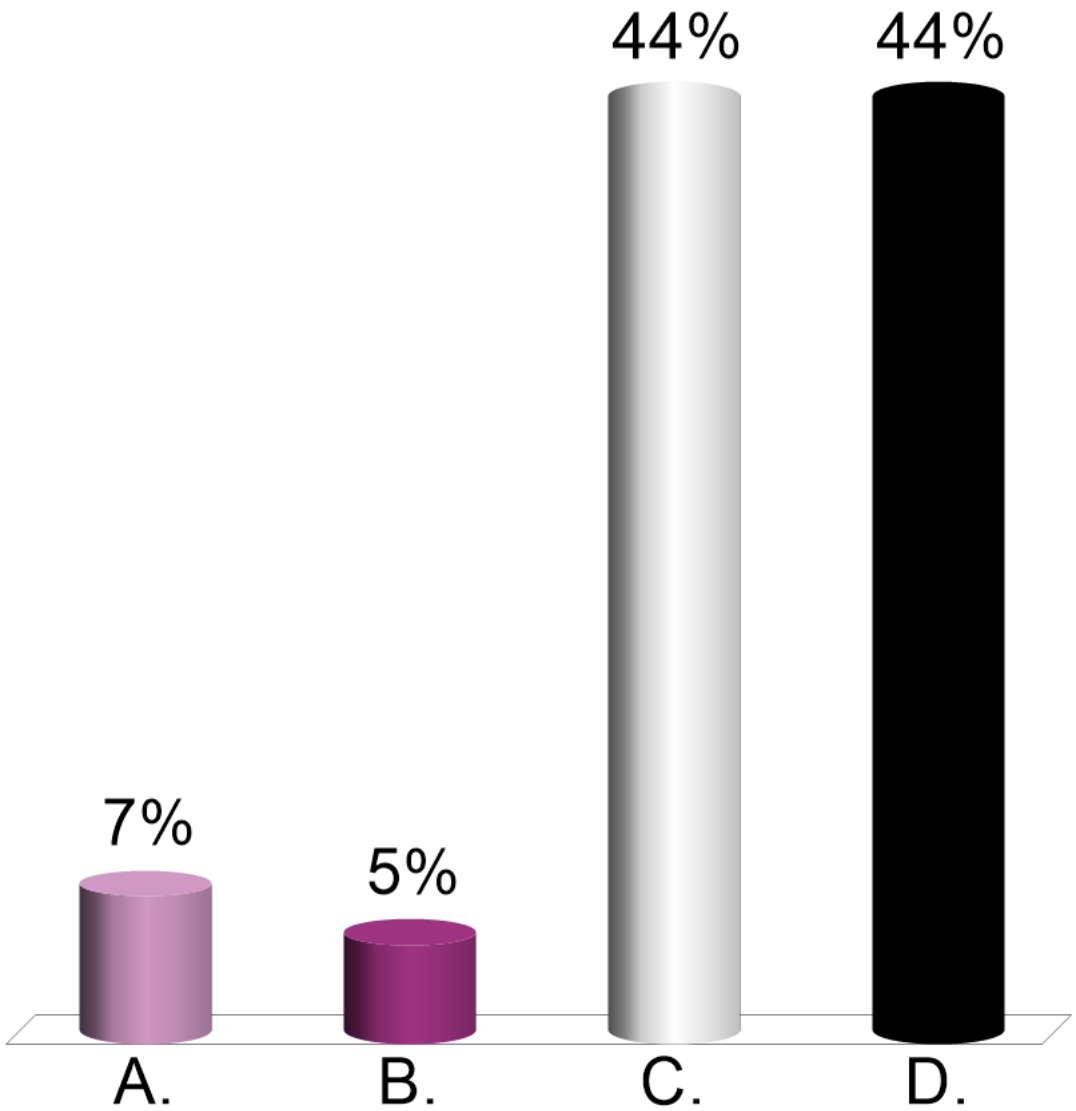
Do you test HPV status in your center?

A. Never
B. Sometimes
C. Routinely
D. I don’t know



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PTV prescription: SIB treatment

- 1) **Primary + Positive lymph nods** (GTV + margin)
  - PTV1: **66 Gy @ 2.2 Gy/fr**

- 2) **High risk lymph-nodal compartments** (CTV1 + margin) **(r2, r3, r5)**
  - PTV2: **60 Gy @ 2 Gy/fr**
- 3) **Low risk lymph-nodal compartments** (CTV2 + margin) **(r4, l2, l3, l4, l5, r1b, l1b, retropharyngeal)**
  - PTV3: **54 Gy @ 1.8 Gy/fr**

95% of Dose at **95%** of volumes
105% of Dose at **5%** of volumes

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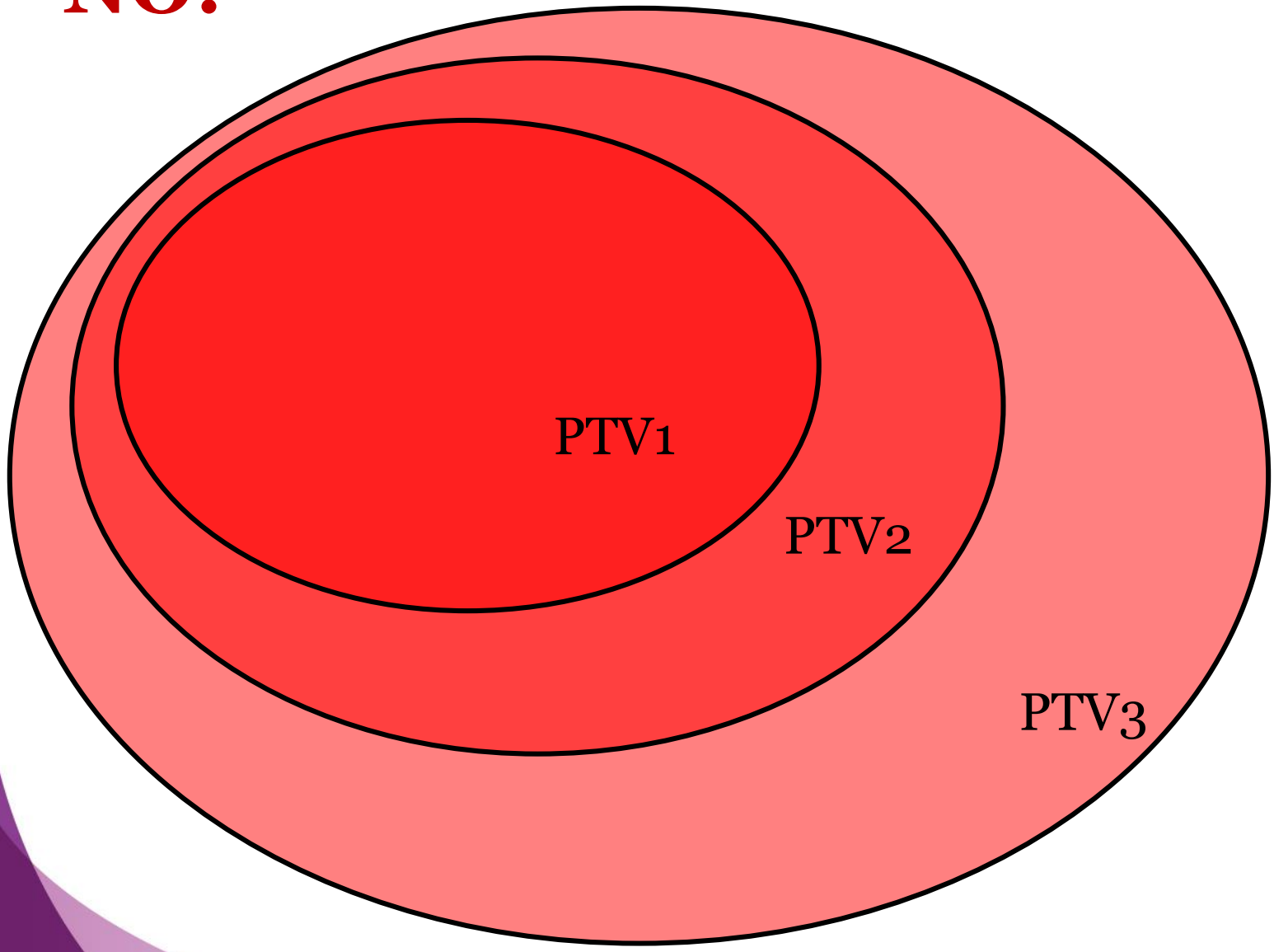
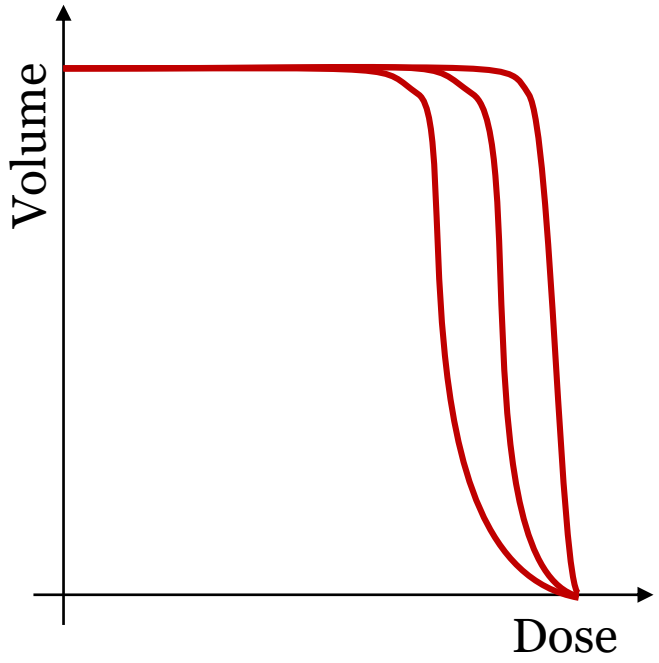
PTV prescription: SIB definition

NO!





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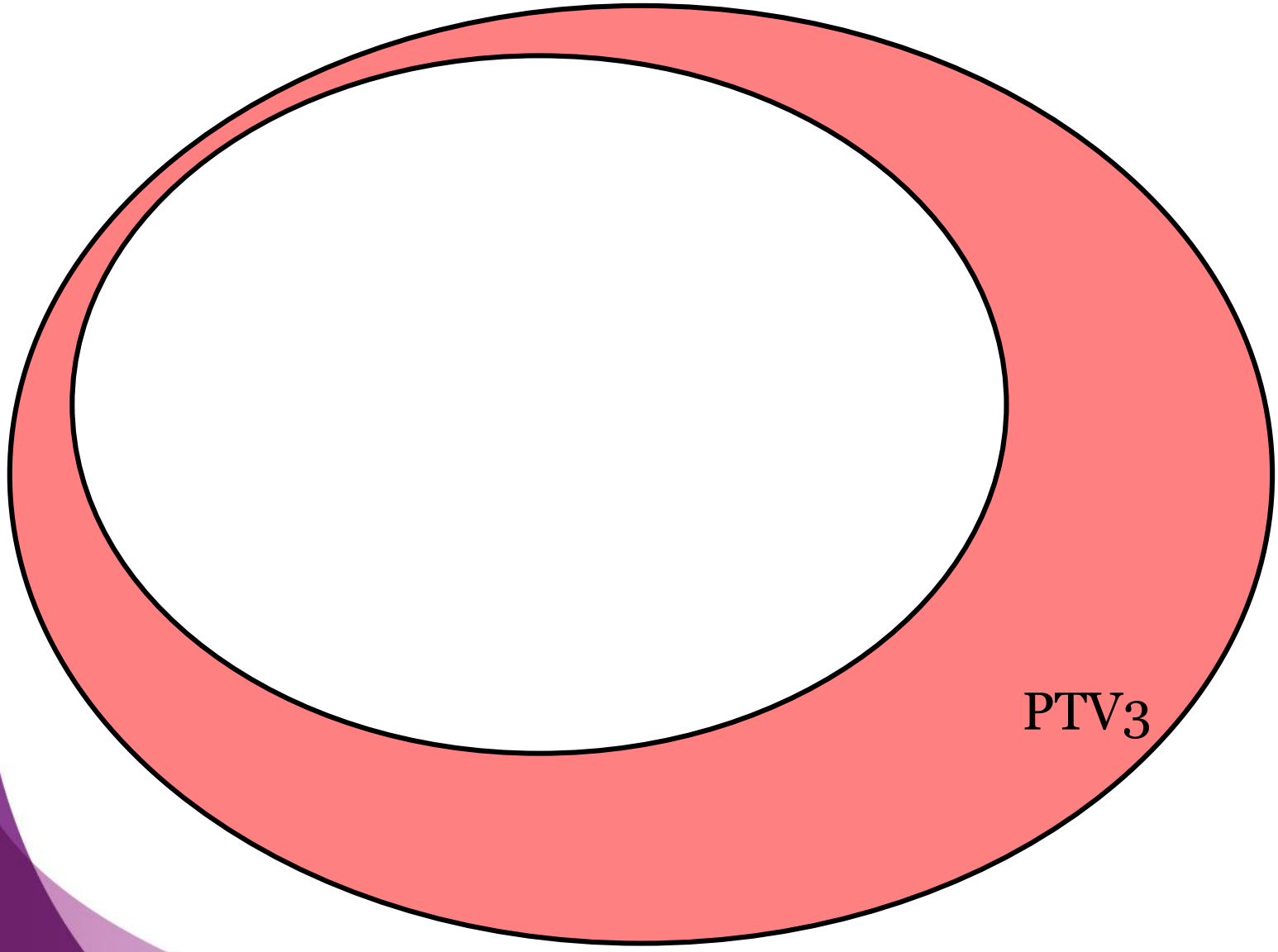
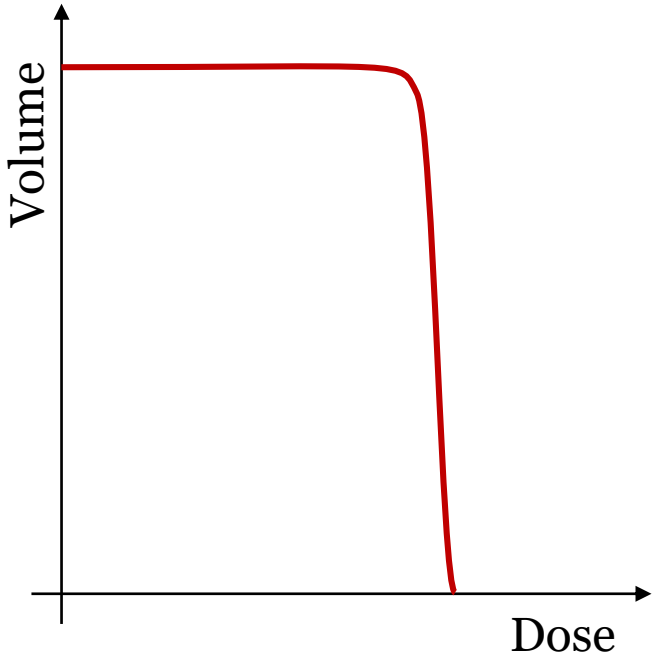
PTV prescription: SIB definition





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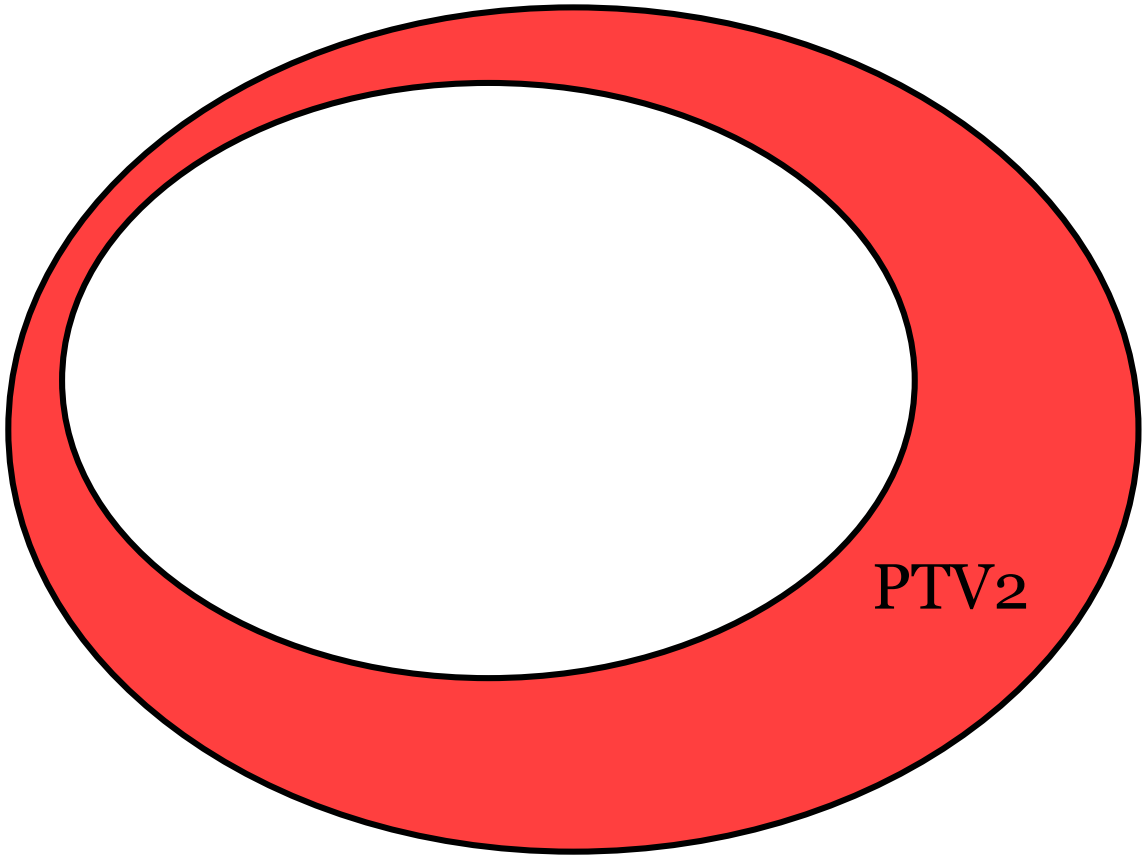
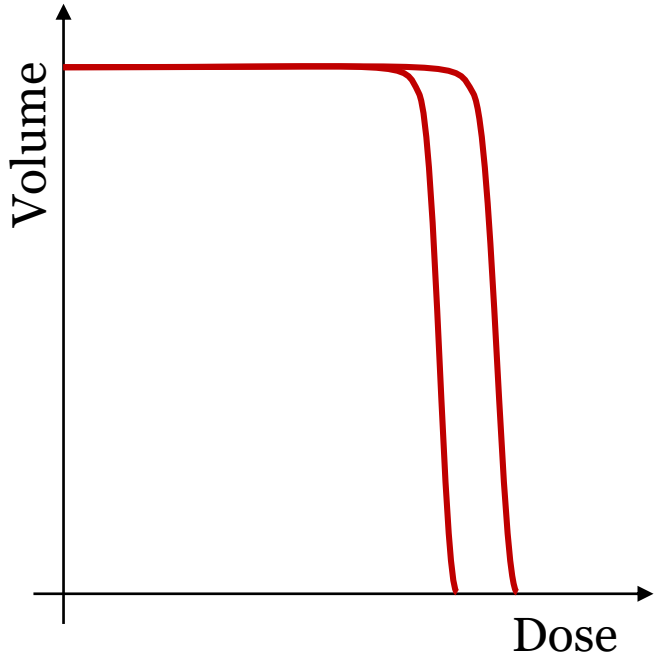
PTV prescription: SIB definition





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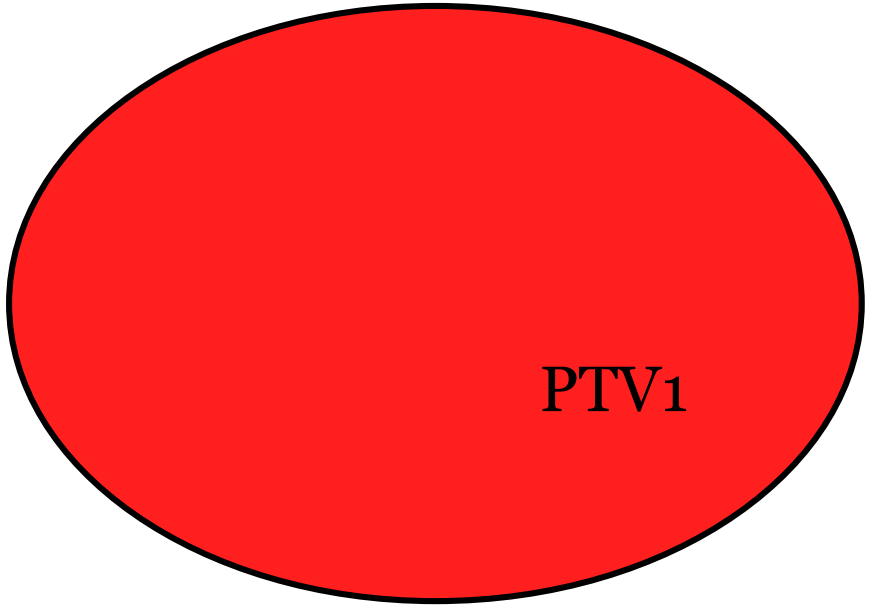
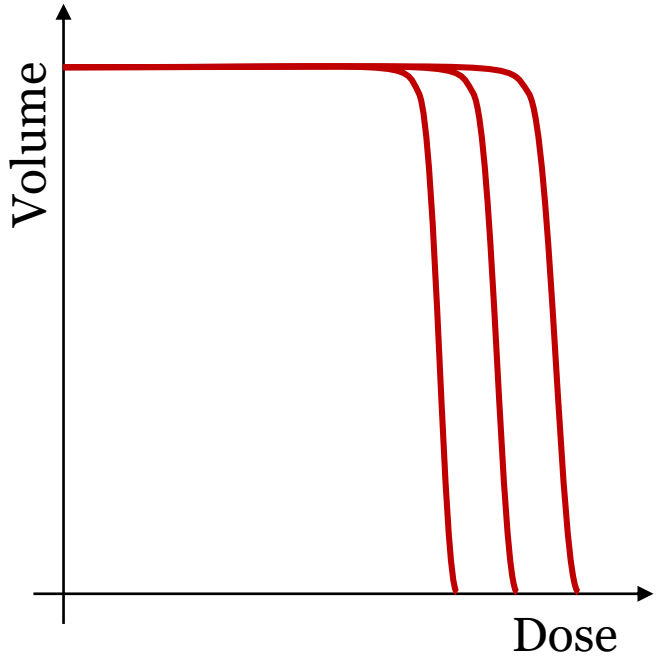
PTV prescription: SIB definition





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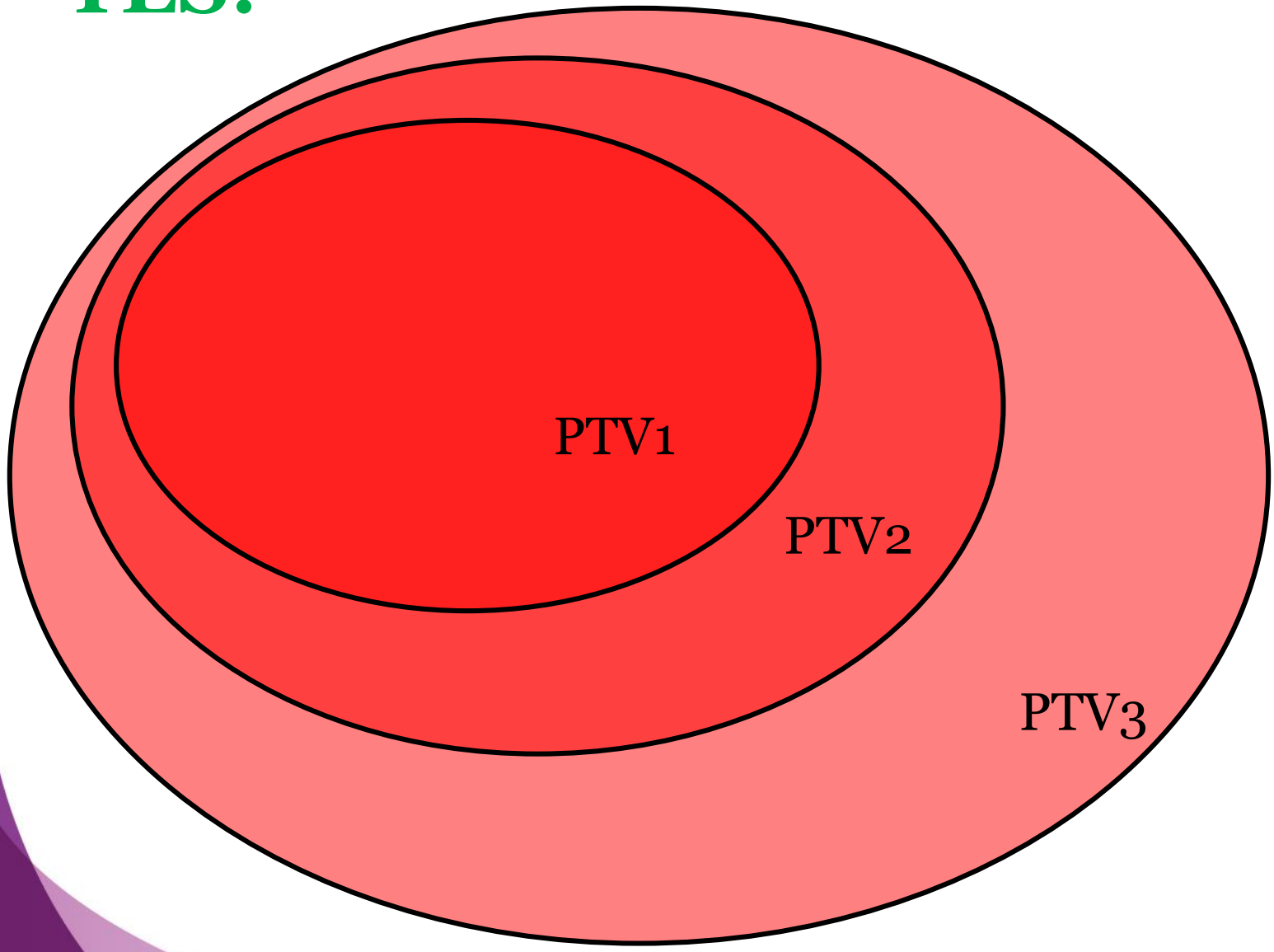
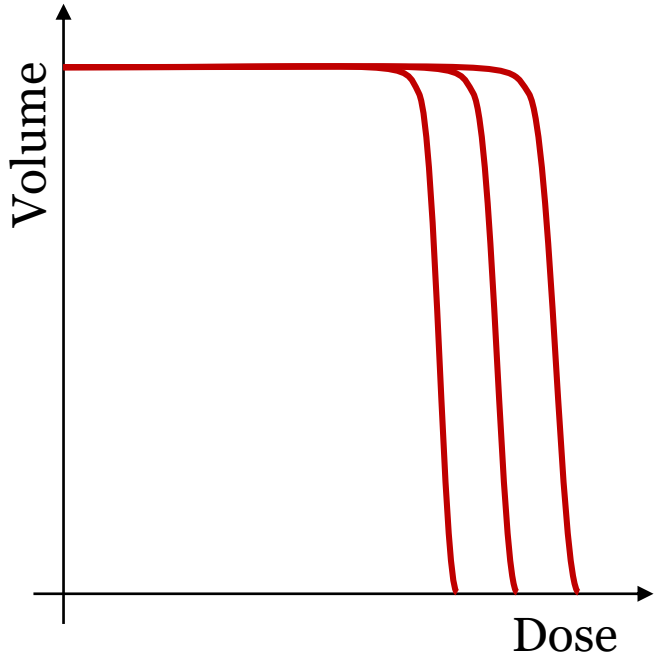
PTV prescription: SIB definition

YES!





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THE LANCET
www.thelancet.com

Parotid-sparing intensity modulated versus conventional radiotherapy in head and neck cancer (PARSPORT): a phase 3 multicentre randomised controlled trial

*Christopher M Nutting, James P Morden, Kevin J Harrington, Teresa Guerrero Urbano, Shreerang A Bhide, Catharine Clark, Elizabeth A Miles, Aisha B Miah, Kate Newbold, MaryAnne Tanay, Fawzi Adab, Sarah J Jefferies, Christopher Scrase, Beng K Yap, Roger P A'Hern, Mark A Sydenham, Marie Emson, Emma Hall, on behalf of the PARSPORT trial management group**

Lancet Oncology. 2011;12:127-36.

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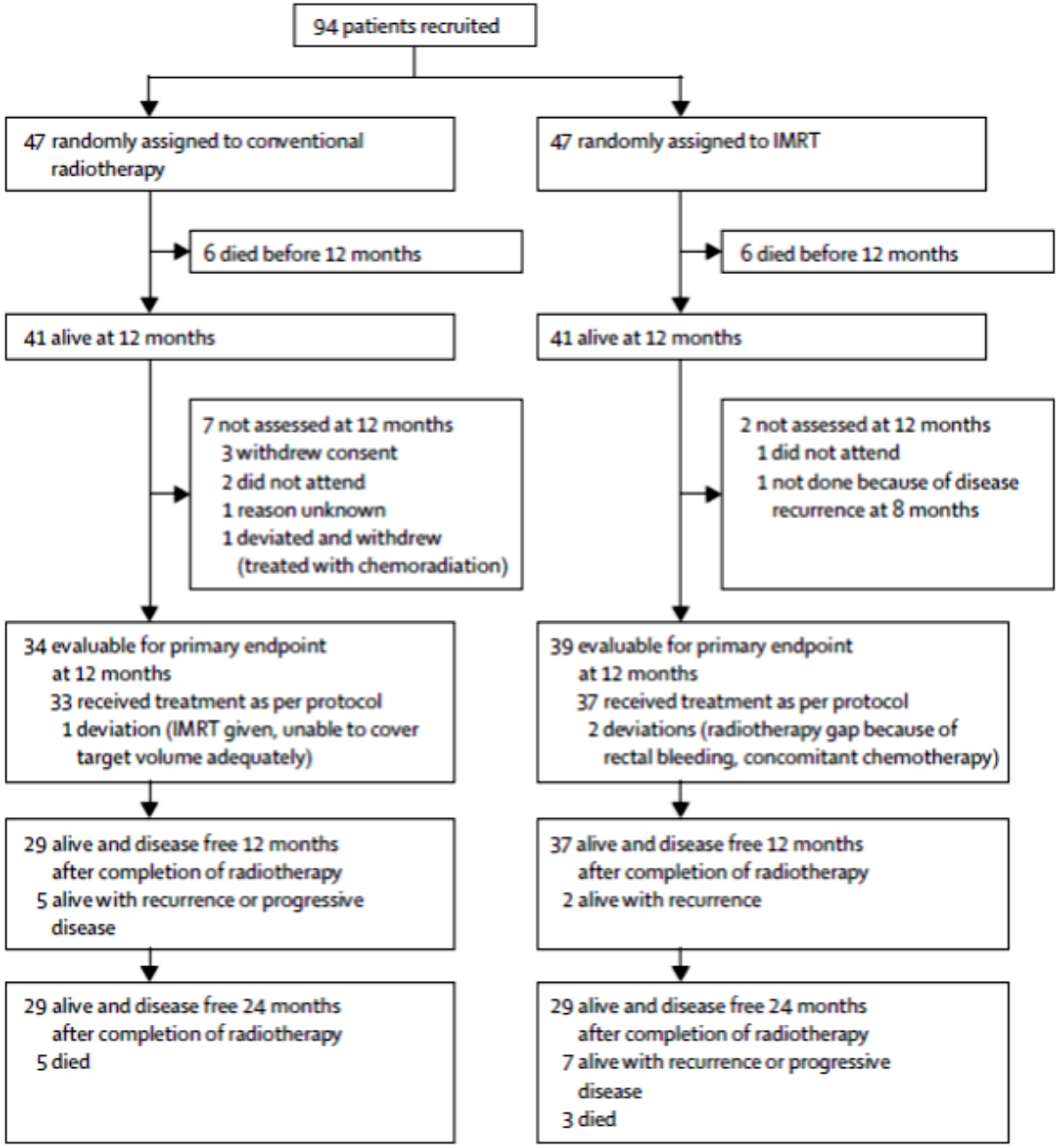
THE LANCET
www.thelancet.com



Lancet Oncology. 2011;12:127-36.

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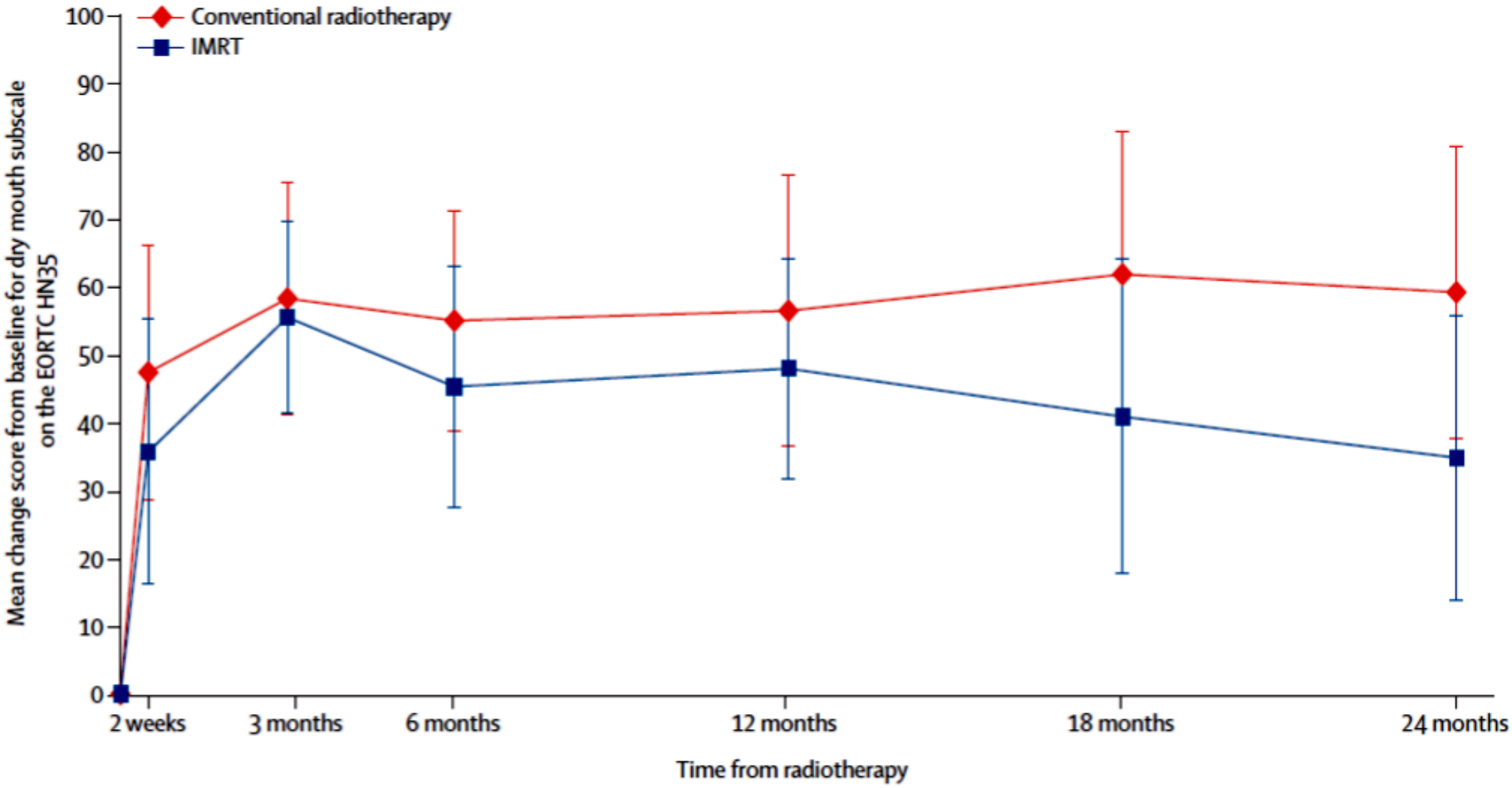

Conventional radiotherapy	26	24	23	23	21	18
IMRT	28	30	25	25	22	22
Difference in mean (99% CI)	11·7 (−14·4 to 37·8)	2·8 (−18·4 to 24·0)	9·7 (−13·5 to 32·9)	8·5 (−15·9 to 33·0)	21·0 (−8·9 to 50·9)	24·4 (−4·3 to 53·2)

Lancet Oncology. 2011;12:127-36.

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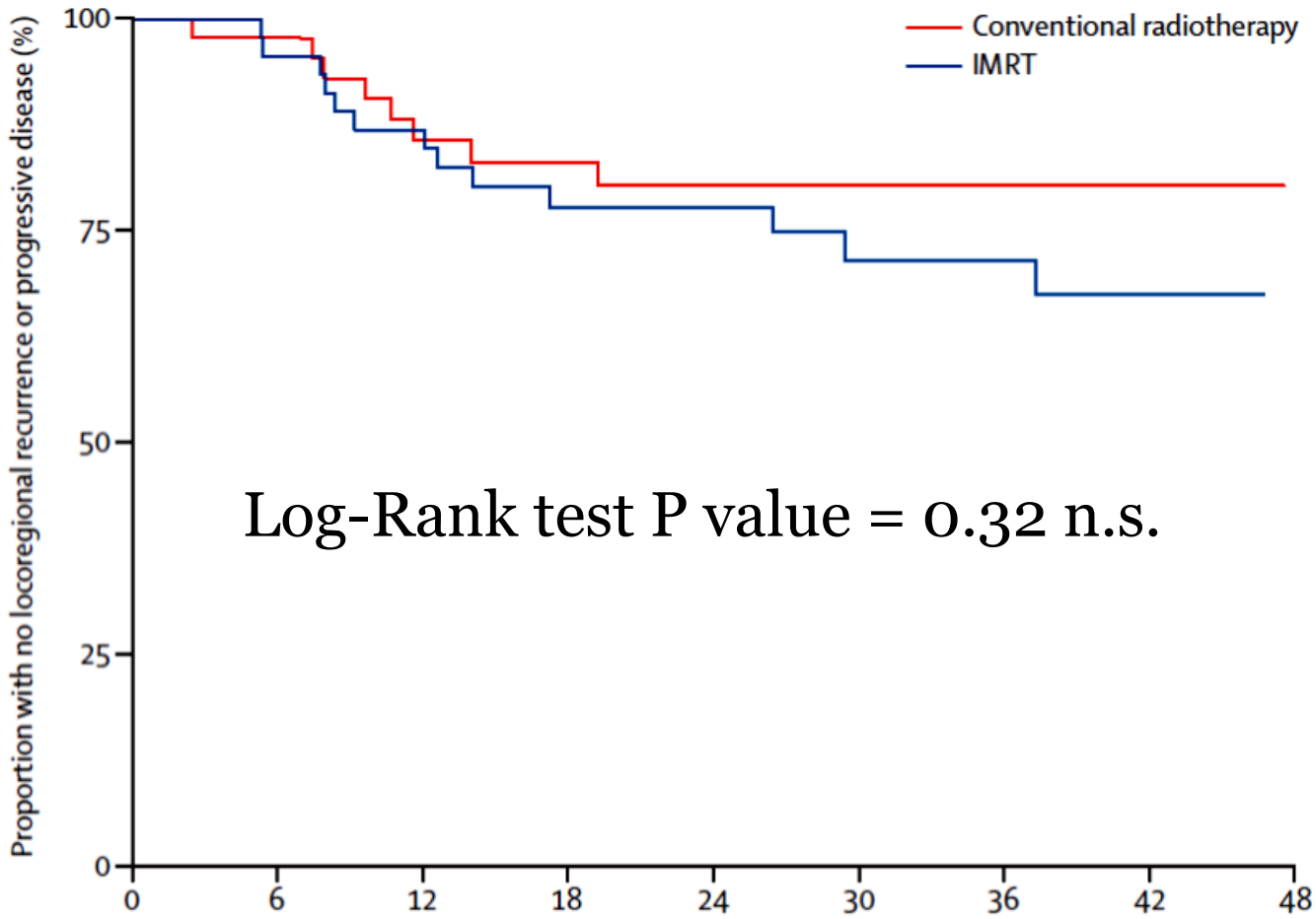

Log-Rank test P value = 0.32 n.s.

Number of events/at risk									
Conventional radiotherapy	0/47	1/42	5/34	1/30	1/29	0/23	0/19	0/15	0/8
IMRT	0/47	2/44	4/39	4/31	0/28	2/22	0/18	1/15	0/11

Lancet Oncology. 2011;12:127-36.

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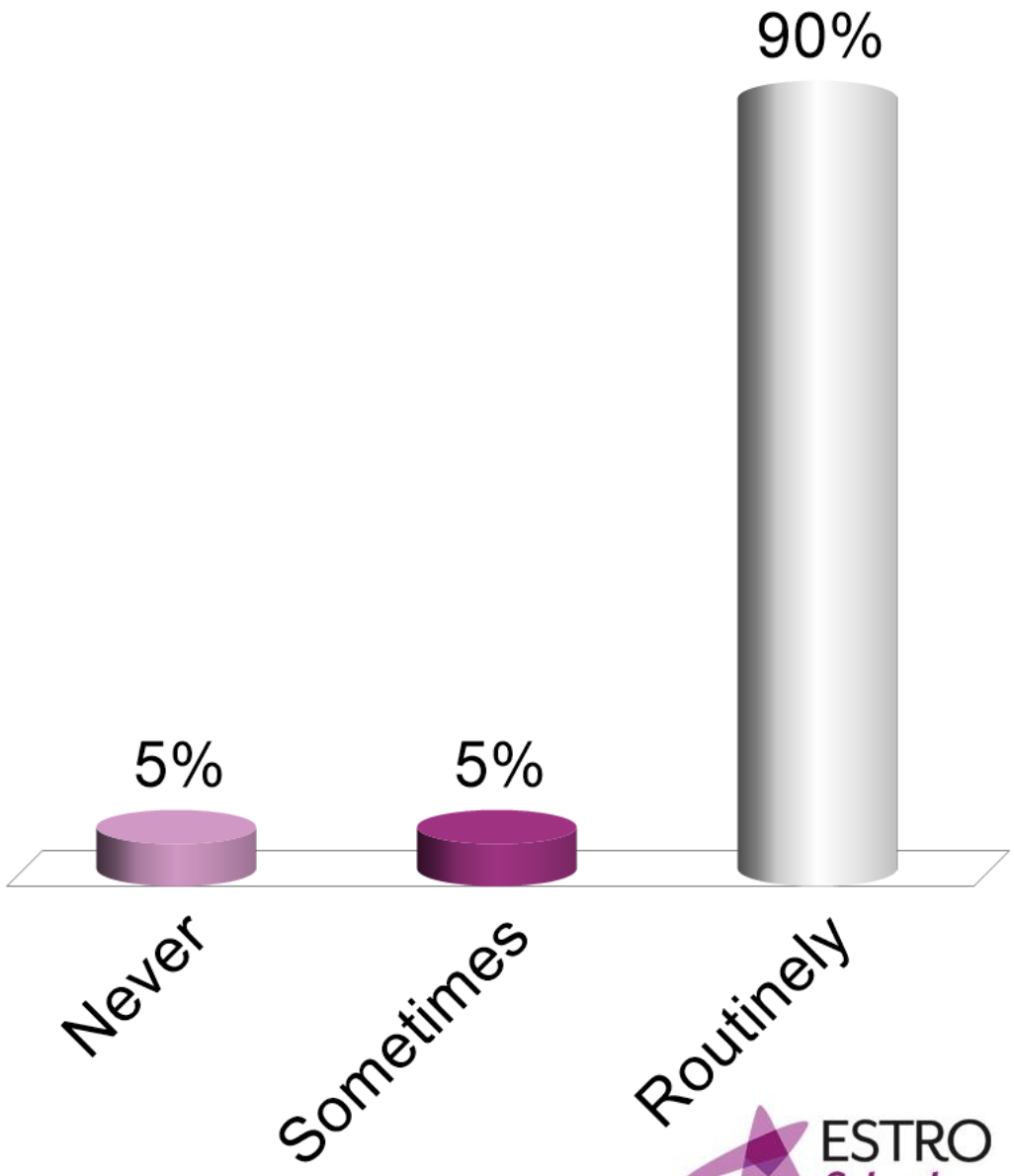
Do you treat H&N cases with IMRT?

A. Never

B. Sometimes

C. Routinely



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Recommendations for IMRT use

1) If the **reduction of xerostomia** and improved quality of life are the main outcomes of interest, then **IMRT** is the **recommended** treatment

2) If **blindness** is to be minimized or avoided, **IMRT** is **indicated** in the definitive or adjuvant radiotherapy setting for nasal and paranasal sinus cancers

3) If **osteoradionecrosis** is to be minimized or avoided, **IMRT** is **indicated** in the definitive or adjuvant radio- therapy of tumours in the oral cavity, oropharynx, paranasal sinuses and nasopharynx

O'Sullivan, B., Rumble, R. B., & Warde, P. (2012). Intensity-modulated Radiotherapy in the Treatment of Head and Neck Cancer. Clinical Oncology, 24(7), 474–487

Recommendations for IMRT use

4) **Treatment related outcome** (local control, disease free survival, overall survival) show not homogenous evidences

1. *Mok G, Gauthier I, Jiang H, et al. Outcomes of intensity-modulated radiotherapy versus conventional radiotherapy for hypopharyngeal cancer. Head Neck. United States; 2015;37:655–661.*

2. *Moon SH, Cho KH, Lee C-G, et al. IMRT vs. 2D-radiotherapy or 3D-conformal radiotherapy of nasopharyngeal carcinoma: Survival outcome in a Korean multi-institutional retrospective study (KROG 11-06). Strahlentherapie und Onkol Organ der Dtsch Rontgengesellschaft . [et al]. Germany; 2016;192:377–385.*

3. *Moretto F, Rampino M, Munoz F, et al. Conventional 2D (2DRT) and 3D conformal radiotherapy (3DCRT) versus intensity-modulated radiotherapy (IMRT) for nasopharyngeal cancer treatment. Radiol Med. Italy; 2014;119:634–641.*

4. *Marta GN, Silva V, De Andrade Carvalho H, et al. Intensity-modulated radiation therapy for head and neck cancer: Systematic review and meta-analysis. Radiother Oncol. Elsevier Ireland Ltd; 2014;110:9–15.*

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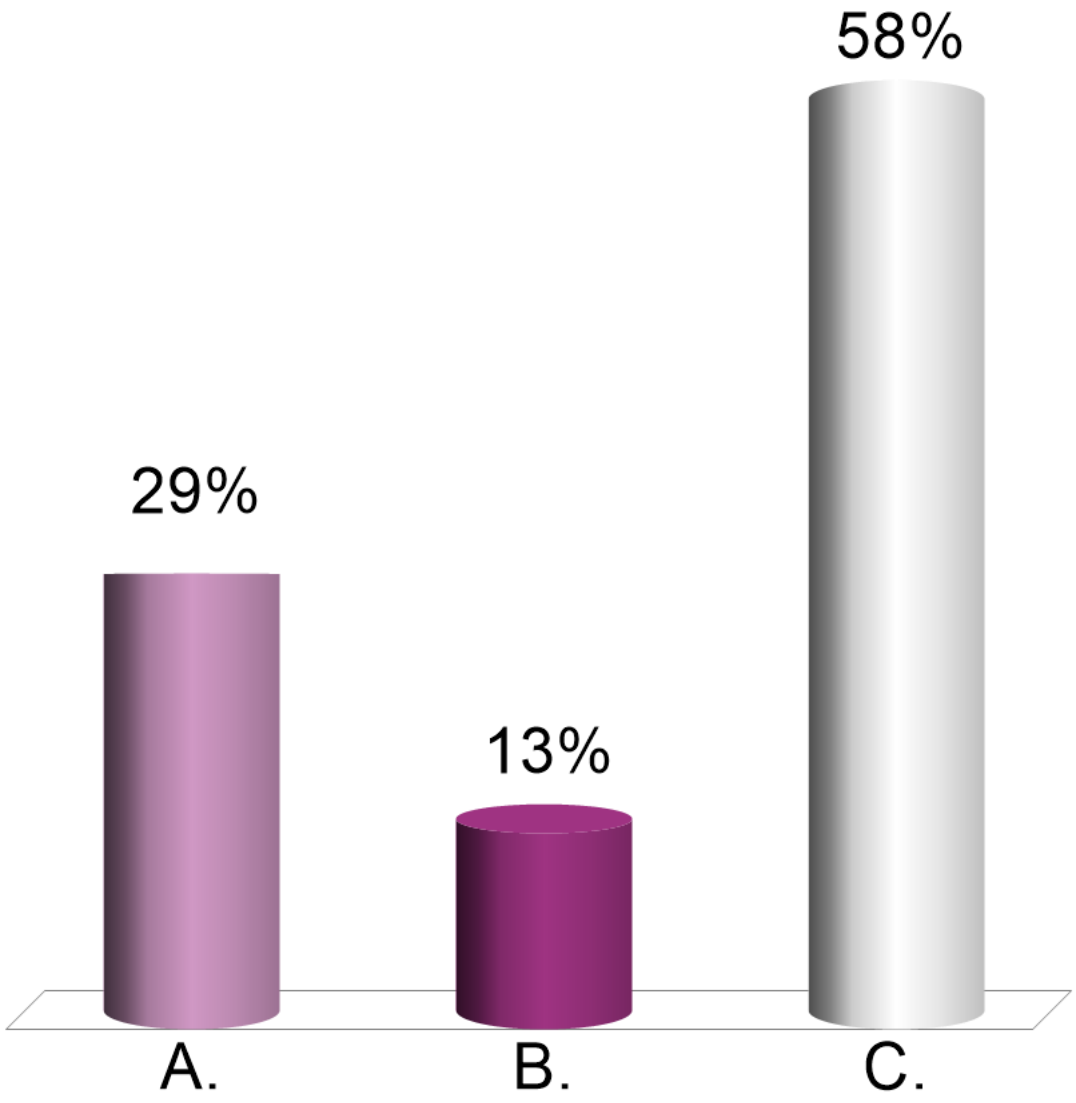
Which is your priority in H&N IMRT planning?

A. PTV coverage

B. Parotid sparing

C. Spinal cord sparing



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OARs constraints

- Create your workflow!
  - 1) Dose at PTV1 66 Gy, Dmax to spinal cord
  - 2) Dose at PTV2-3, Dmean to parotids
  - 3) Decide if spare only one parotid gland (controlateral to the tumor) or both

OARs constraints

- Create your workflow:
  - Be careful of Hot Spots! (**Overall Dmax ≤ 110%**)
  - Find the location of hot spots (skull base is worse than neck base or PTV)

OARs constraints

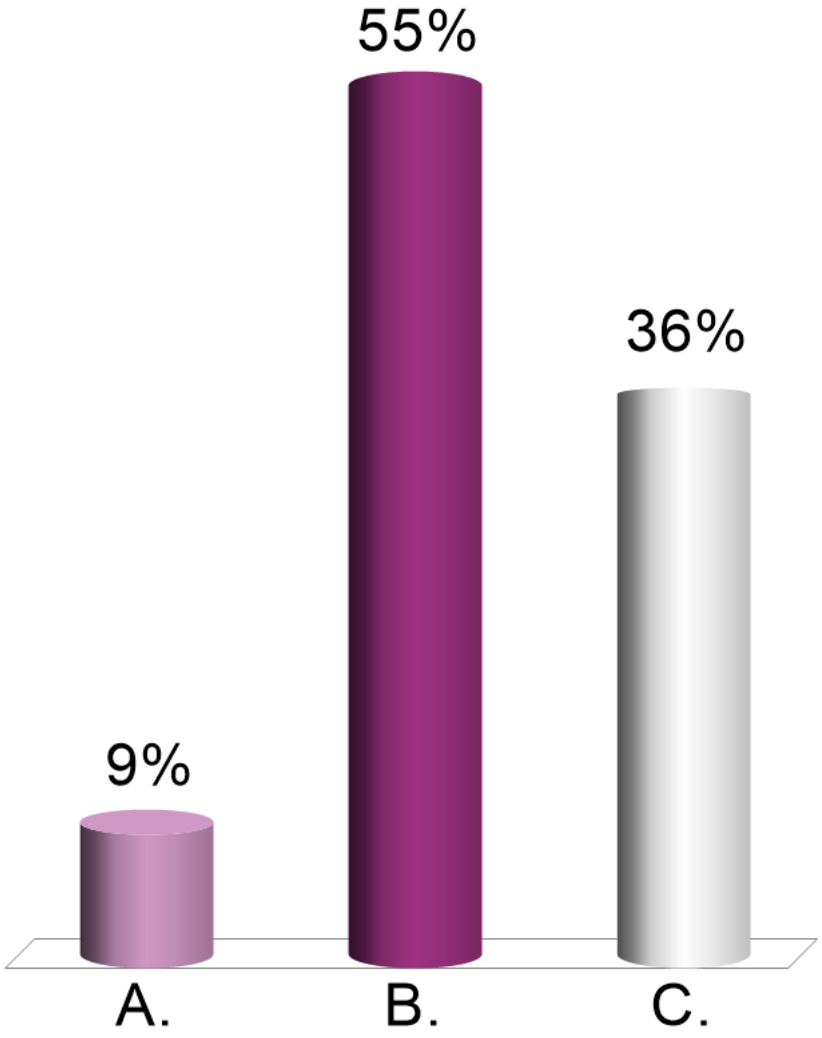
- Parotid sparing: one or two?

Parotid glands: spare one or both?

A. Always both glands, same mean dose

B. At least one gland under 25 Gy

C. At least one gland under 25 Gy if overall mean dose is > 25 Gy



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Parameters for clinical outcome: Salivary glands

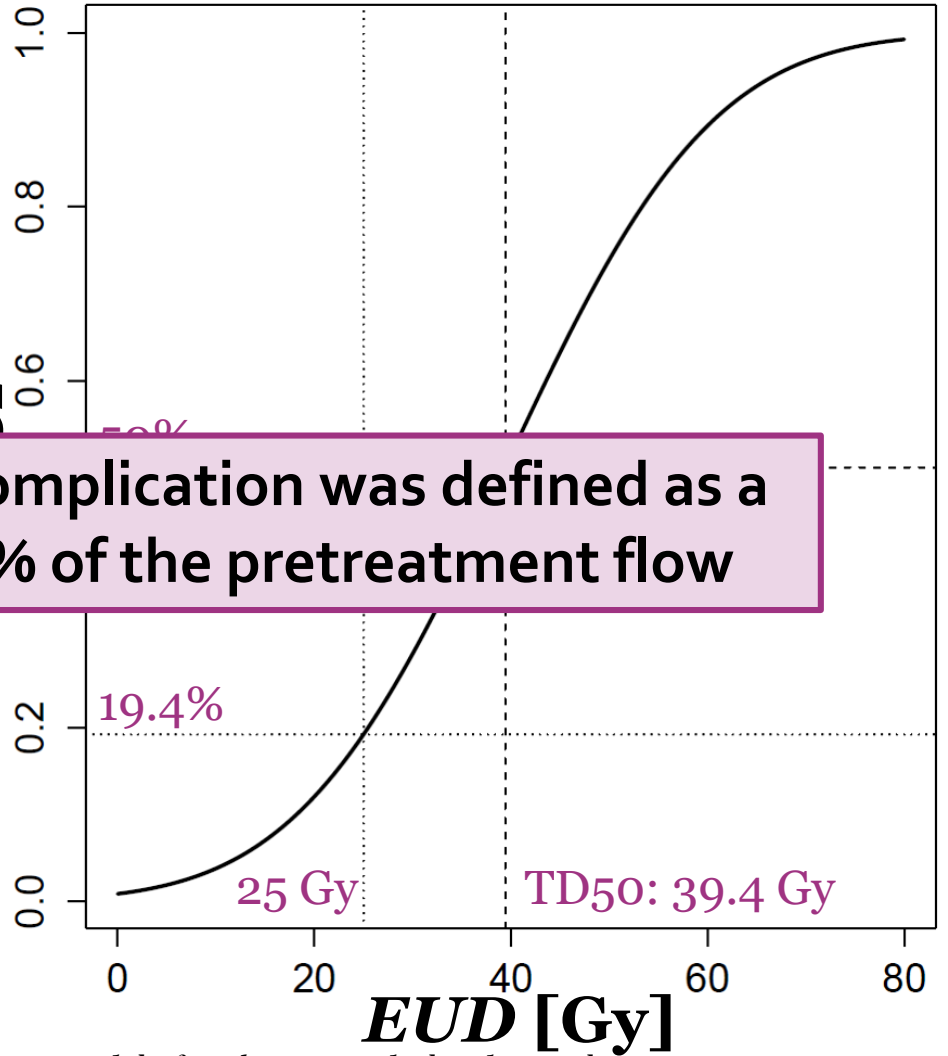
NTCP dose-response models evaluation for analysis of parotid gland function:

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	38.8	36.5–43.5		
Critic					
	N_{FSU}	219	18–298		
Parallel FSU	D_{50}	32.5	15.0–95.0	336.44	0.55
	k	2.75	0.50–4.50		
	TD_{50}	37.0	32.0–44.0		
	m	0.35	0.30–0.60		
V_{Dth}	D_{th}	30.5	25.0–37.0	342.98	0.58
	rdV_{50}	0.68	0.60–0.80		
	m	0.48	0.35–0.65		

Abbreviations: CI = confidence interval; Δ_{LL} = deviance.

For each individual parotid gland, a complication was defined as a reduction in salivary flow to below 25% of the pretreatment flow



Houweling AC et al. A comparison of dose-response models for the parotid gland in a large group of head-and-neck cancer patients. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 4, pp. 1259–1265, 2010.

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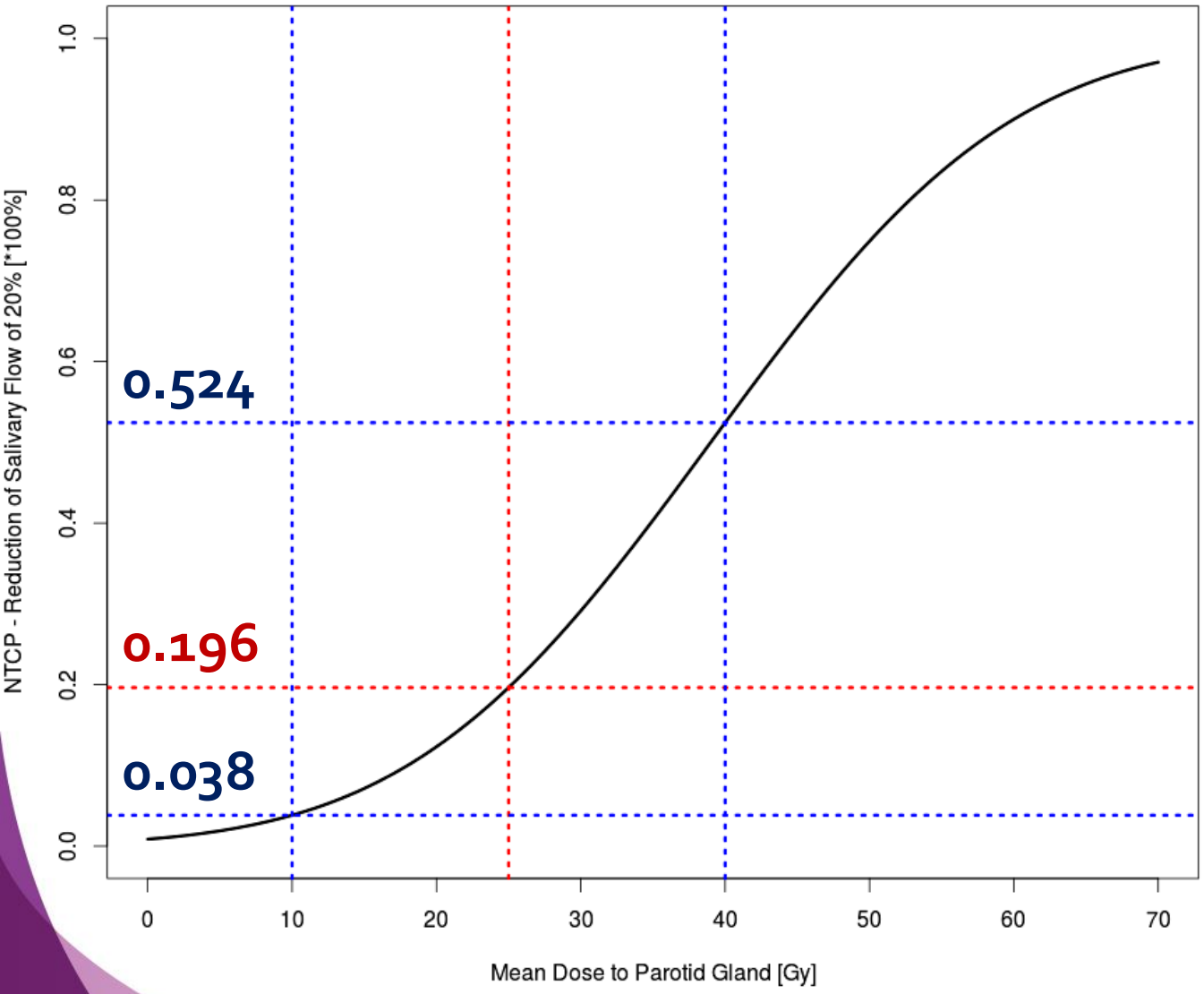
Mean dose to both parotids 25 Gy

Assumption: both parotid have the same volume

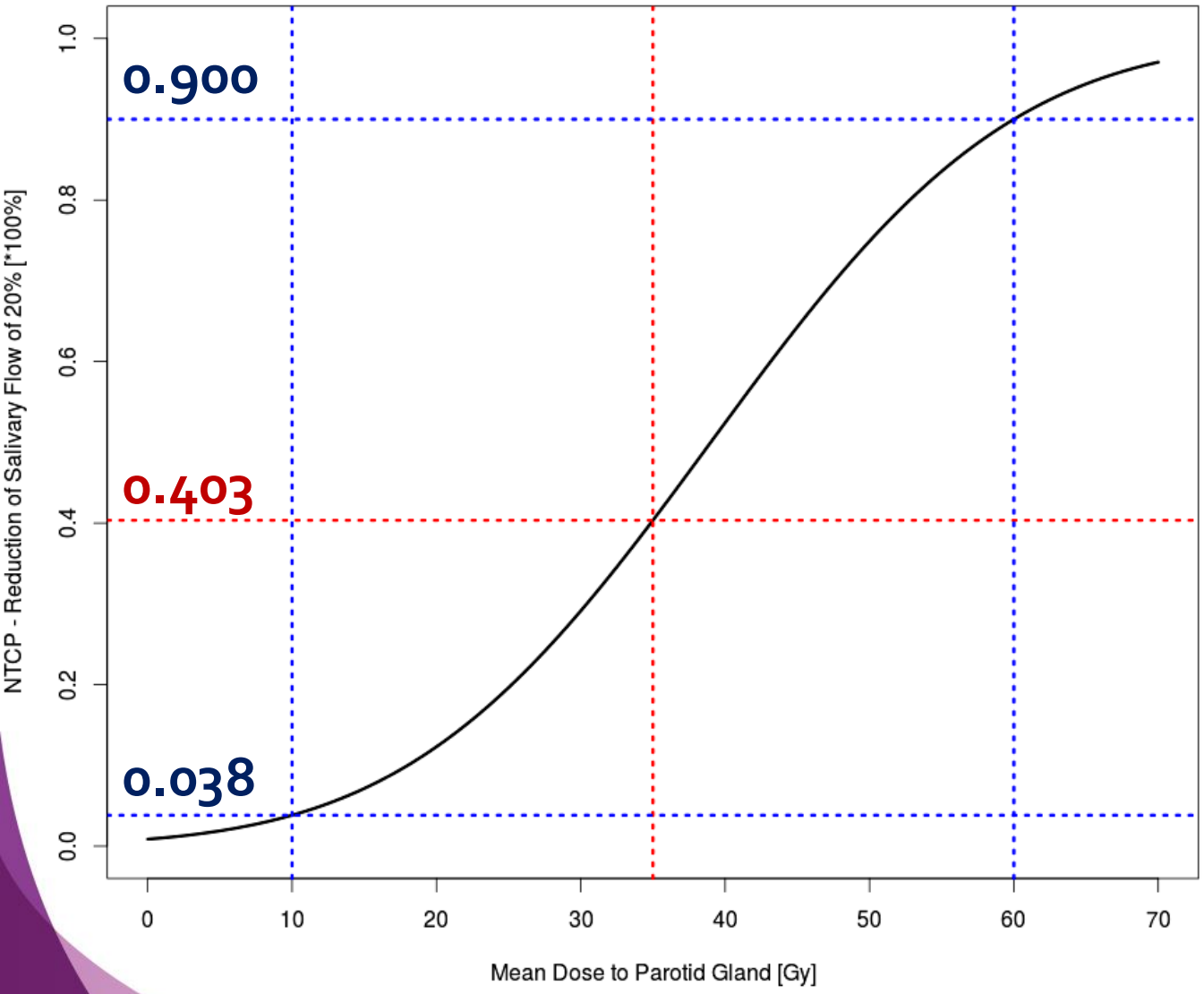


$NTCP_{asym}$ = 0.524 * 0.038 = 0.02

$NTCP_{sym}$ = 0.196 * 0.196 = 0.038

Mean dose to both parotids 35 Gy

Assumption: both parotid have the same volume



$NTCP_{asym}$= 0.900 * 0.038 = 0.034

$NTCP_{sym}$= 0.403 * 0.403 = 0.162

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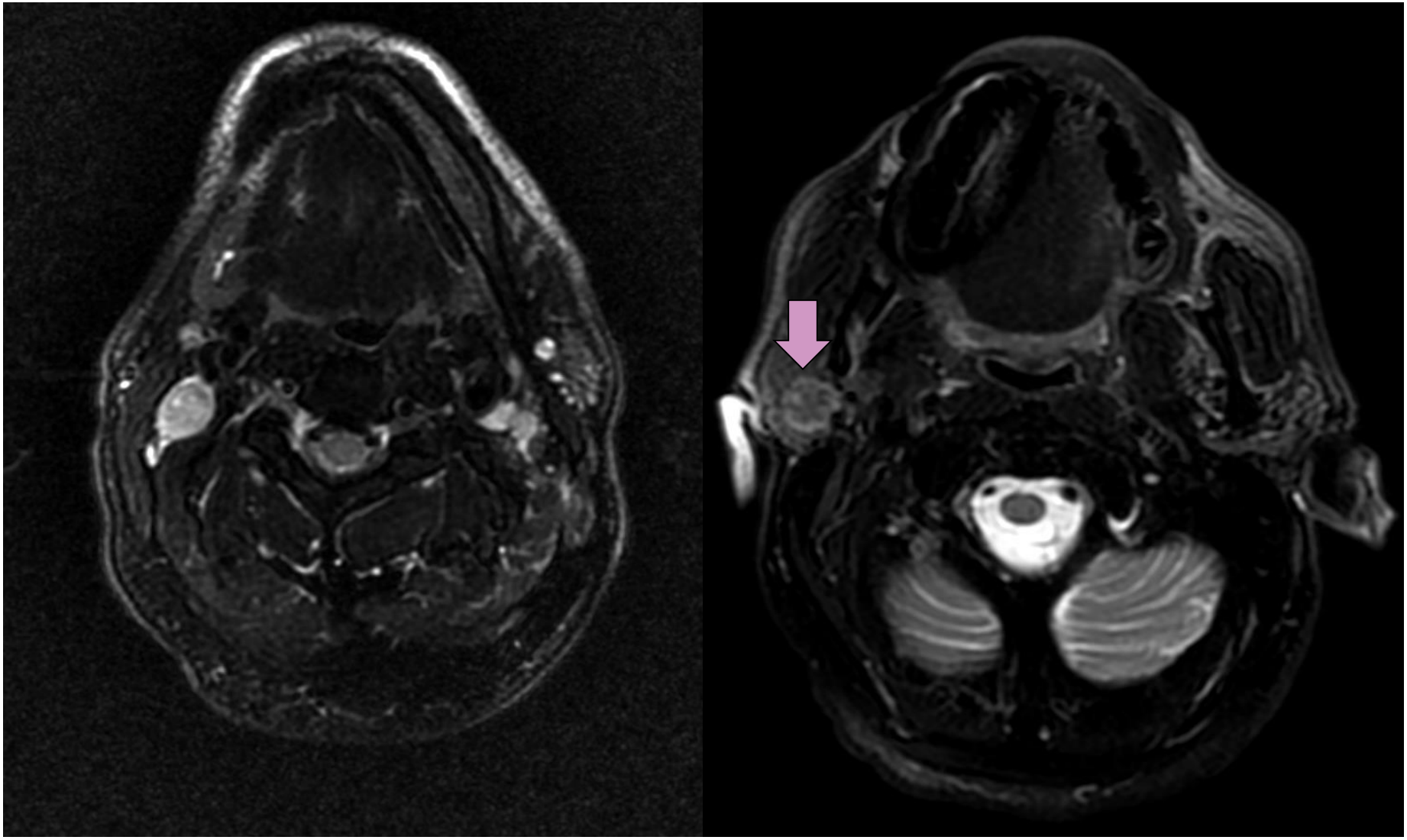
OARs constraints

- Parotid sparing: one or two?
  - Try both, if you get **Dmean > 25 Gy** on both try to sacrifice the ipsilater gland
  - In case of **bulky lymph nodes** involving one gland please sacrifice it (and try to spare the controlateral)

OARs constraints



N Dinapoli, R Autorino, et al. Recurrence in region of spared parotid gland in patient receiving defi nitive intensity-modulated radiotherapy for nasopharyngeal cancer: A case report. Acta Oncol. 2012 Apr 23.

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OARs constraints/objectives

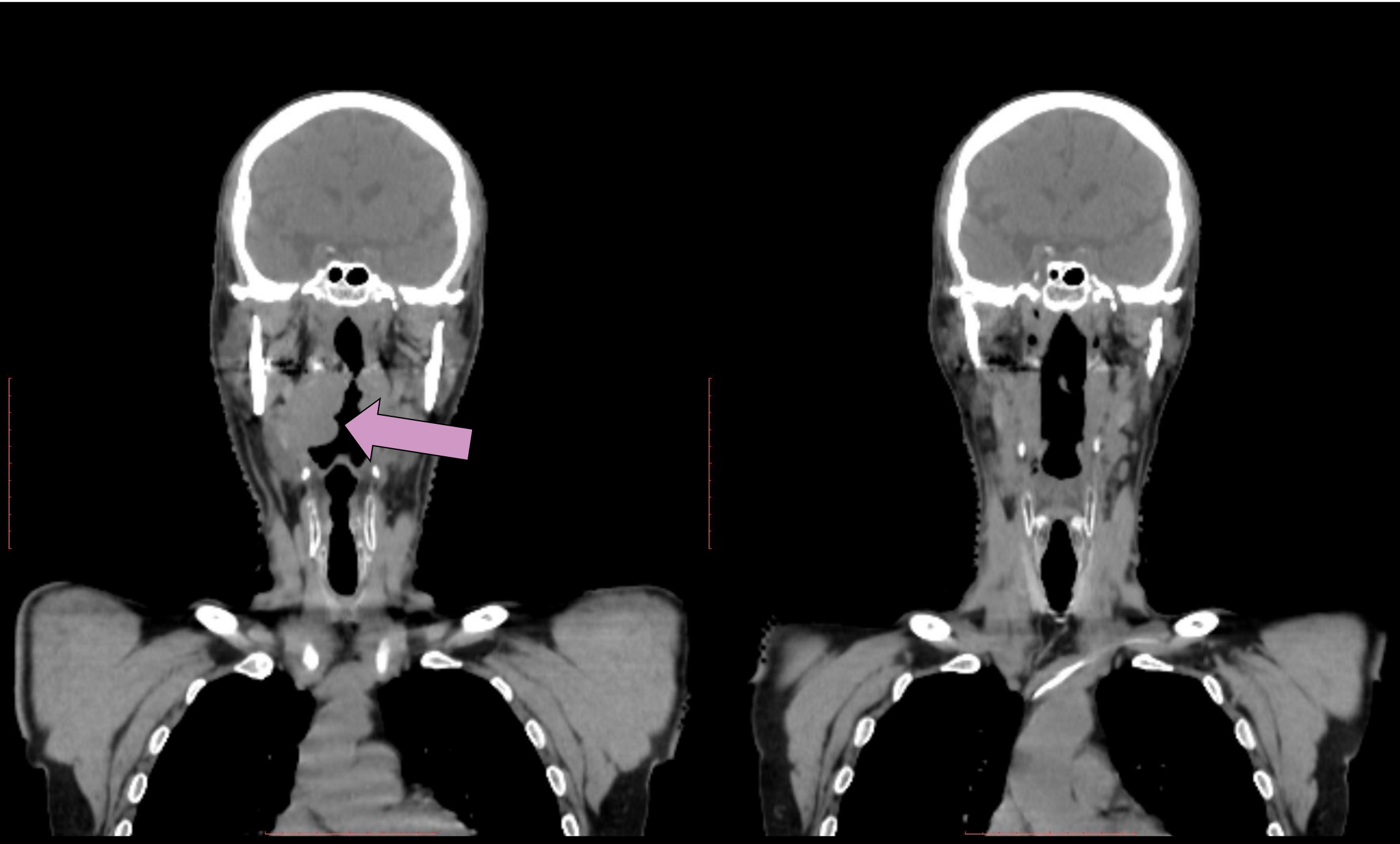
- **Constraints:**

1.	Spinal cord:	Dmax < 45 Gy	
2.	PRV Spinal cord:	Dmax < 50 Gy	
3.	Brainstem:	V59 Gy < 1 cc	(QUANTEC)

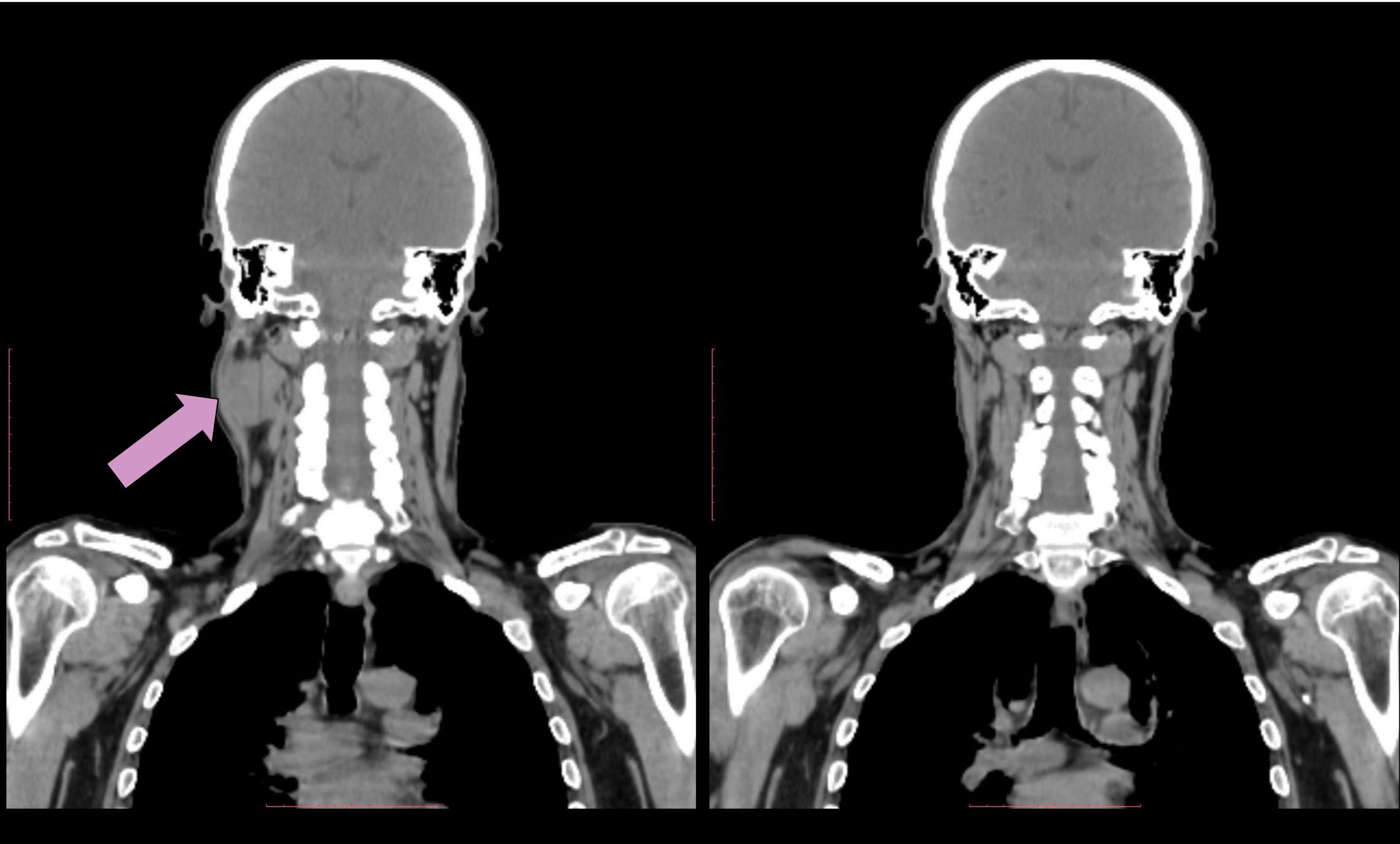
- **Objectives:**

1.	Parotids:	Dmean < 25 Gy	(primary objective, Ptox < 20%)
		Dmean < 39 Gy	(secondary objective, Ptox < 50%)
2.	Mandible:	EQD2 Dmax < 70 Gy	(RTOG 0615)
3.	Cochlea:	Dmean < 35 Gy	(QUANTEC)
4.	Lens	Dmax < 7 Gy	(RTOG 0539)
5.	Brain:	EQD2 Dmax < 72 Gy	(QUANTEC)
6.	Thyroid:	Dmean < 45 Gy	(RTOG 0225)
		V30 Gy < 62.5 %	(RTOG 0615)

Replanning H&N IMRT patients (15 fractions)

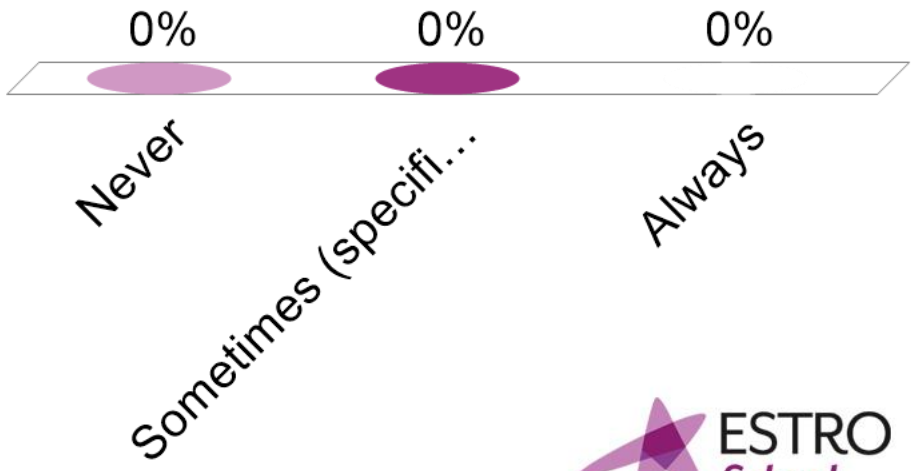


Replanning H&N IMRT patients (15 fractions)



Do you perform replanning in H&N patients?

A. Never
B. Sometimes (specific protocols)
C. Always



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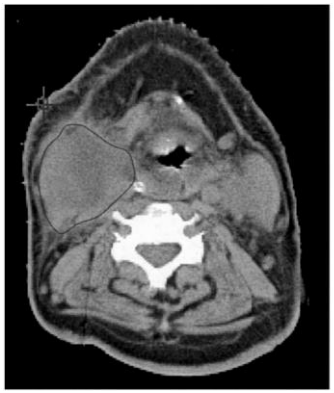
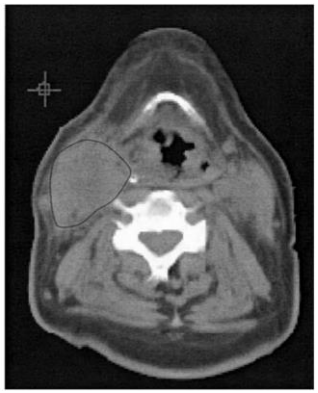
Replanning H&N IMRT patients

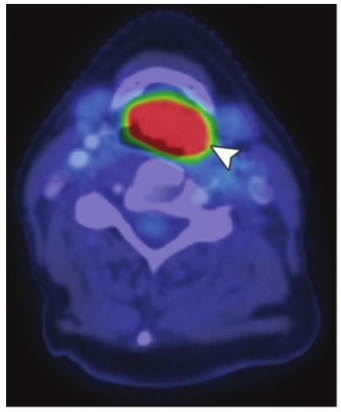


Planning CT

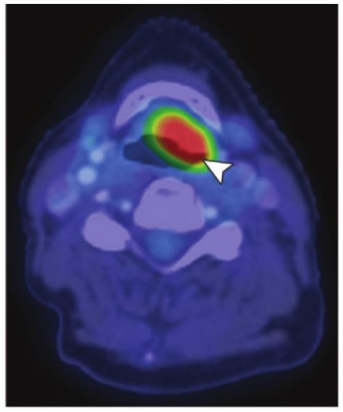


After 3 weeks

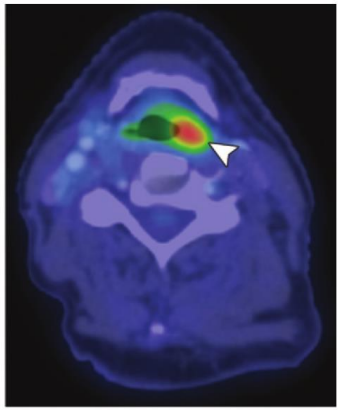
Barker, J. L. *et al.* Quantification of volumetric and geometric changes occurring during fractionated radiotherapy for head-and-neck cancer using an integrated CT/linear accelerator system. *Int. J. Radiat. Oncol. Biol. Phys.* **59,** 960–970 (2004).



Planning PET-CT



11 fractions later



21 fractions later

Bhatnagar, P., Subesinghe, M., Patel, C., Prestwich, R. & Scarsbrook, A. F. Functional imaging for radiation treatment planning, response assessment, and adaptive therapy in head and neck cancer. *Radiographics* **33,** 1909–29 (2013).

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Replanning H&N IMRT patients

- Causes of anatomy variations:
  - Tumor shrinkage
  - Weight loss (mucositis, reduced caloric intake)
  - Radiation induced anatomical changes (parotid glands)

- Significant variations for dose to OAR (generally increased)
- Variations of target coverage

Adaptive RT

Castadot, P., Lee, J. a., Geets, X. & Grégoire, V. Adaptive Radiotherapy of Head and Neck Cancer. Semin. Radiat. Oncol. 20, 84–93 (2010).

Replanning H&N IMRT patients

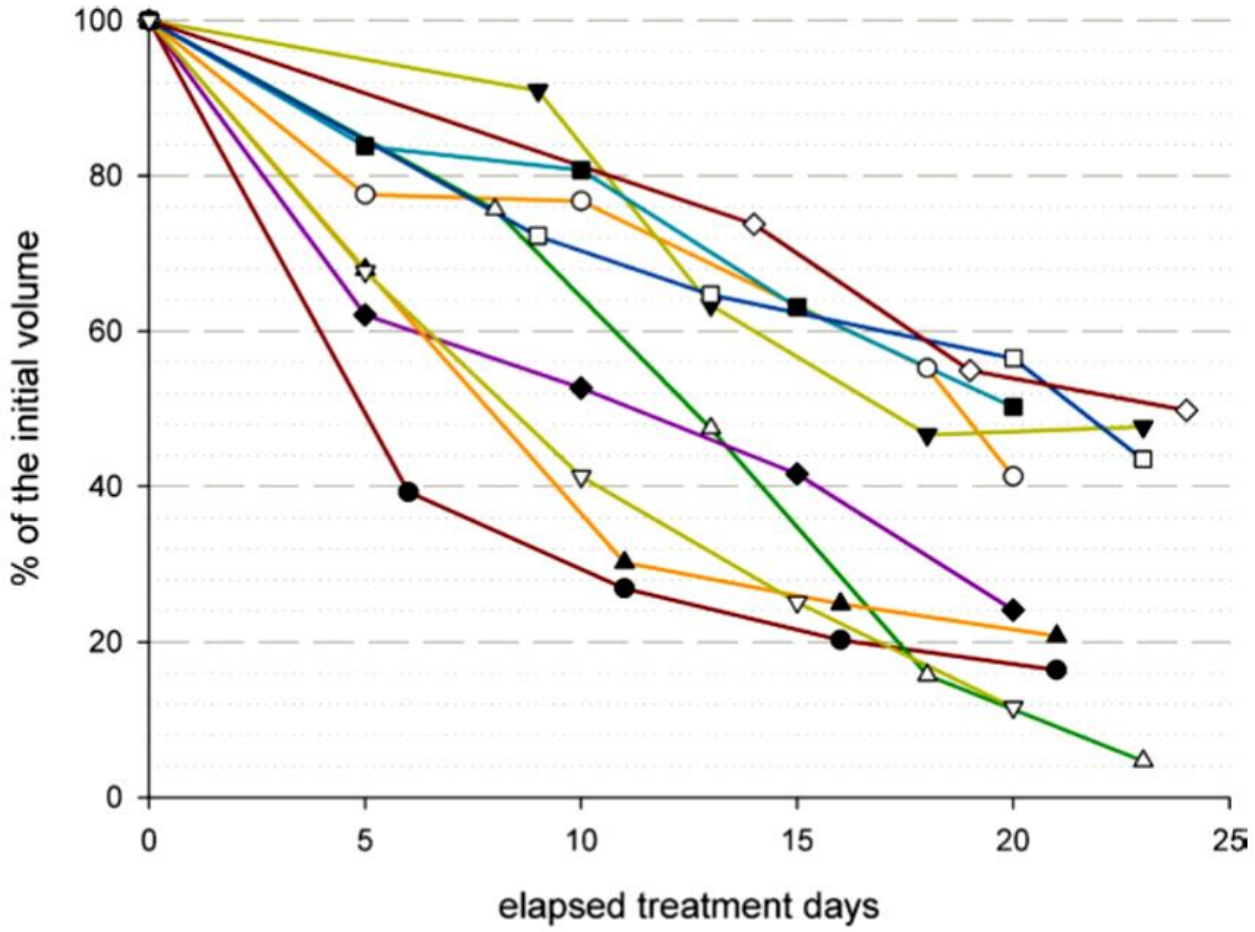

Figure 2 Volumetric changes in the primary tumor gross tumor volume (GTV) during treatment of pharyngolaryngeal tumors.

Castadot, P., Lee, J. a., Geets, X. & Grégoire, V. Adaptive Radiotherapy of Head and Neck Cancer. Semin. Radiat. Oncol. 20, 84–93 (2010).

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Author	No. of Patients	Per-Treatment Imaging	Image Registration	Volume Analysis	Shape and Positional Analysis
Barker et al (2004)[6]	14	In-room CT-on-rail 3 times/wk; no iv contrast	Rigid	Reduction of: • GTV: 1.8% per treatment day • PGs: 0.6%/treatment day	• GTV: COM displacement: 3.3 mm (asymmetric shrinkage) • PG: COM shift medially by 3.1 mm
Geets et al (2007)[50]	10	CT scan at mean doses of 14, 25, 35, and 45 Gy; iv contrast	Rigid	After a mean dose of 45 Gy: • GTV_T: mean decrease of 65.5% • High dose CTV_T: mean decrease of 50.9% • High dose PTV_T: mean decrease of 47.9%	NA
Han et al (2008)[43]	5	Daily helical MVCT	Rigid	At the end of treatment: PGs had decreased from 20.5 to 13.2 cm^3, ie, an average decrease of 0.21 cm^3/treatment day or 1.1%/treatment day	NA
Vasquez Osorio et al (2008)[51]	10	CT scan at 46 Gy; iv contrast	Deformable	Reduction after 46 Gy: • GTV: 25 ± 15% • Homolat PG: 17 ± 7% • Heterolat PG: 5 ± 4% • Homolat SMG: 20 ± 10% • Heterolat SMG: 11 ± 7%	After 46 Gy: • Lateral and inferior regions of homolat PG: medial and posterior shift (3 mm) • Homolat SMG: medial, cranial, and posterior shift (4 mm)
Hansen et al (2006)[52]	13	CT scan after a mean dose of 38 Gy	Rigid	Reduction: • GTV: no change • Right PG: 15.6% • Left PG: 21.5%	NA
Robar et al (2007)[53]	15	Weekly CT scans; no iv constrast	Rigid	Reduction of superficial regions of both PGs: 4.9%/wk	Superficial regions show medial translation of: left PGs: medial shift of 0.91 ± 0.9 mm/wk right PGs: medial shift of 0.78 ± 0.13 mm/wk
Castadot et al (2008)	10	CT scan at mean doses of 14, 25, 35, and 45 Gy; iv contrast	Deformable	Reduction of • GTV_T: 3.2%/treatment day • GTV_N: 2.1%/treatment day • Homolateral PG: 0.9%/treatment day • Heterolat PG: 1.0%/treatment day • Low dose homolat CTV_N: 0.5%/treatment day • low dose heterolat CTV_N: 0.4%/treatment day	After 5 treatment wks: • Homolat PG: medial shift of 3.4 mm • GTV_T: lateral shift of 1.3 mm • GTV_N: medial shift of 0.9 mm • Low dose homolat CTV_N: medial shift of 1.8 mm No shift for the heterolat PG and heterolat low dose CTV_N.

CT, computerized tomography; GTV, gross tumor volume; CTV, clinical target volume; PTV, planning target volume; PG, parotid gland; COM, center of mass; MV, mega-voltage; SMG, submandibular gland; homolat, homolateral; heterolat, heterolateral; CTV_T, primary tumor CTV; PTV_T, primary tumor PTV; CTV_N, nodal CTV; GTV_T, primary tumor GTV; GTV_N, nodal GTV; NA, not applicable.

Anatomical modifications

Castadot, P., Lee, J. a., Geets, X. & Grégoire, V. Adaptive Radiotherapy of Head and Neck Cancer. Semin. Radiat. Oncol. 20, 84–93 (2010).

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Author	No. of Patients	Per-Treatment Imaging	Image Registration	Results	Comments
O'Daniel et al (2007)[44]	11	In-room CT-on-rail scans twice/wk; no iv contrast	Deformable	Cumulative PG dose greater than planned; median dose increase: 1 Gy No impact on tumor dose coverage	If no image-guidance for daily setup error correction, cumulative PG dose greater than planned; median dose increase: 3 Gy for homolat PG and 1 Gy for heterolat PG
Hansen et al (2006)[52]	13	CT scan after a mean dose of 38 Gy	Rigid	• High dose PTV D_{99}, D_{95}, $V_{93\%}$ decreased by 12.1, 12.2 Gy, and 7%, respectively • Low dose PTV D_{99}, D_{95}, $V_{93\%}$ decreased by 12.6, 11.3 Gy, and 8.2%, respectively • Right PG V_{26Gy} increased by 10.9% • Mandible V_{60Gy} increased by 7.2%	If replanning; significant improvement of: • Low and high dose PTVs D_{99} D_{95} and $V_{93\%}$ • Spinal cord D_{max}, D_{1cc} • Brainstem D_{max} • Right parotid PG D_{mean}, D_{50}, and V_{26Gy} • Mandible D_{max} and V_{60Gy}
Robar et al (2007)[53]	15	Weekly CT scan; no iv contrast	NA	• Left PG D_{mean} increased by 2.6 ± 4.3%, V_{26Gy} increased by 3.5 ± 5.2% • Right PG D_{mean} increased by 0.2 ± 4.0%, V_{26Gy} increased by 0.3 ± 4.7%	
Han et al (2008)[43]	5	Daily helical MVCT	Rigid	PG D_{median} increased from 0.83 to 1.42 Gy with an average increase rate of 0.17 Gy/treatment day corresponding to an average increase of 2.2%/treatment day	Strong correlation between the volume and the median parotid dose during the treatment (correlation coefficient, −0.95)
Lee et al (2008)[56]	10	Daily helical MVCT	Deformable	• PG daily D_{mean} differed from the planned dose by an average of 15% • PG cumulative D_{mean}: planned: 29.7 Gy actual: 32.7 Gy (110% of planned dose)	• Changes in the distance between the COMs of the left and right PGs correlated strongly with the mean parotid dose changes (R^2 = 0.88) • Correlation between the relative weight loss and higher parotid mean doses (R^2 = 0.58)
Castadot et al (2009)	10	CT scan at mean doses of 14, 25, 35, and 45 Gy; iv contrast	Deformable	• PGs D_{mean}: planned: 17.9 Gy, actual 18.7 Gy • SMGs D_{mean}: planned 51.9 Gy, actual: 52.8 Gy • OC D_{mean}: planned 26.0 Gy, actual 26.7 Gy • SC D_2: planned 40.1 Gy, actual: 41.0 Gy • Skin V_{60}: planned 17.2 Gy, actual 18.3 Gy • No difference in PTV or CTV coverage	

OC, oral cavity; SC, spinal cord; D_x, dose to x% of the volume; D_{max}, maximum dose; D_{1cc}, dose to 1 cc.; D_{mean}, mean dose; D_{median}, dose to 50% of the volume; V_x, volume receiving a dose of x Gy or x% of the prescribed dose.

Dosimetric modifications

Castadot, P., Lee, J. a., Geets, X. & Grégoire, V. Adaptive Radiotherapy of Head and Neck Cancer. Semin. Radiat. Oncol. 20, 84–93 (2010).

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Patient monitoring: challenges for replanning

- **Single institutions** papers
- Average number of patients **11.1**!
- **Different imaging** equipments
  - (2 CT on rail, 2 MV CBCT, 7 Kv CT)
- **Different registration** techniques
  - (8 rigid, 2 deformable, 1 NA)
- Completely **different timings** for imaging acquisition!
  - (from one acquisition at a given dose level up to daily CBCT)

Patient monitoring: challenges for replanning

- **Take home messages:**
- **Do replanning**
- At least once during the treatment
- Most important changes occur after before 2nd, 3rd treatment week (20 – 30 Gy delivered dose)
- Consider monitoring weight loss or additive risks (mucositis, chemo, absence of feeding tube)

Good work!!!

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On the Pareto Front

Advanced Treatment Planning Course
23-27 September 2018 – Athens, Greece

Markus Stock

MedAustron
Ion Therapy Center

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**.

‘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:

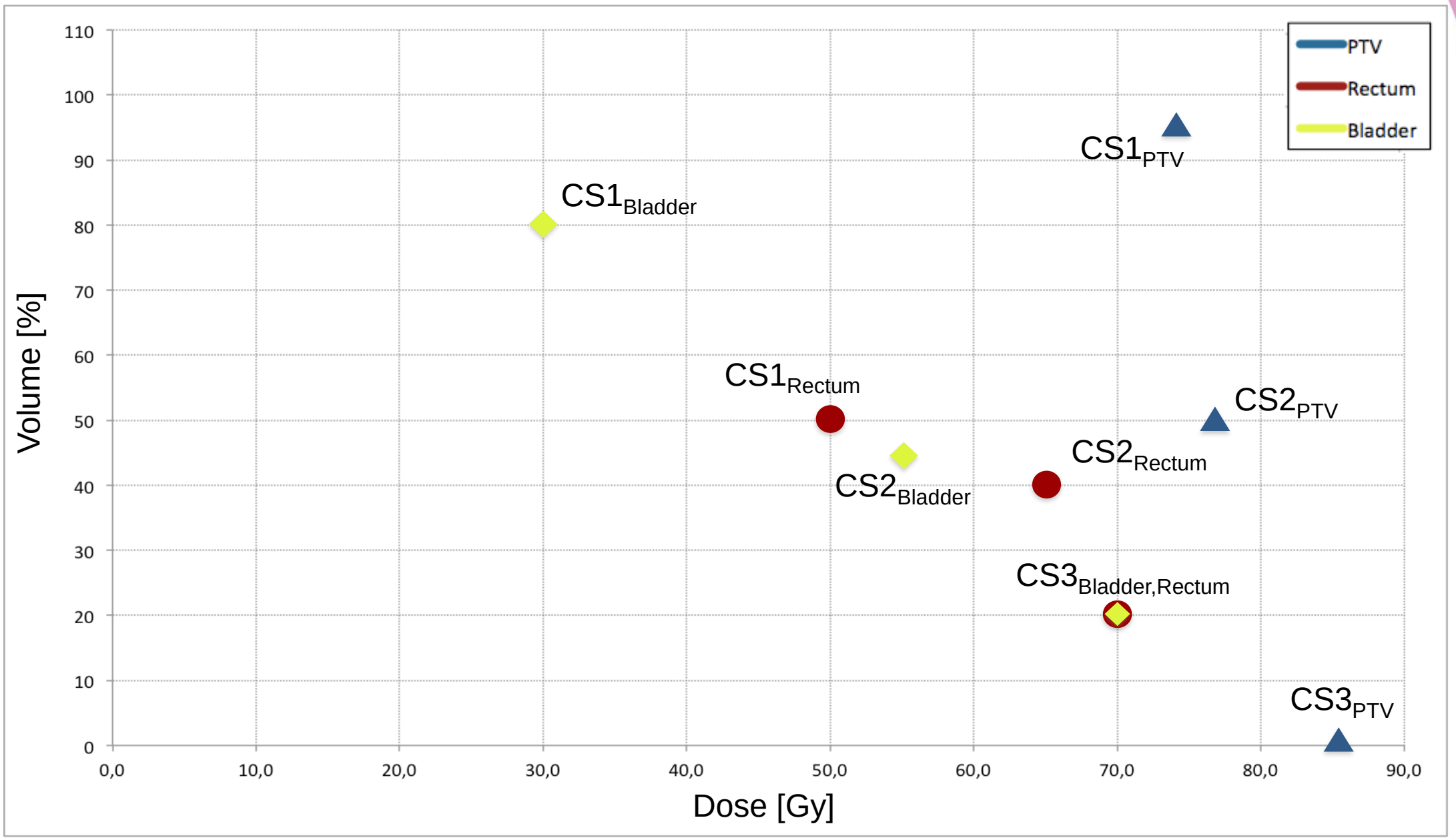
- ‘optimal’ dose coverage
- optimal sparing: as low as possible

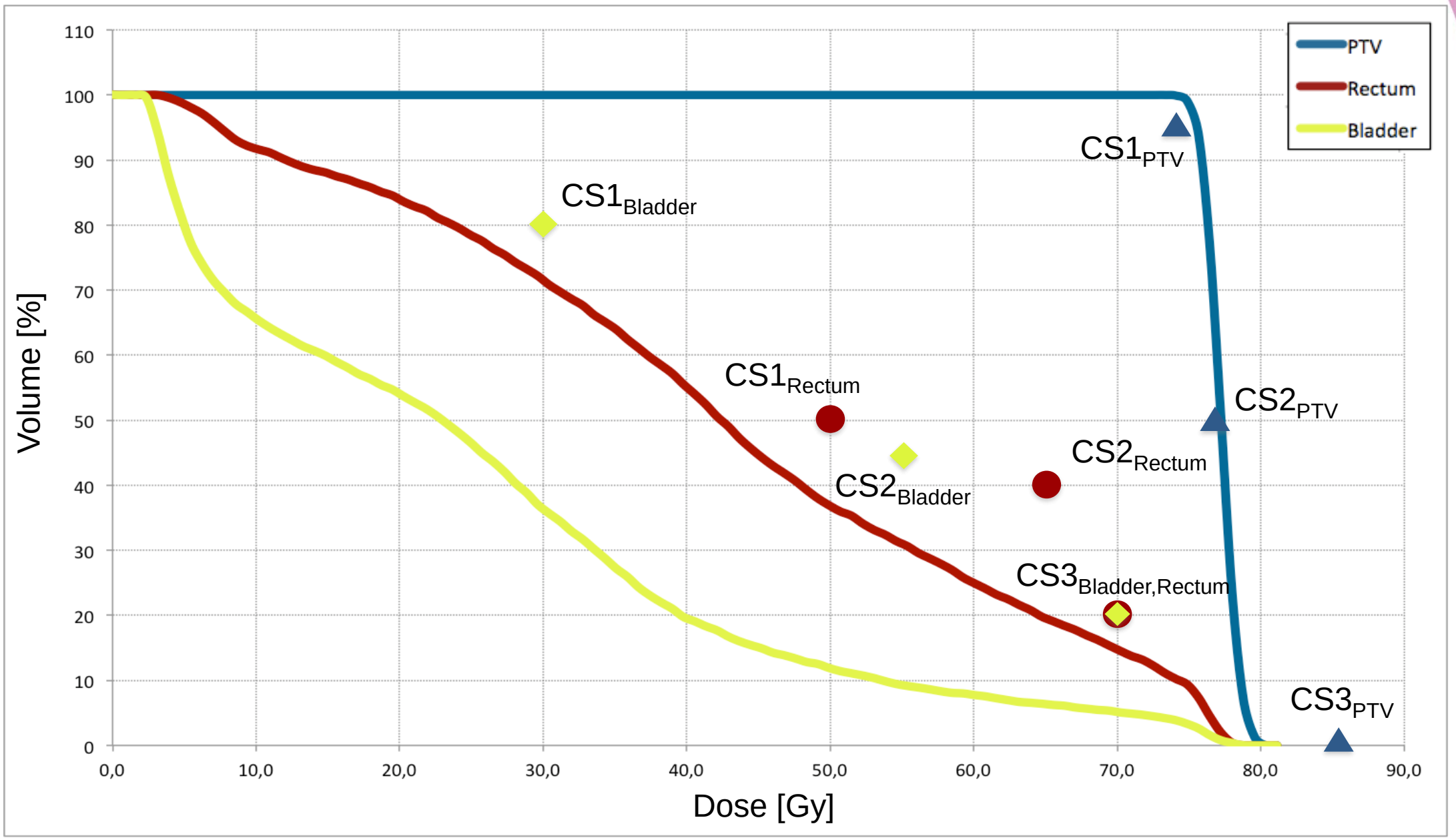
Planning problem in manual planning

- 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?

The „manual“ way to get there

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CS1Bladder
CS1Rectum
CS2PTV
CS2Rectum
CS2Bladder
CS3Bladder,Rectum
CS3PTV
Volume [%]
Dose [Gy]
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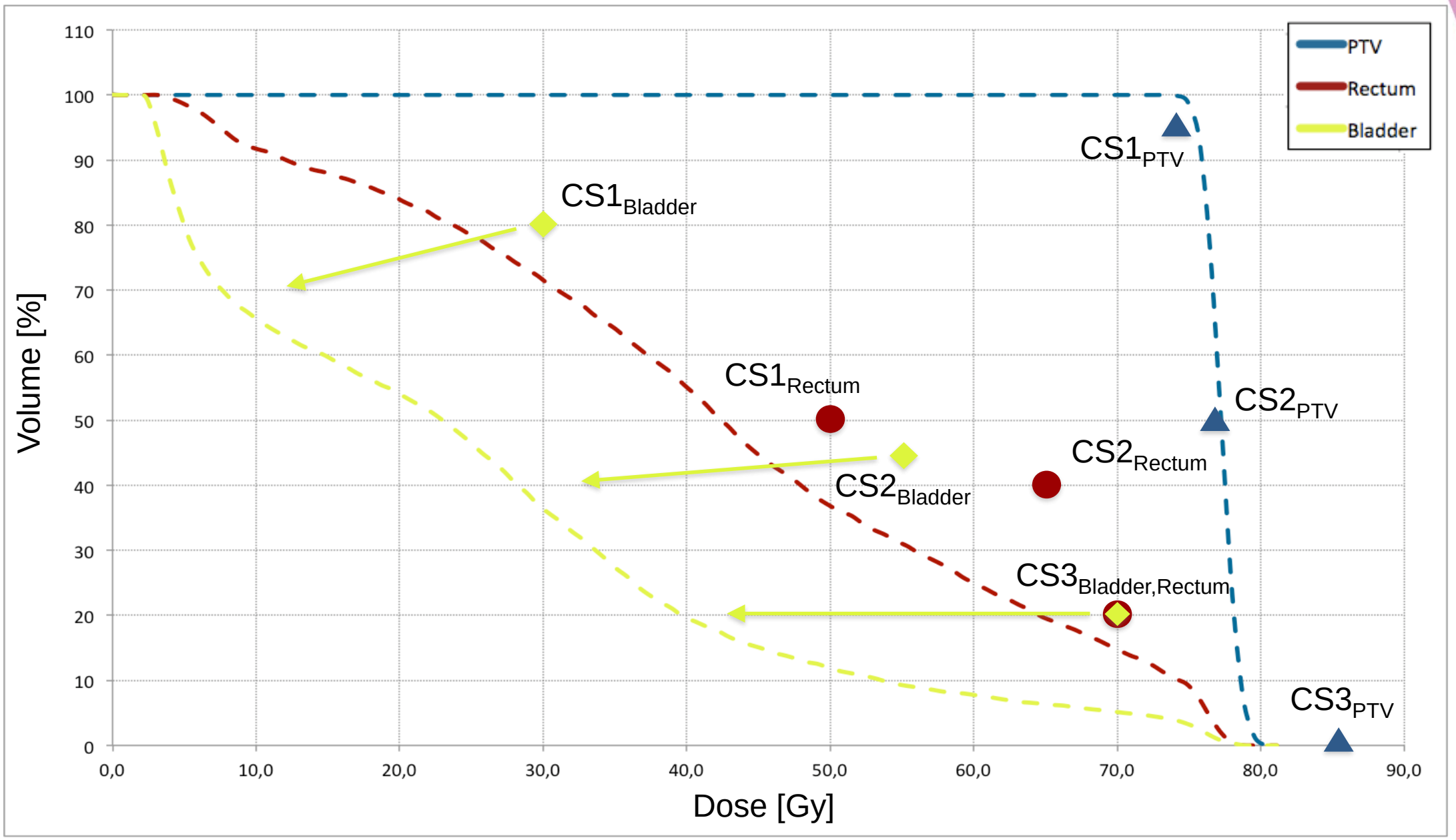
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Dose [Gy]
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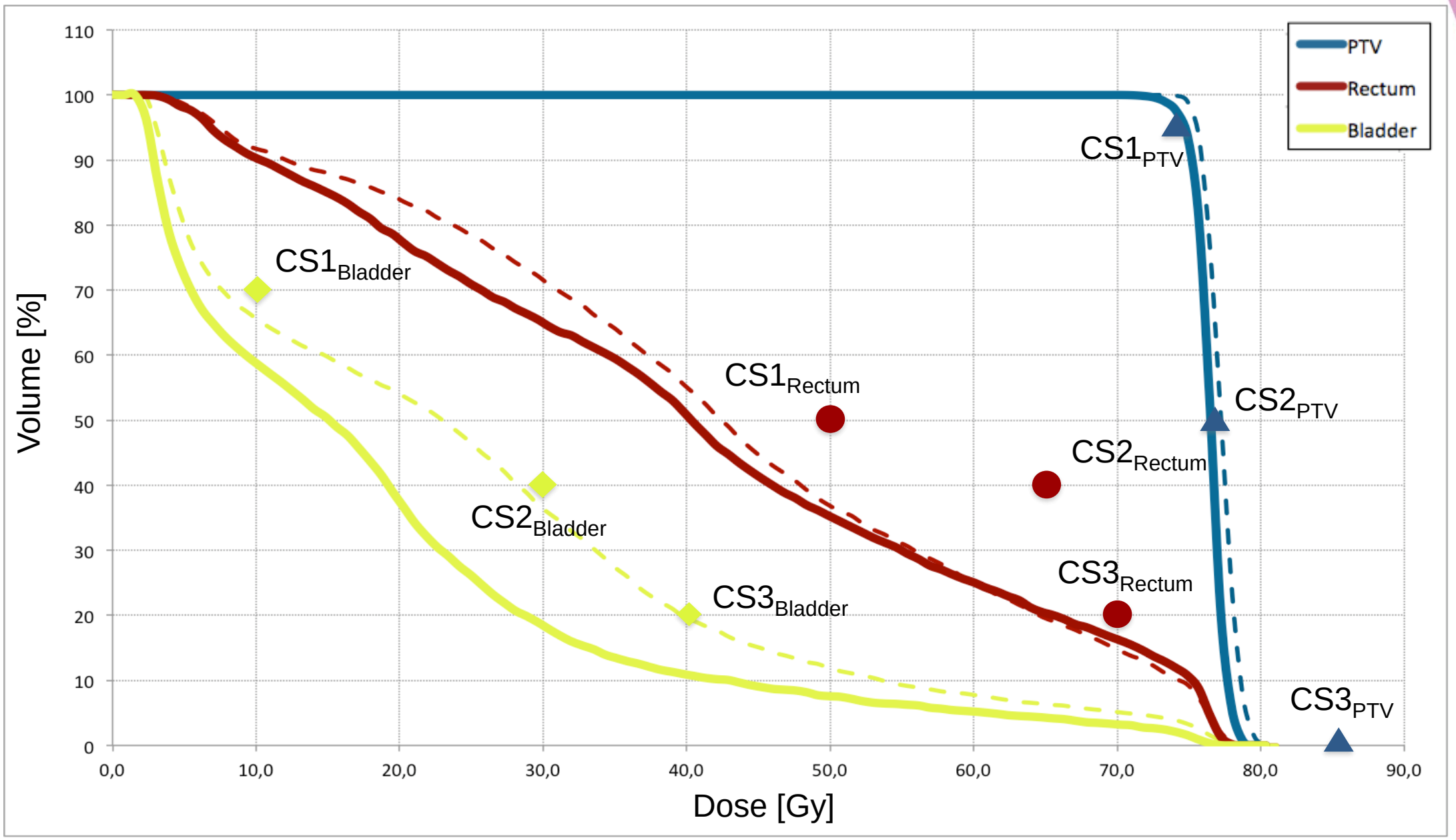
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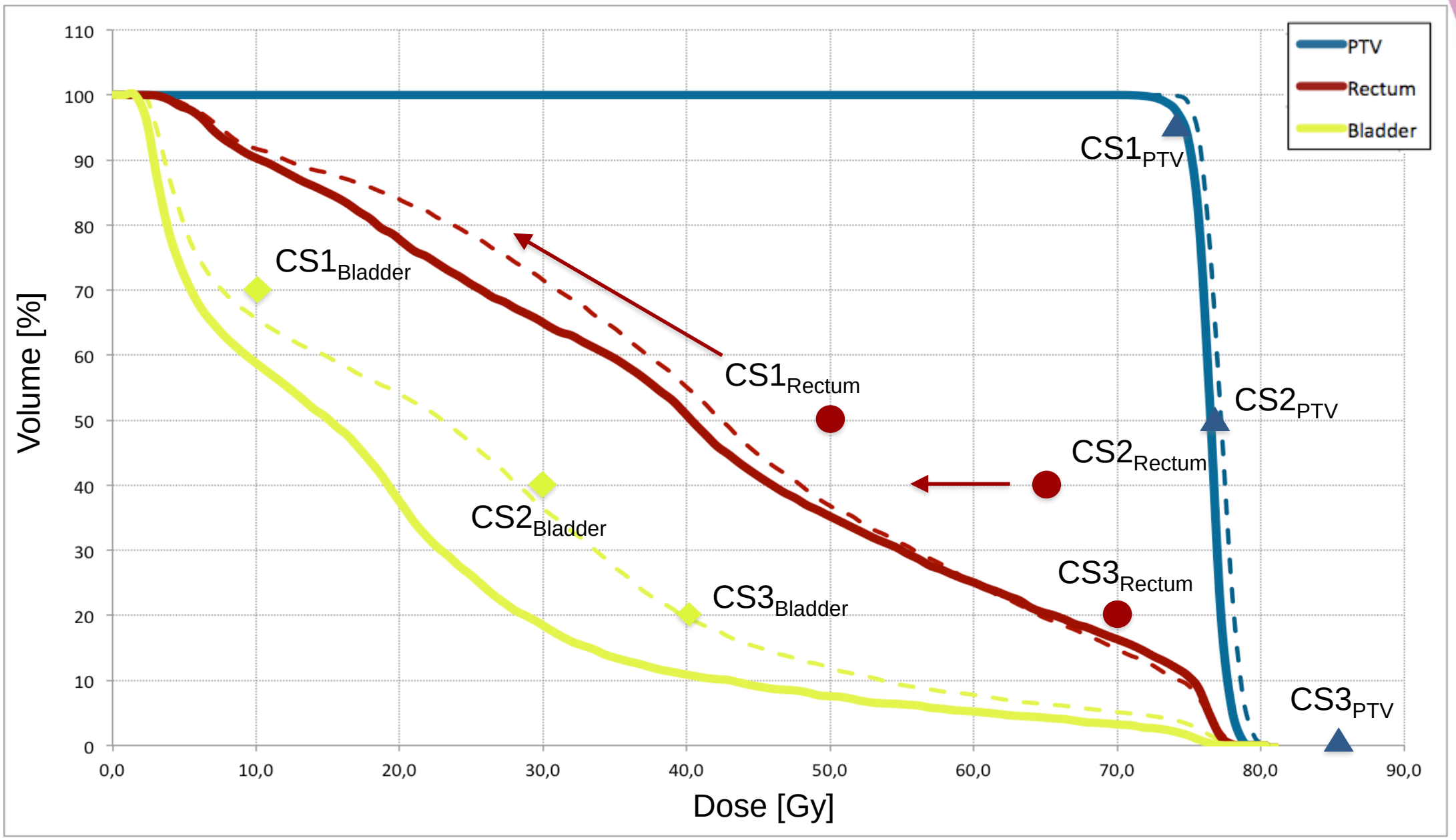
CS3Rectum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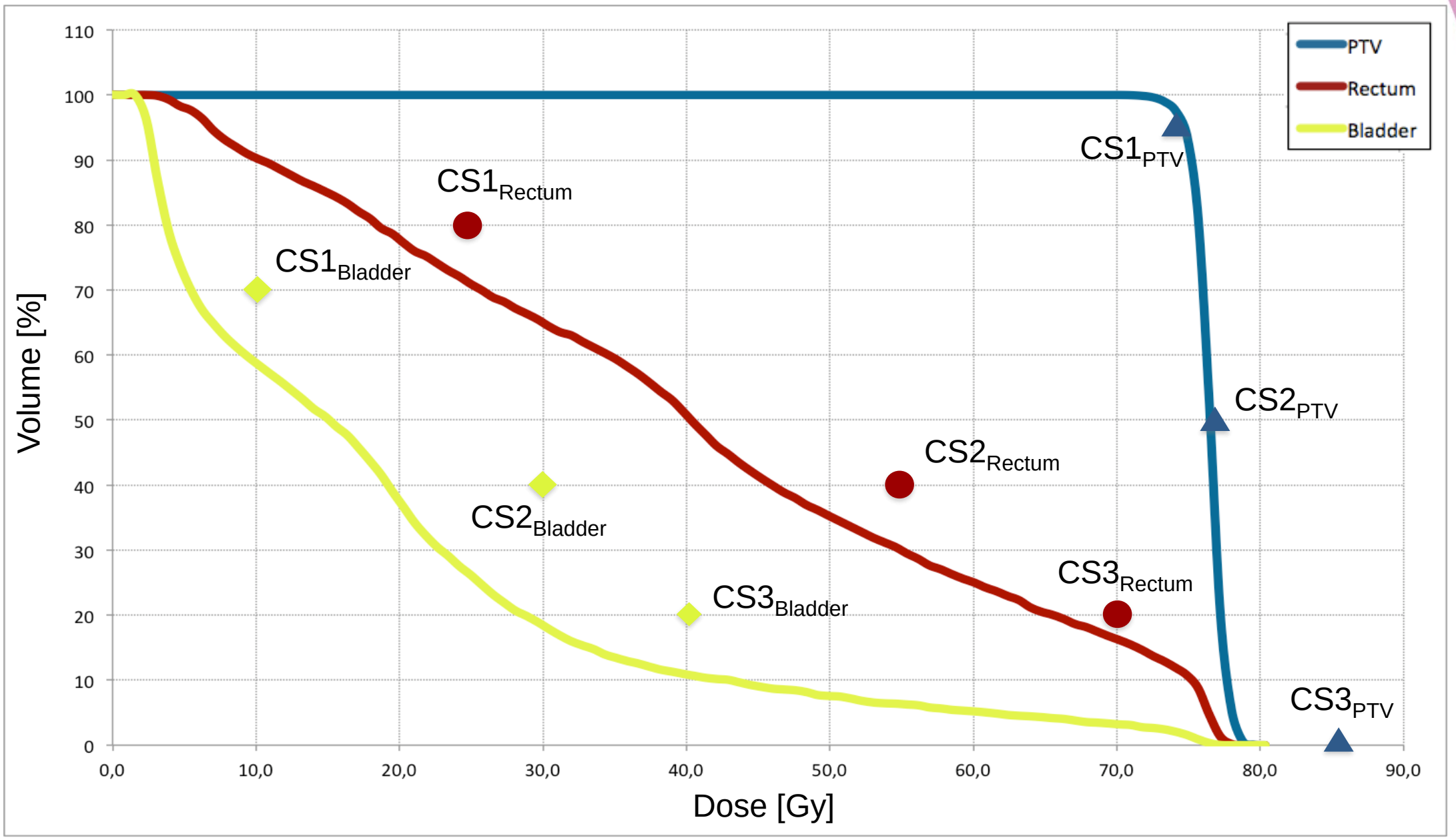
CS1Rectum
CS2PTV
CS2Rectum
CS2Bladder
CS3Rectum
CS3Bladder
CS3PTV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CS2Bladder
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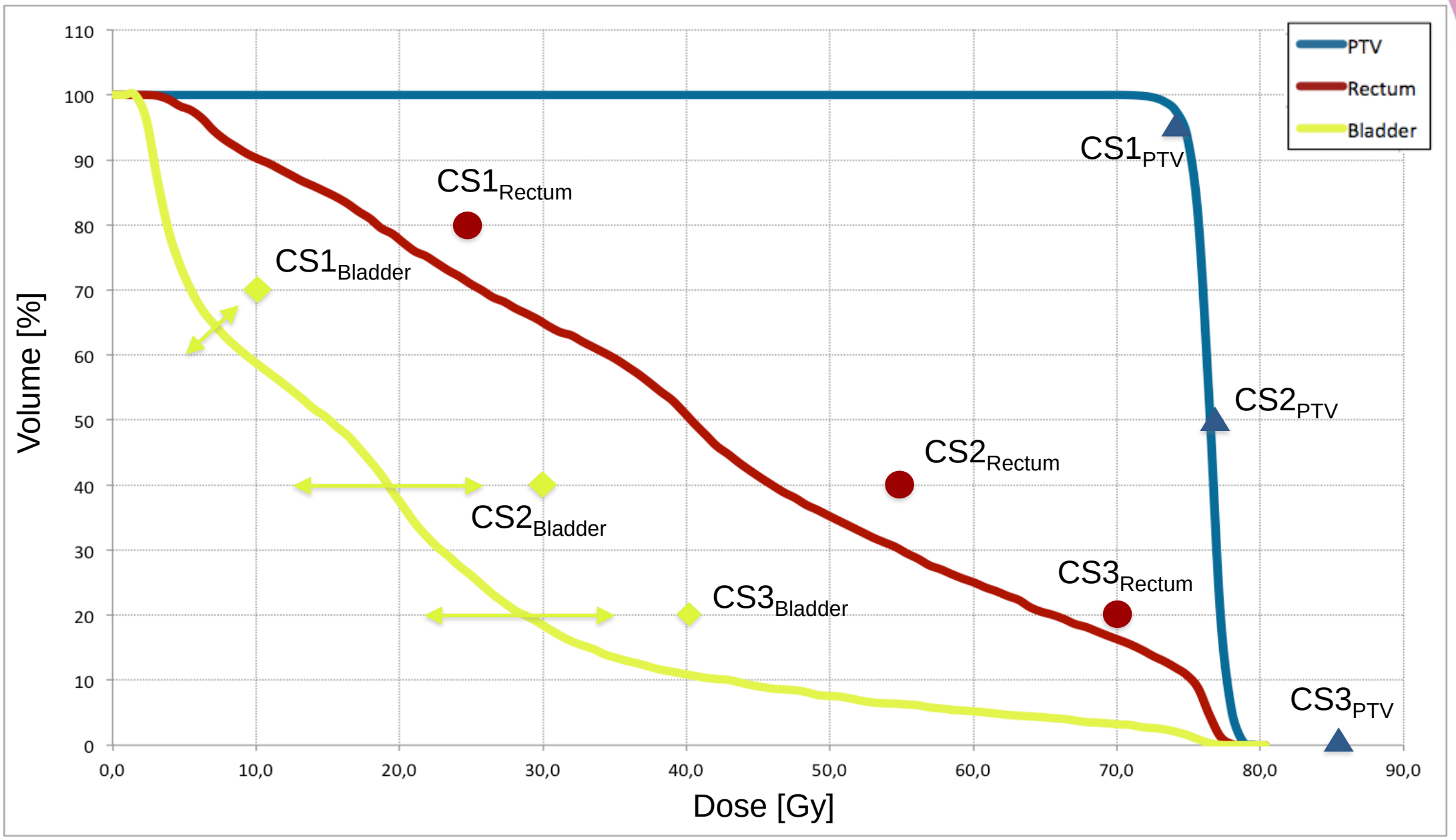
CS3Bladder
CS3PTV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Volume [%]
Dose [Gy]
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CS1PTV
CS2PTV
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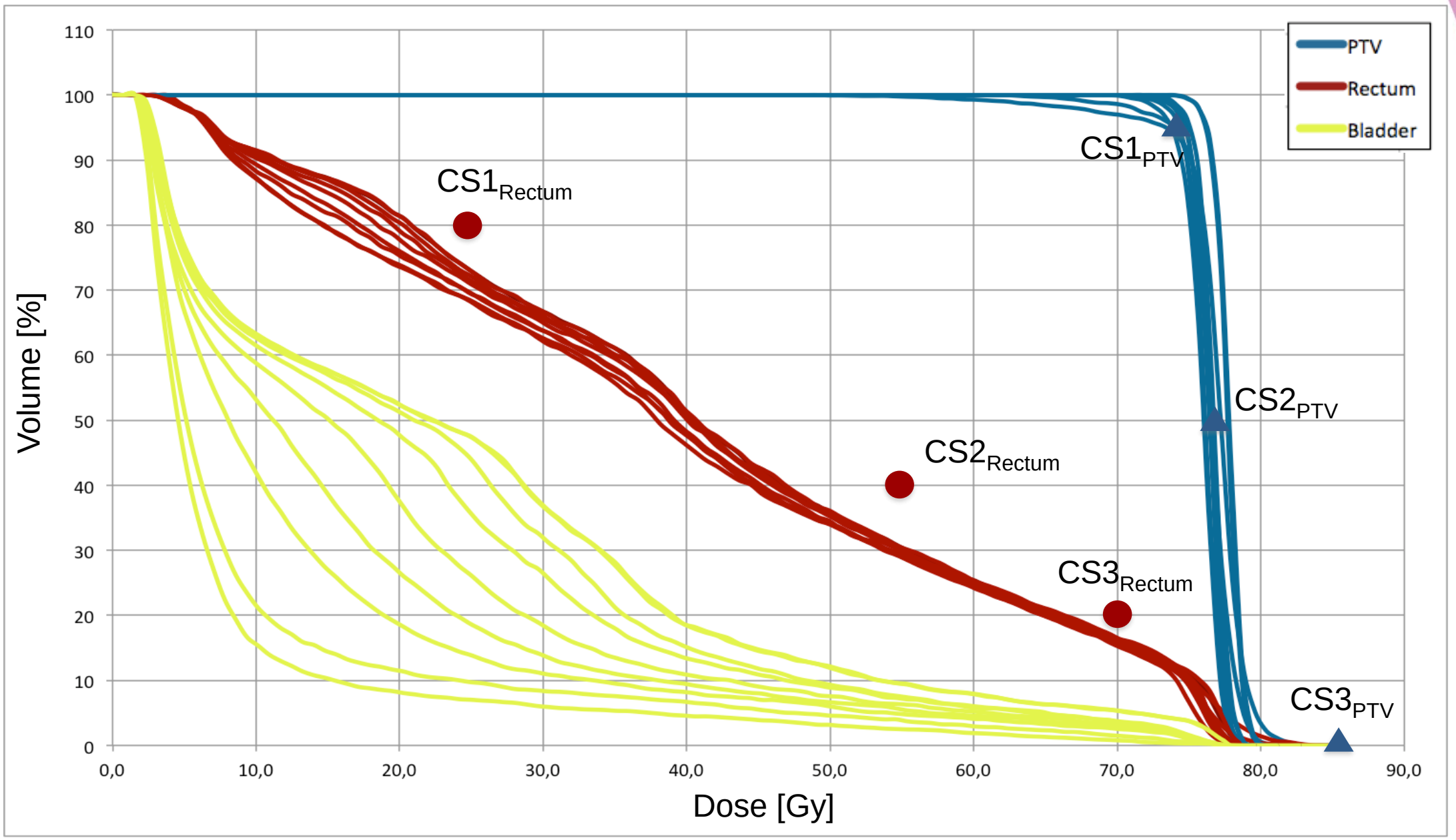
CS3Rectum
CS3Bladder
CS3PTV


PTV
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CS1Rectum
CS1PTV
CS2Rectum
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CS3Rectum
CS3PTV
Volume [%]
Dose [Gy]
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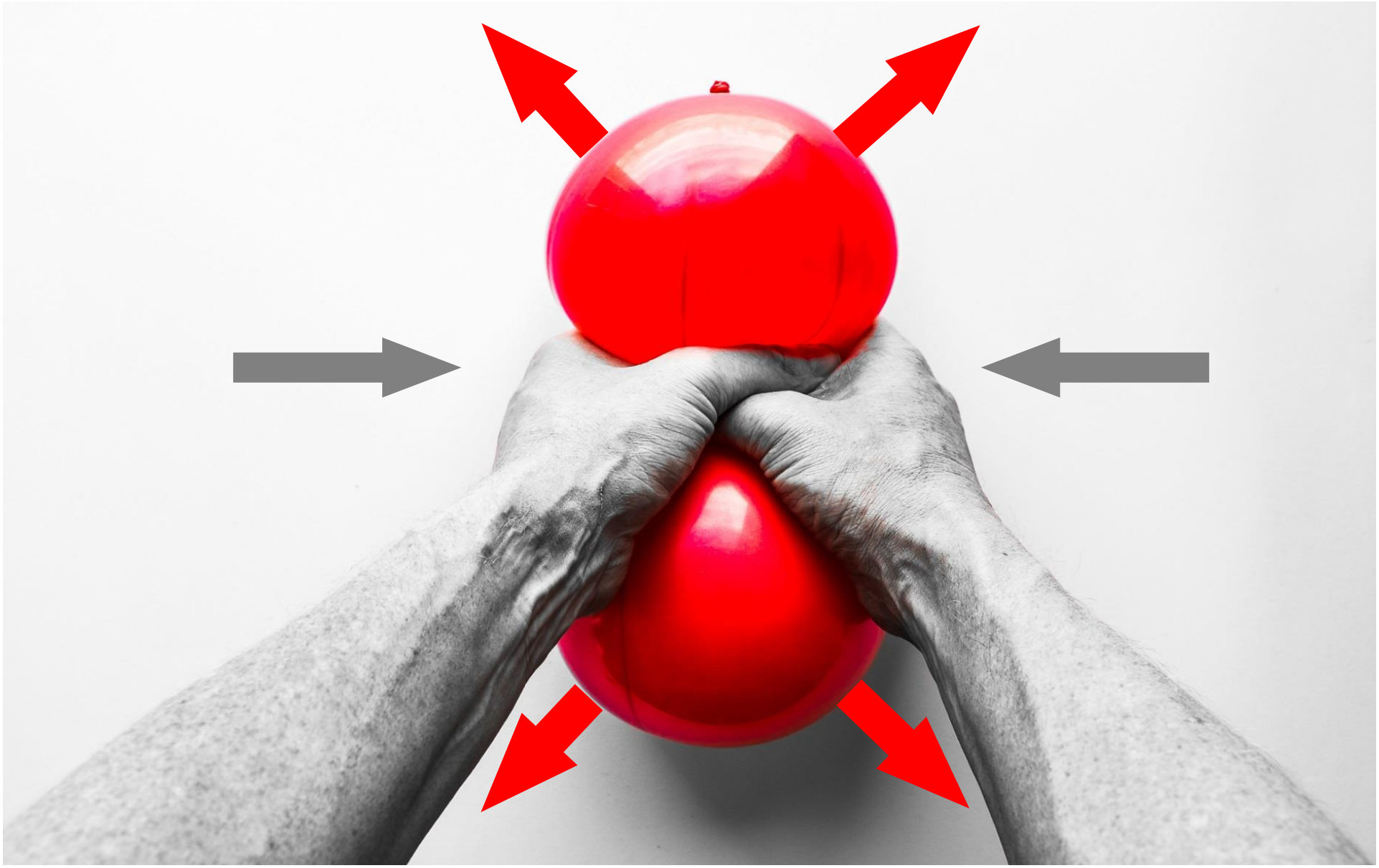
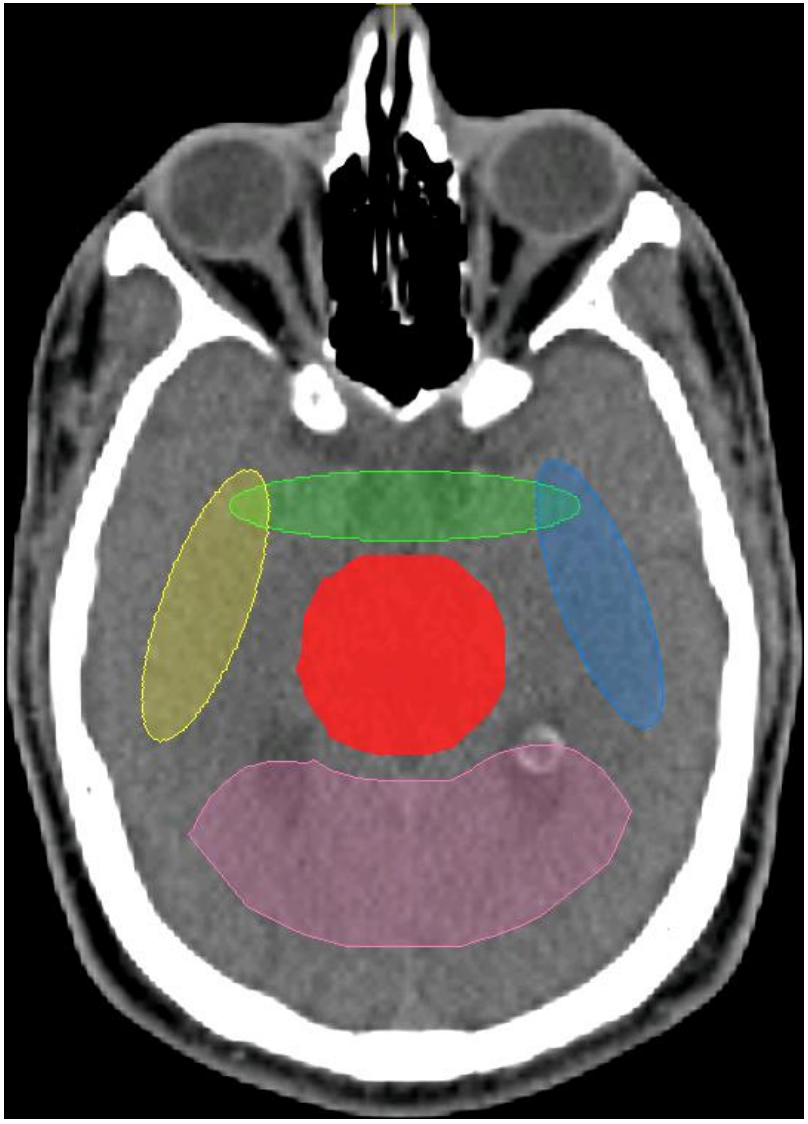
Sweeping dose

- 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



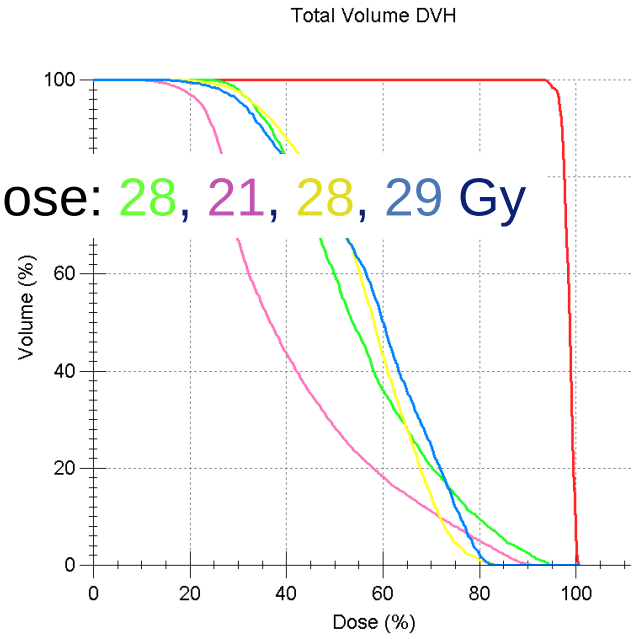
PTV_pareto
OAR_1
OAR_2
OAR_3
OAR_4

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

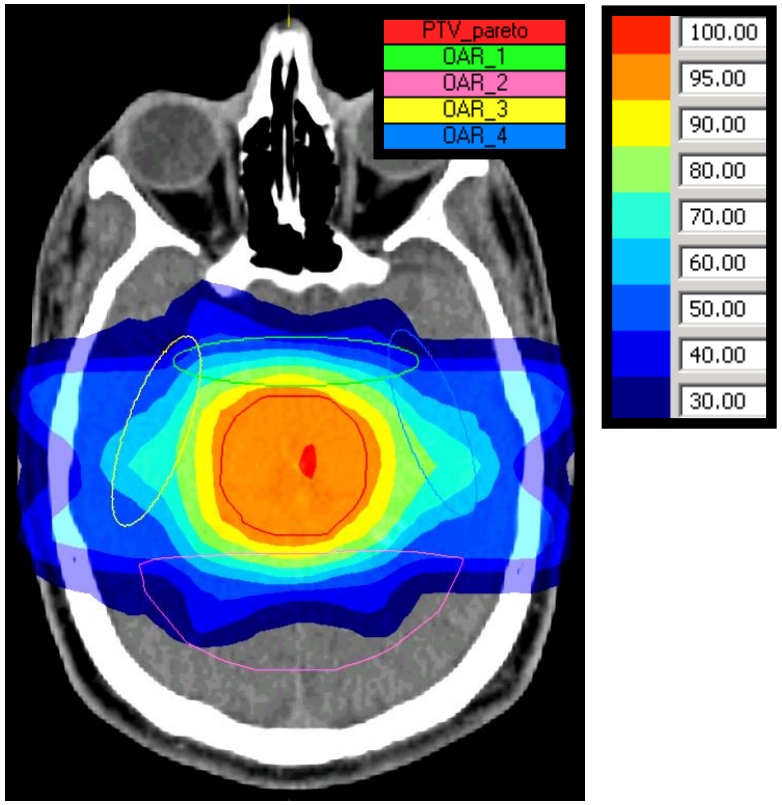
Sweeping dose theoretical example

Option 1:
Conformal dose around PTV, no constraints on individual OAR's

'*Completely random*' shape of dose distribution in surrounding OAR's



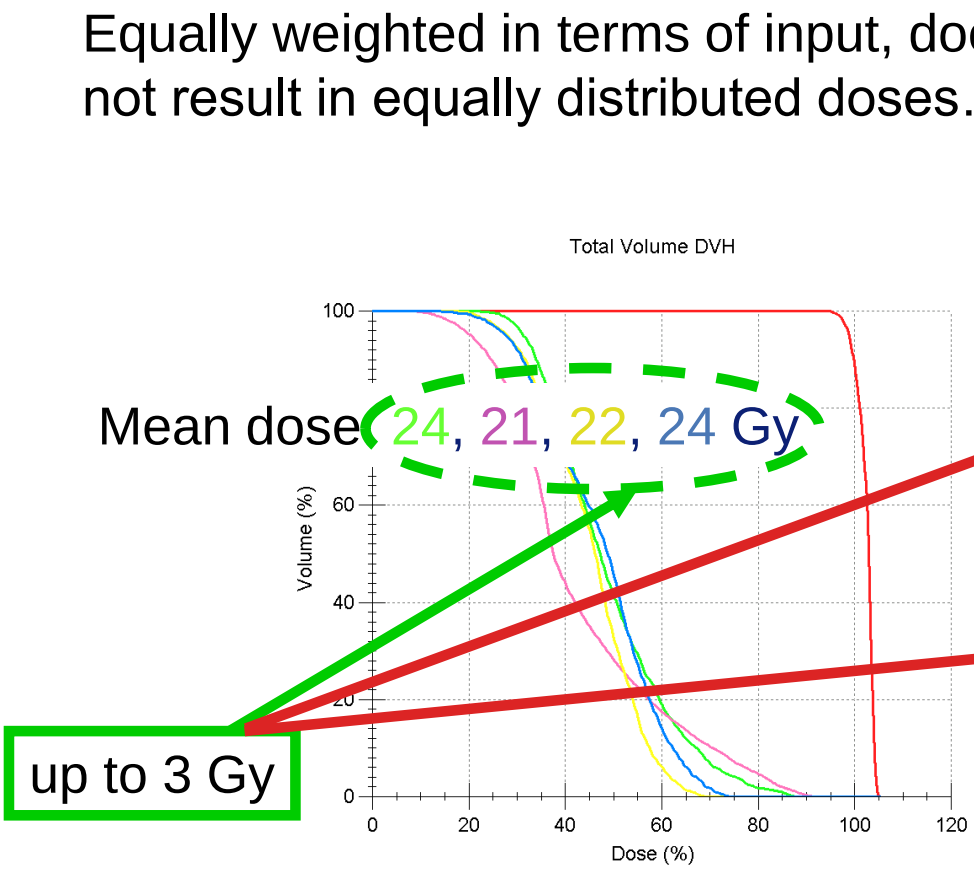
Mean dose: 28, 21, 28, 29 Gy



Sweeping dose theoretical example

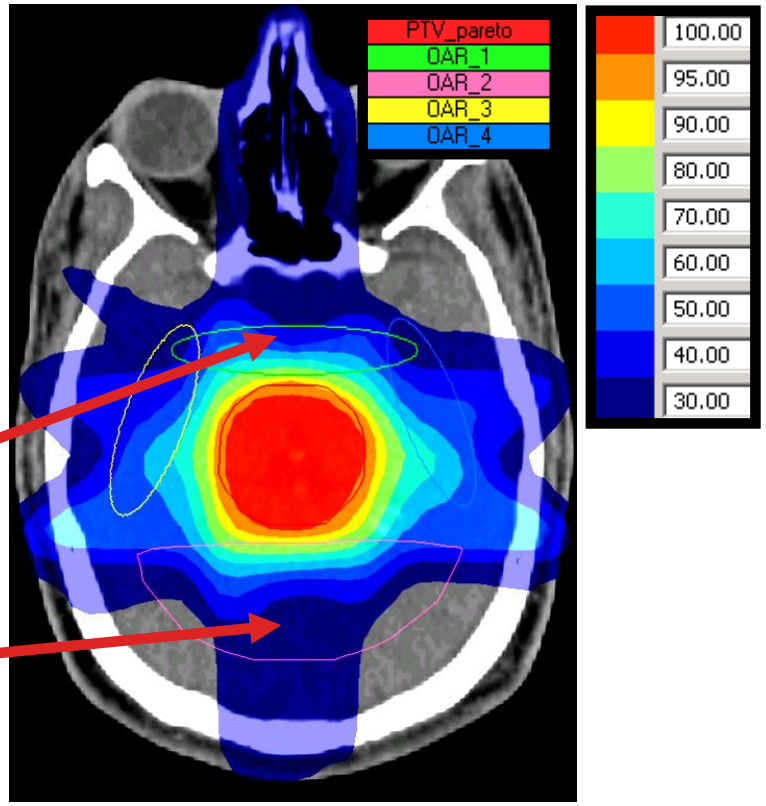
Option 2:
Conformal dose around PTV, equally weighted constraints on all OAR's (mean dose = 25 Gy)

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



Mean dose 24, 21, 22, 24 Gy

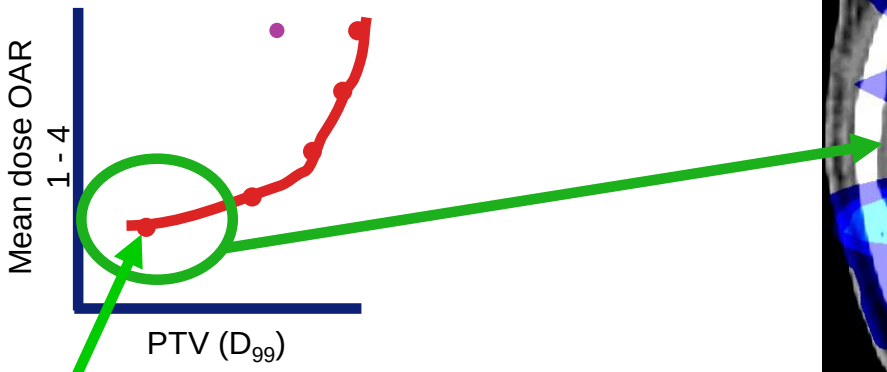
up to 3 Gy

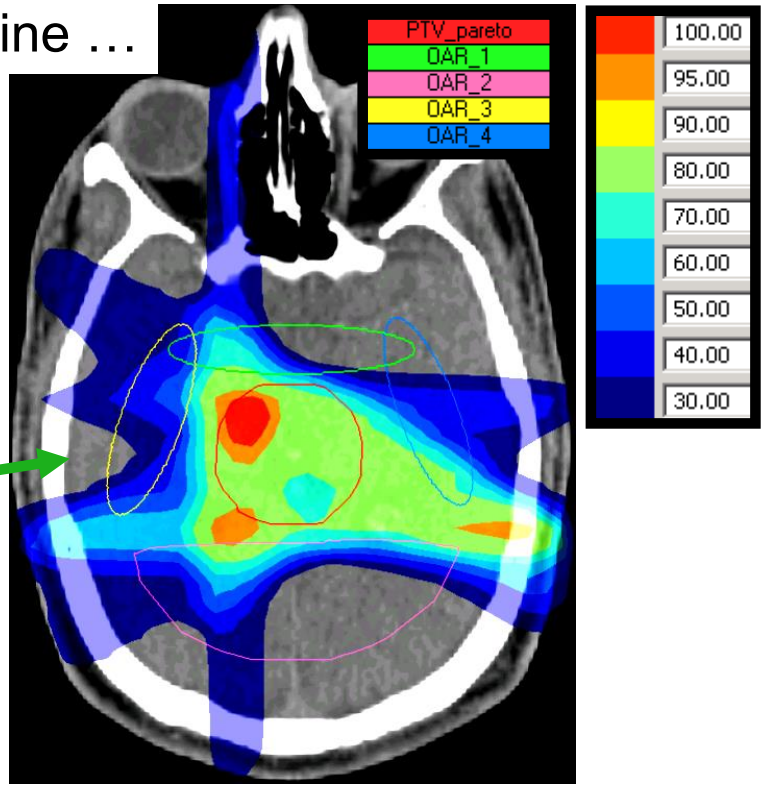


Sweeping dose theoretical example

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 …

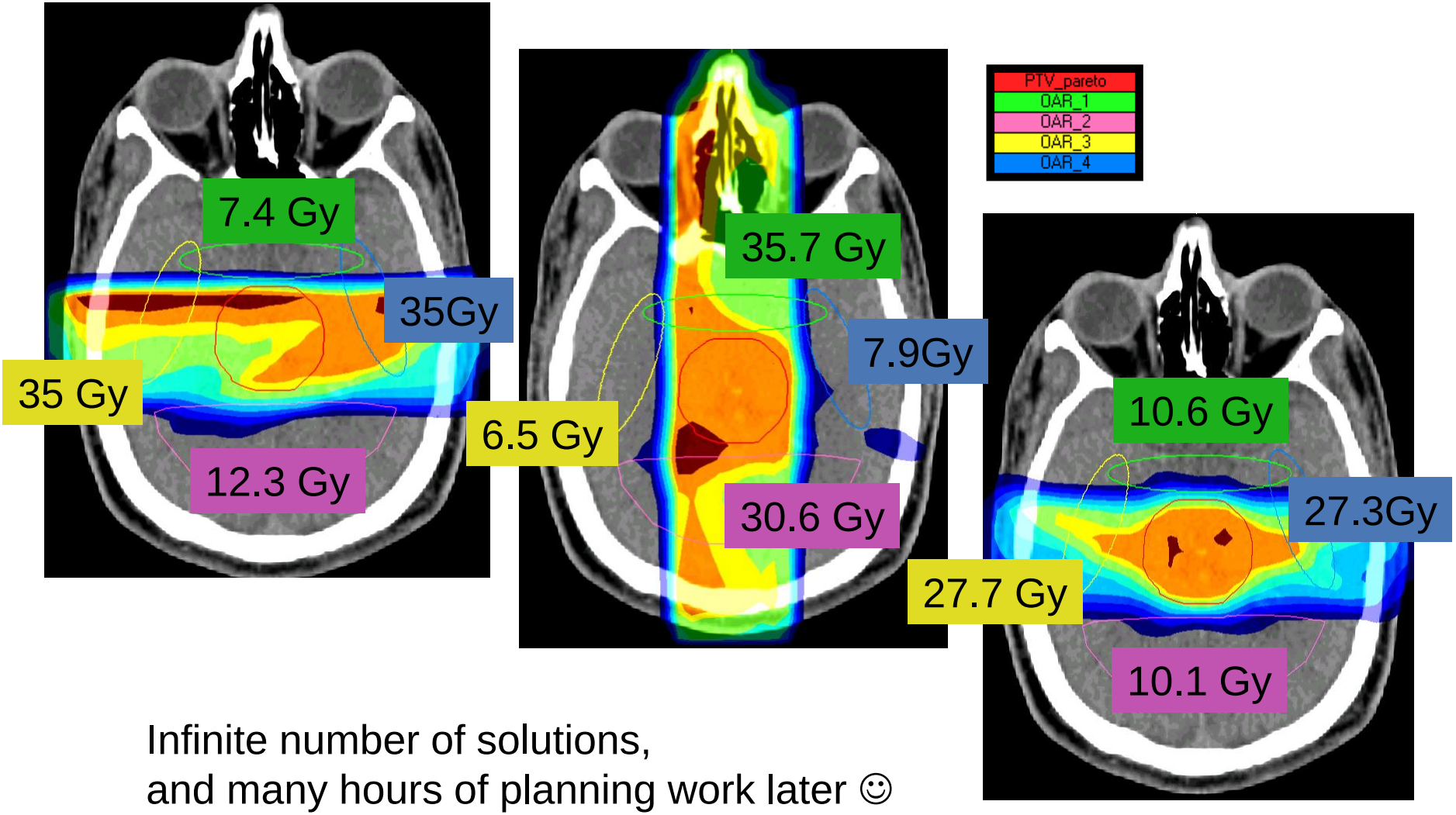




Pareto optimal plan? Sure!
Optimal? No!

Sweeping dose theoretical example, many options …

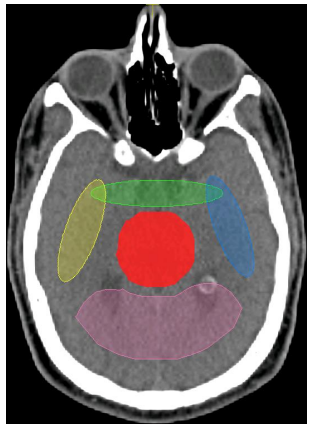
Option 4,5,6, ……. :



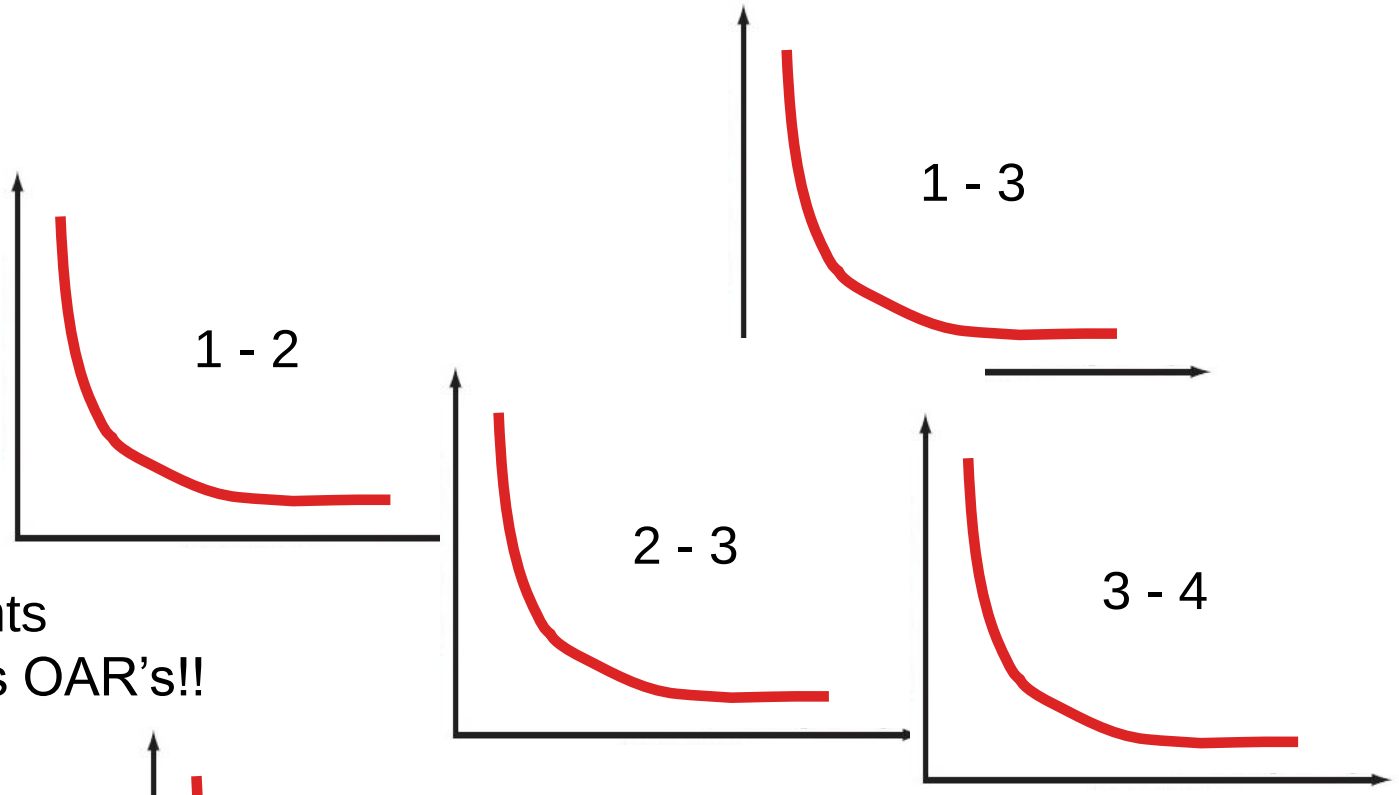
Infinite number of solutions,
and many hours of planning work later ☺

Pareto front versus Pareto surface

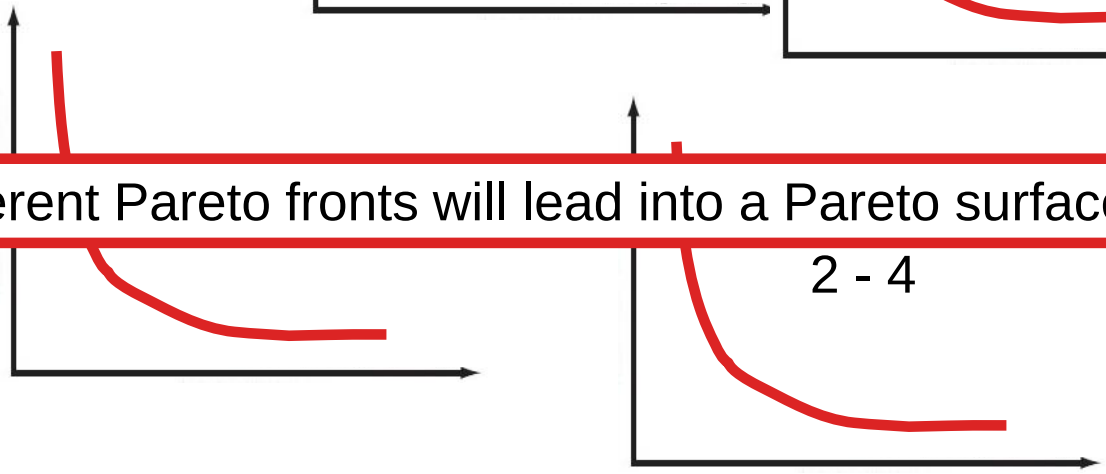
OAR's 1,2,3,4



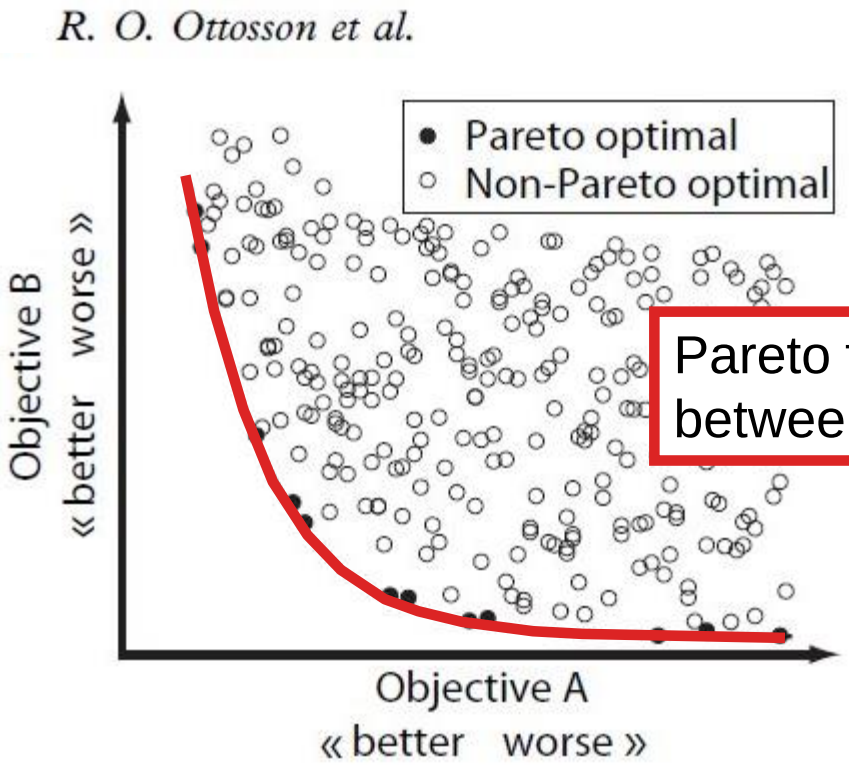
Another set of fronts
With Target versus OAR's!!



Combination of different Pareto fronts will lead into a Pareto surface



Pareto front



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

For two mutually contradicting objectives an endless number of solution exists

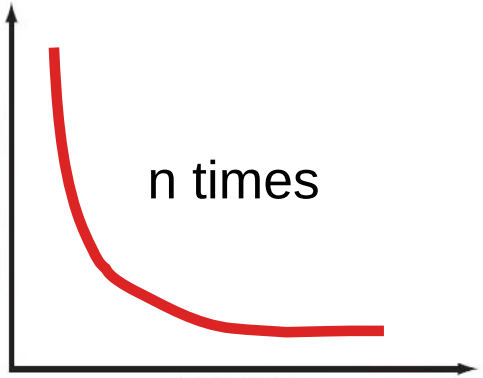
The solutions where one of the objectives can not be improved without deteriorating the other are *Pareto optimal*

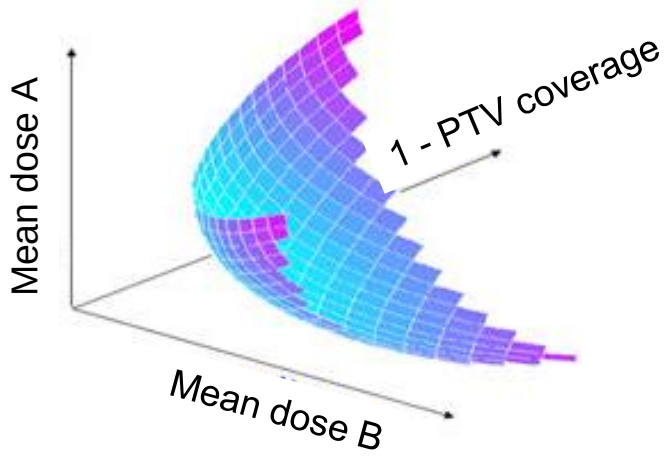
All Pareto optimal solutions lie on the Pareto front

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*





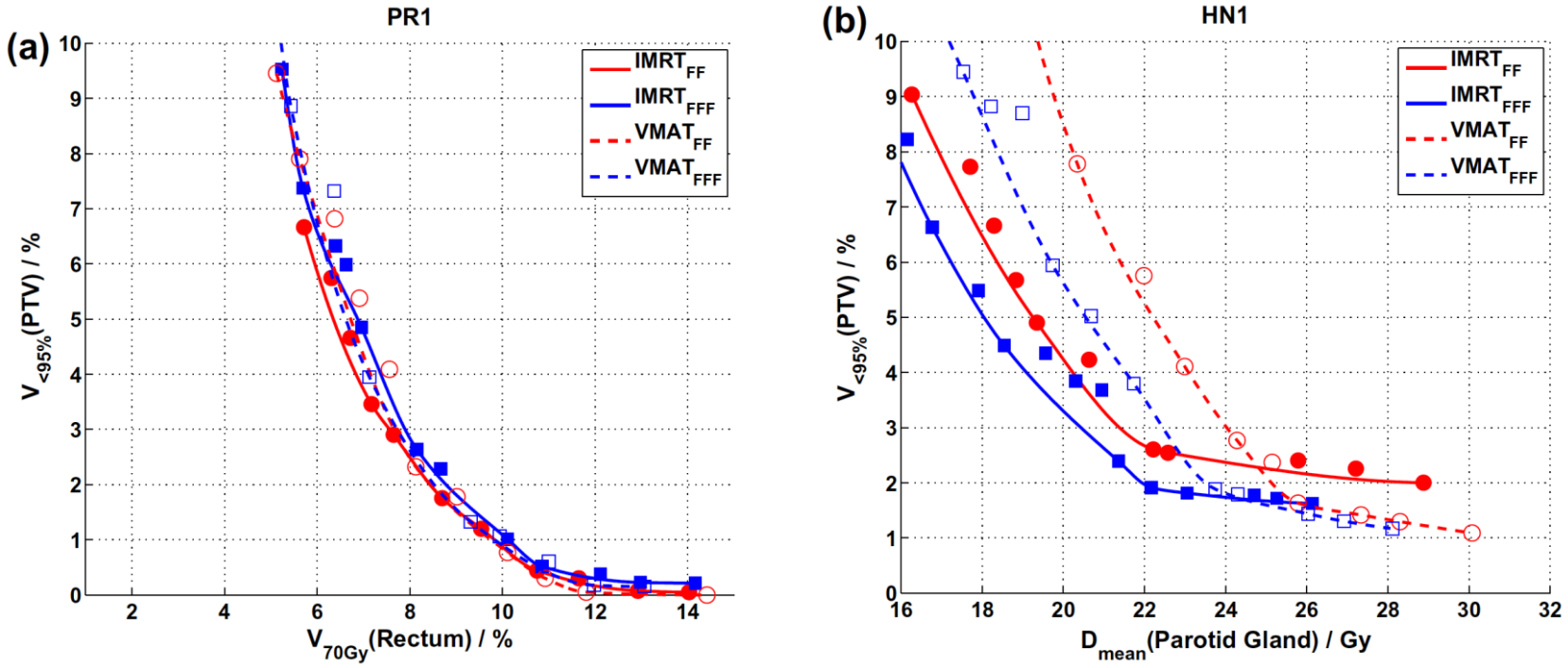
Pareto front

Pareto surface 3 dimensions

Investigate difference between VMAT vs IMRT & FFF vs FF beams

- Prostate and Head and neck

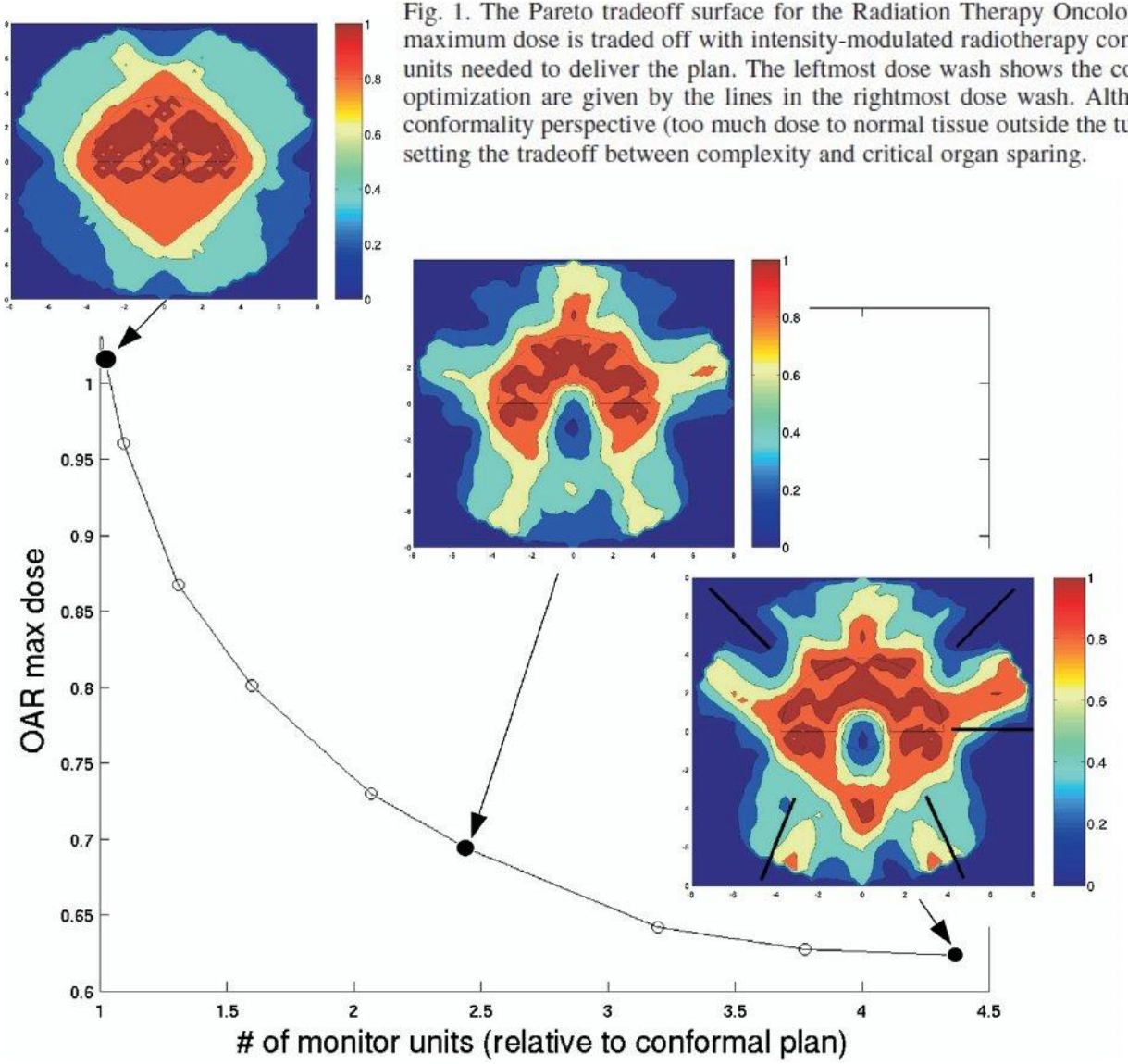
Lechner et al Rad Onc 2013



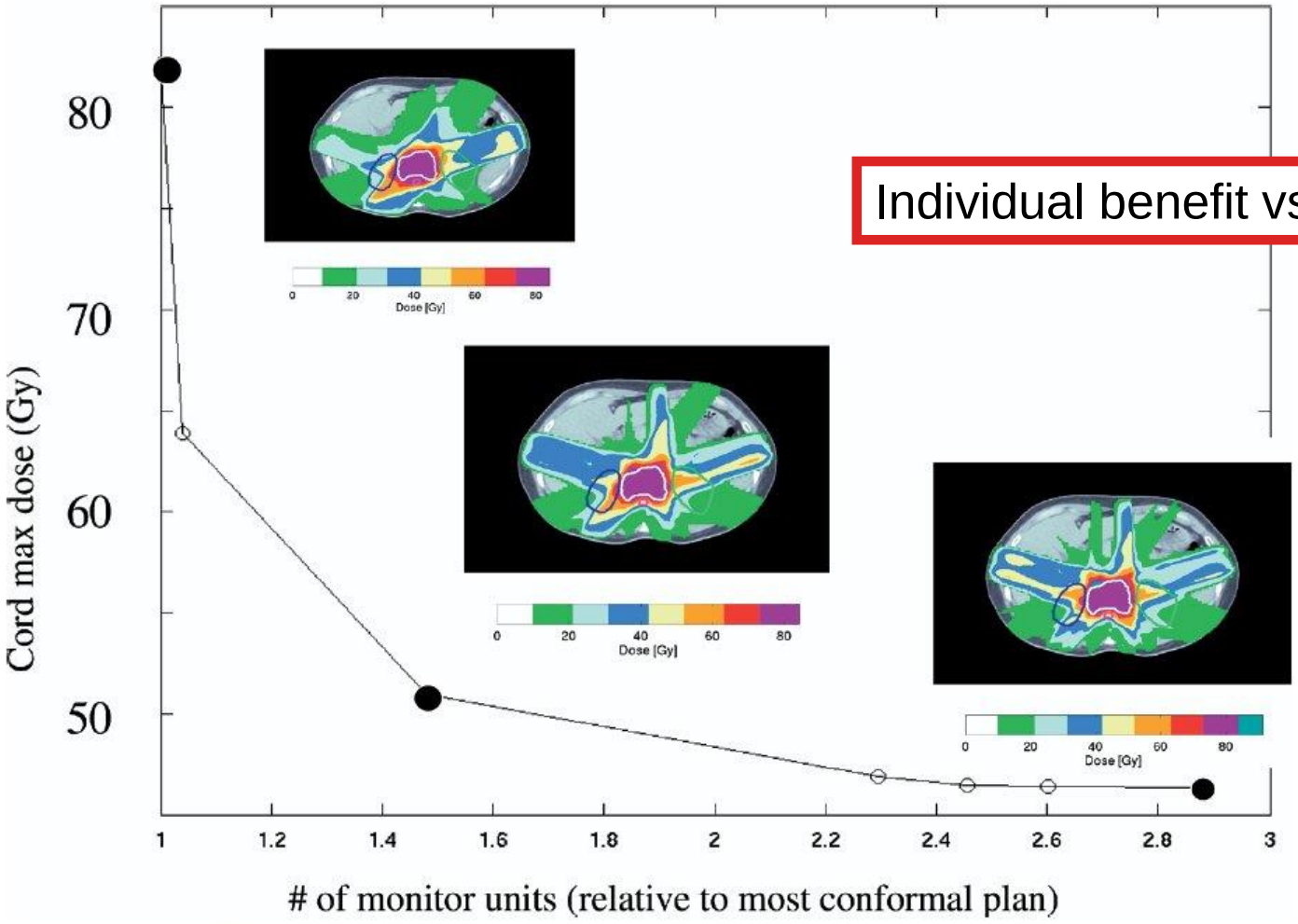
- FFF needed more MU/segments for larger targets to compensate for inhomogeneous dose distribution in case of homogenous prescription
- VMAT inferior quality to IMRT due to single arc

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.

Different plan optimization approaches

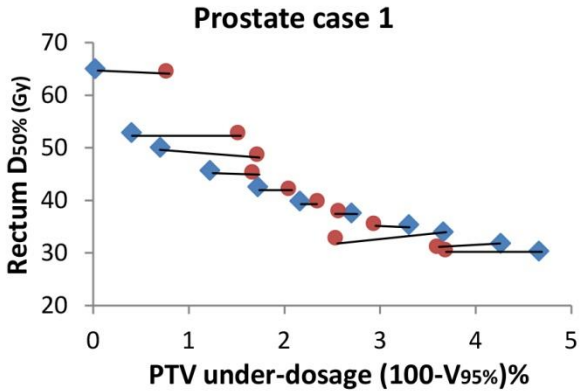
- Fluence map optimization (FMO)
  - Linear relationship between fluence and dose
  - Less computational effort
  - Still leaf-sequencing needs to be done either by optimizing MU or aperture
- Direct machine parameter optimization (DMPO)
  - leaf positions and segment weights as variables during optimization
  - More difficult to solve this problem as more physical constraints exist
  - Uses simulated annealing, column generation, gradient-based methods or genetic algorithms or heuristic methods
- For IMPT FMO is used
- Problem is to translate objectives and constraints with non-clinical meaningful weights into objective function → plan quality still depends on time commitment and experience of planer → multi criteria optimization (weight factors avoided)

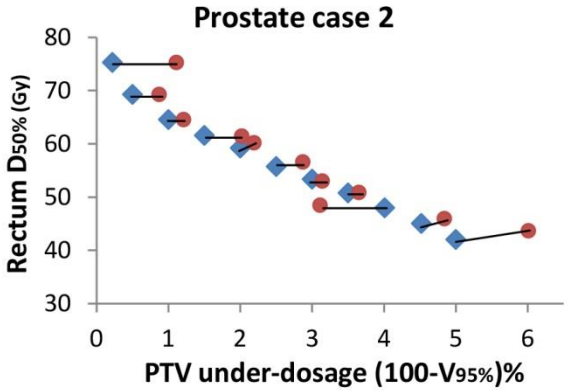
Limitations of FMO approach

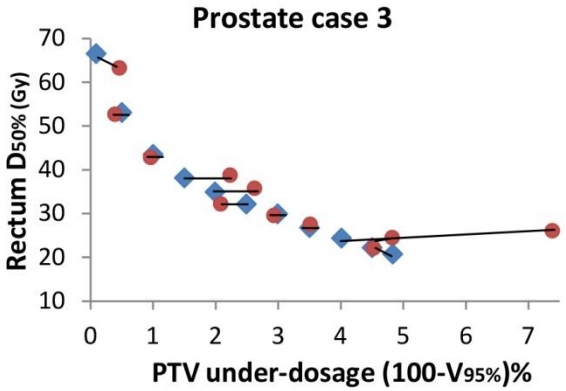
Difference between navigated and delivered plans?

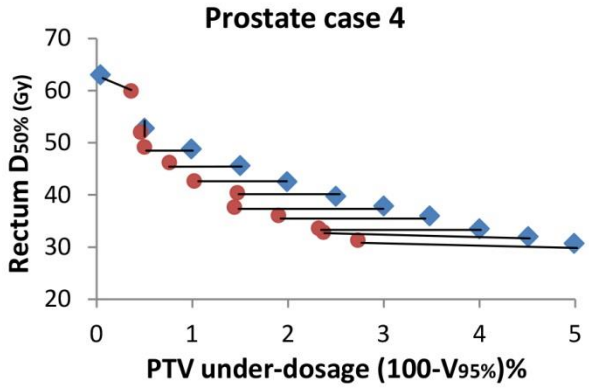
e.g. 5 prostate patients

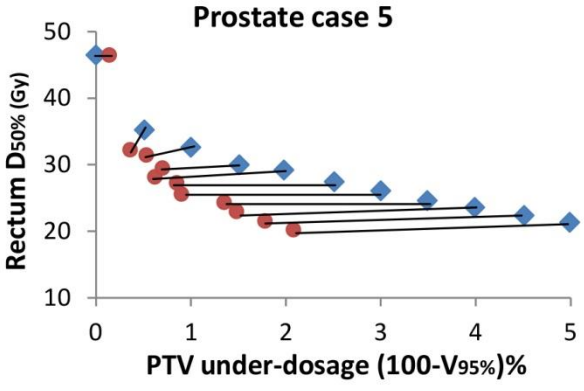
improvement was achieved partly by compromising other parameters, such as increasing doses to other OARs or by creating small “hotspots”











- Pareto plans
- Deliverable plans

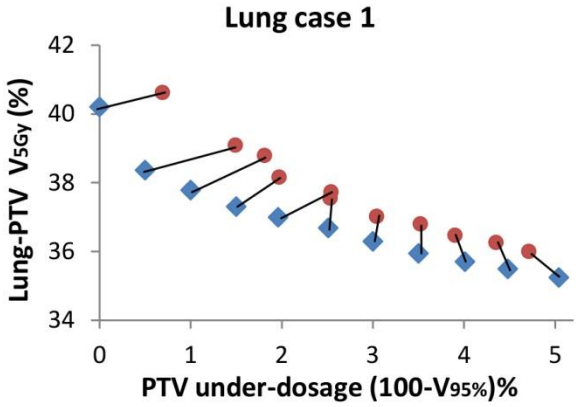
Limitations of this approach

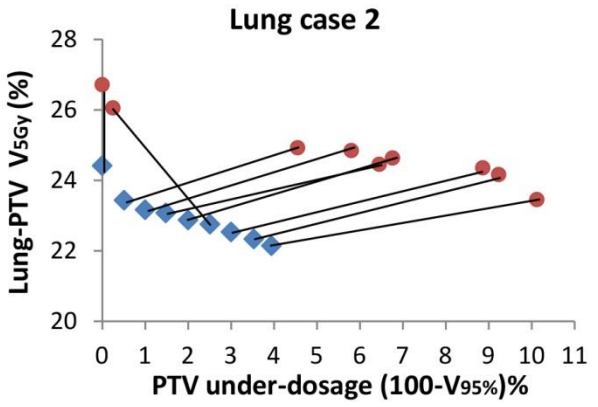
e.g. 5 lung patients

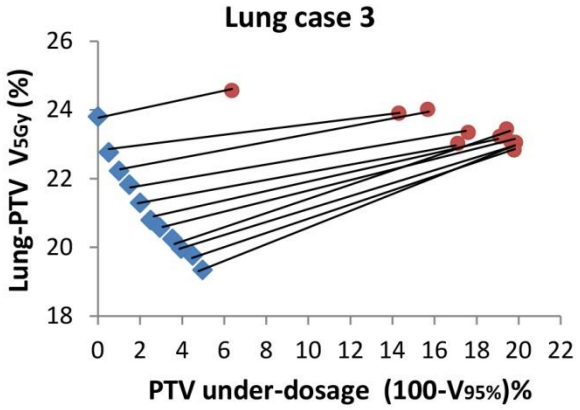
Deliverable plans systematically worse than pareto plans

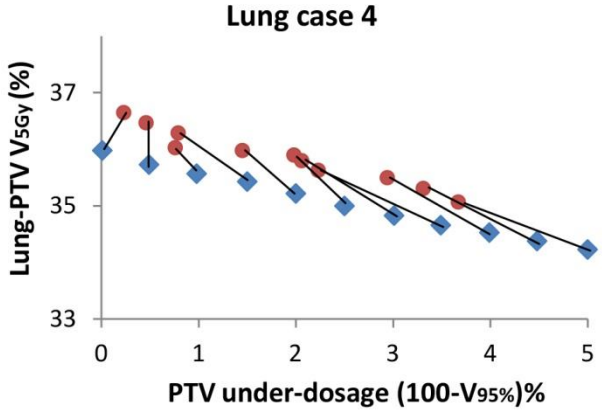
fluence-based treatment plans does not take into account the effect of lateral electron transport in the presence of heterogeneities

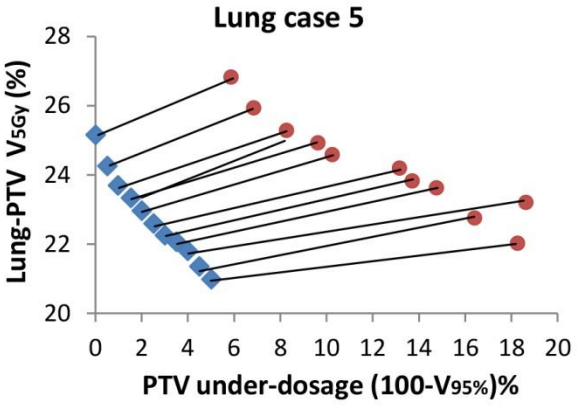
Small PTVs provided bigger differences











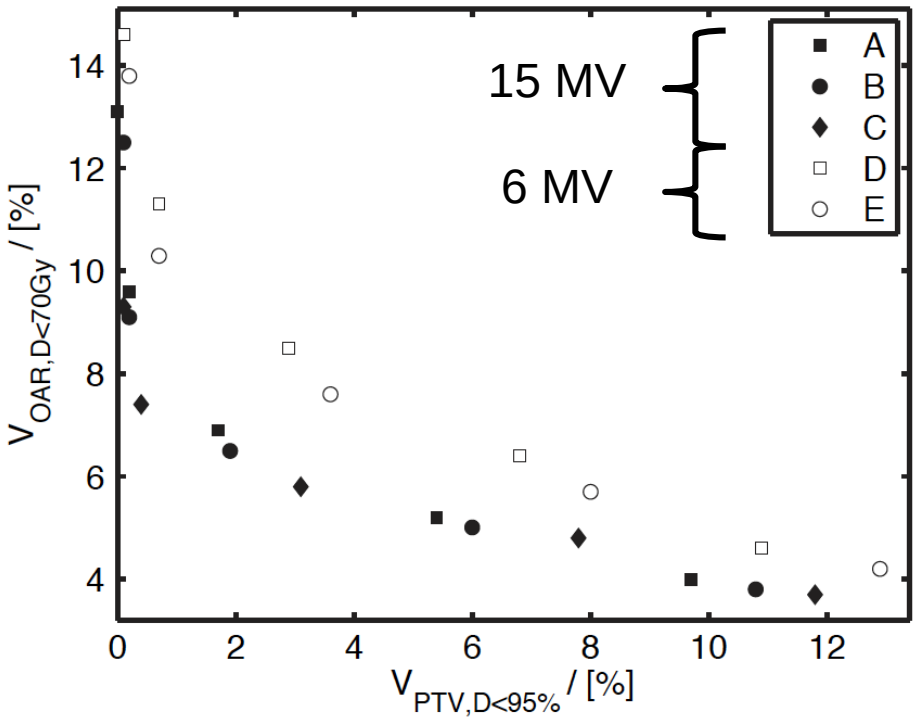
- Pareto plans
- Deliverable plans

MCO - What to use it else for?

- Can be used to compare techniques and approaches
- In this example V_{70Gy} for rectum vs $V_{95\%}$ for PTV for prostate

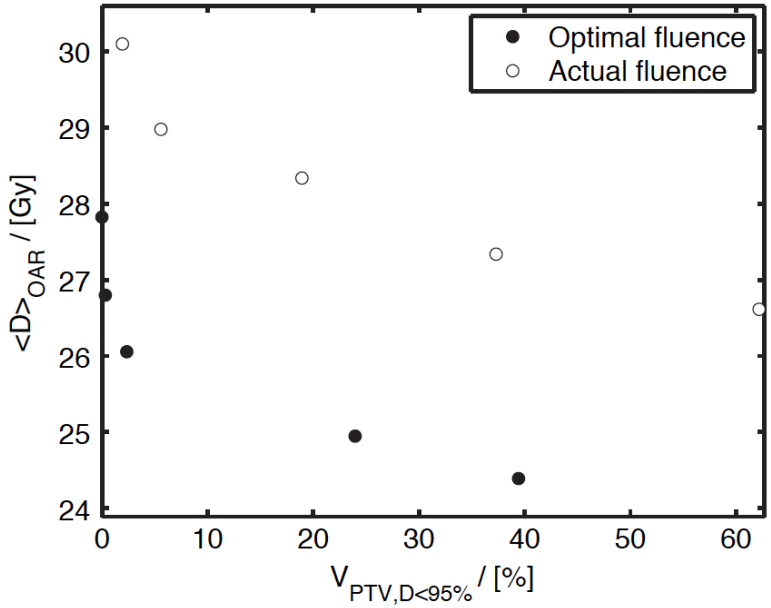
Set	Photon beam energy (MV)	Gantry angles (°)
A	15	0, 45, 115, 285, 315
B	15	45, 115, 180, 285, 315
C	15	36, 103, 180, 257, 324
D	6	0, 45, 115, 285, 315
E	6	45, 115, 180, 285, 315

Ottosson et al Acta Oncol 2009



- What you see is not what you get!

Head and neck case with parotid gland D_{mean} vs $V_{95\%}$ for PTV



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

How to build a library of plans?

Radiotherapy and Oncology 85 (2007) 292–298
www.thegreenjournal.com

Treatment planning

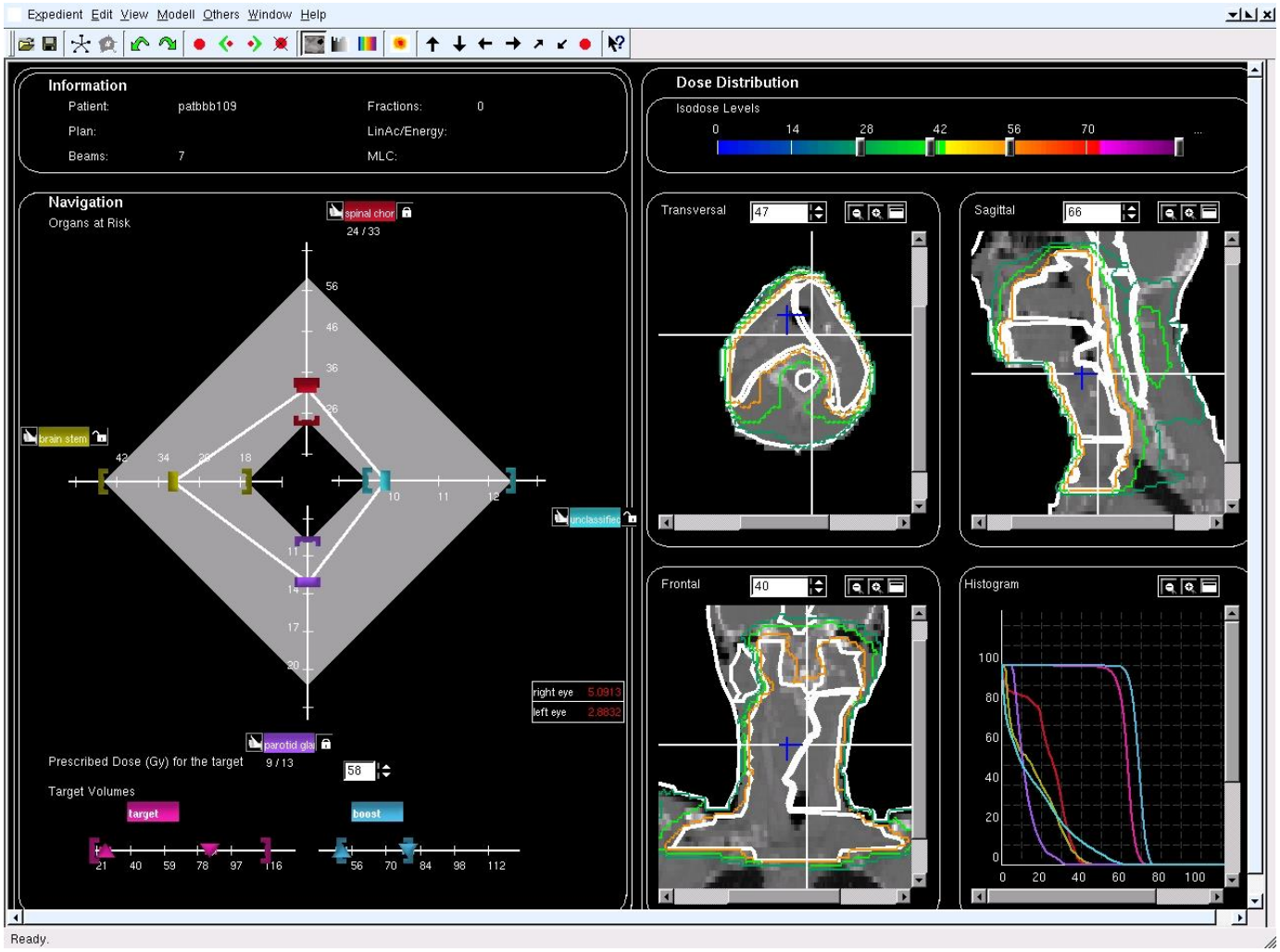
A new concept for interactive radiotherapy planning with multicriteria optimization: First clinical evaluation ☆

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 ☺ ☺

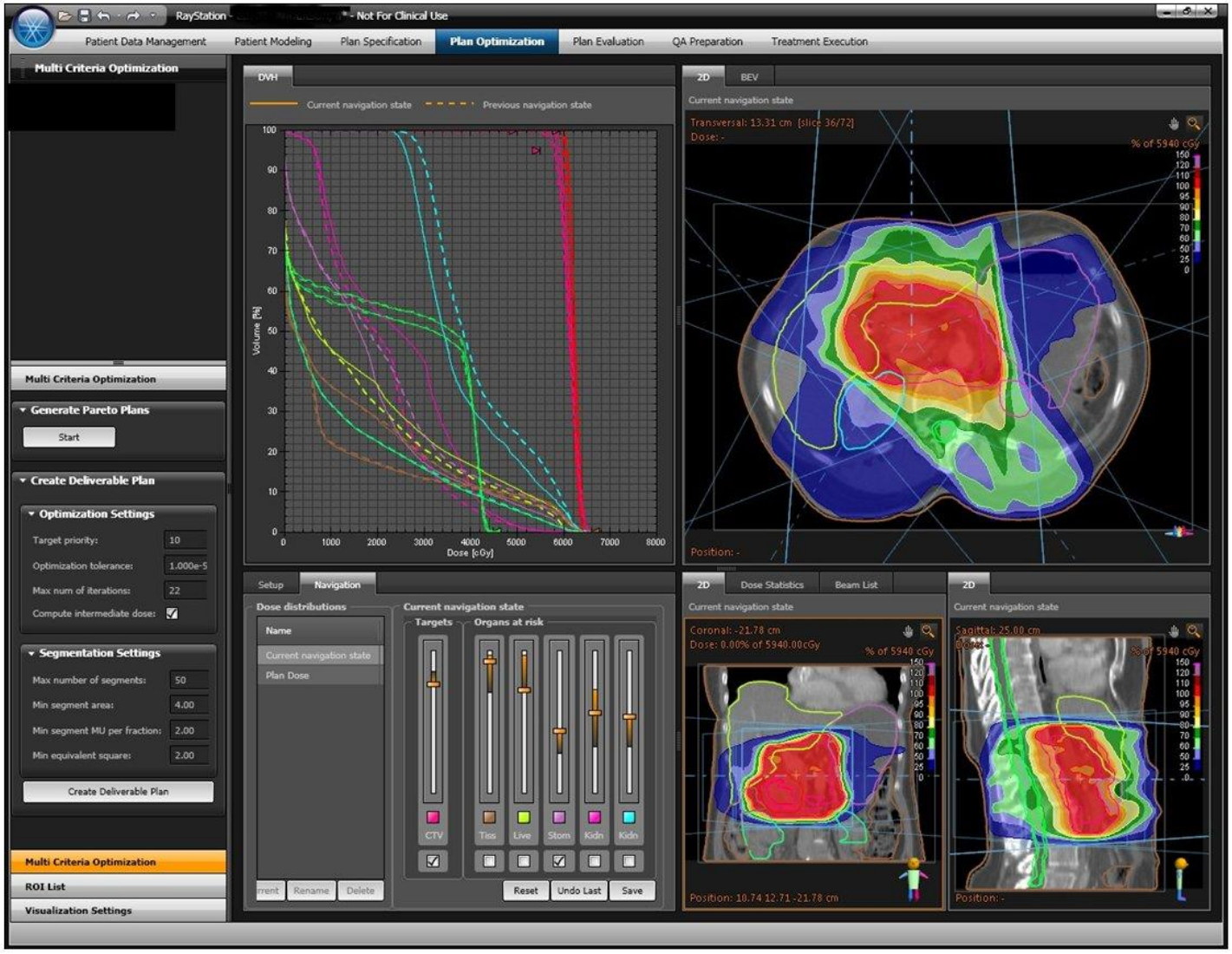
Pareto navigation tool



Courtesy to K.H. Küfer, (FHG-ITWM)

Navigation should be sensitive !!

TPS: Pareto navigation

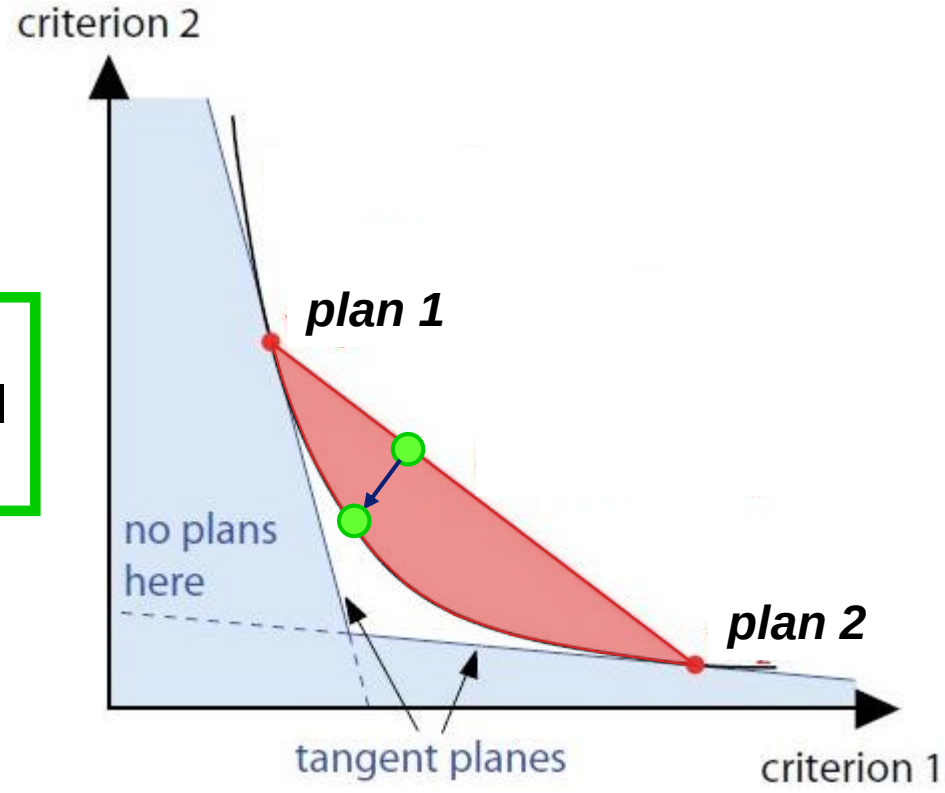


TPS: plan library

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



Conclusion

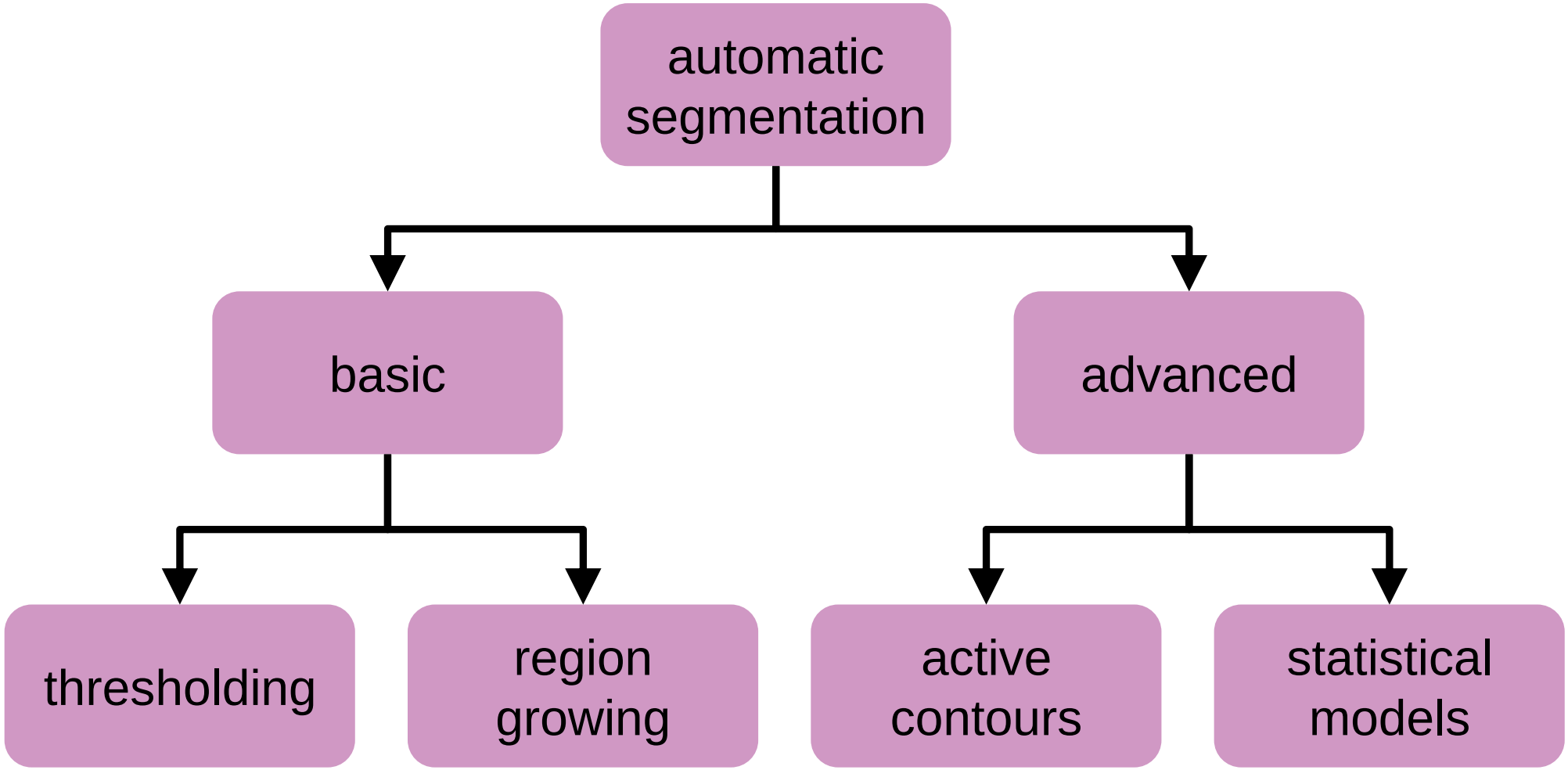
Physicist’s perspective

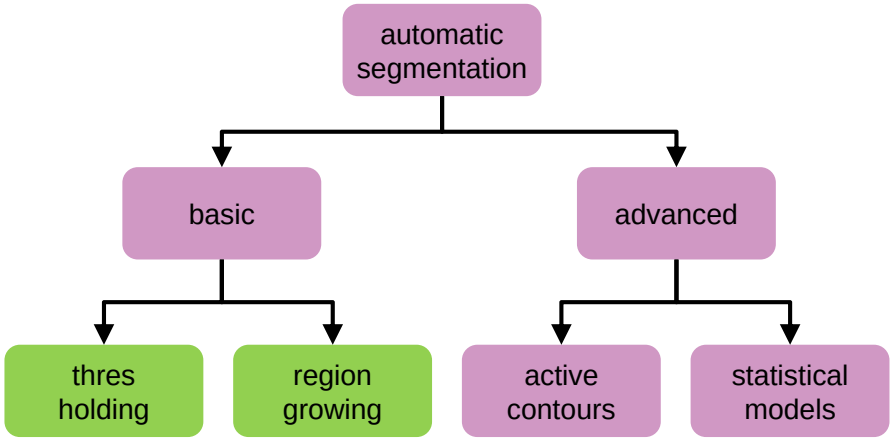
Gert Meijer

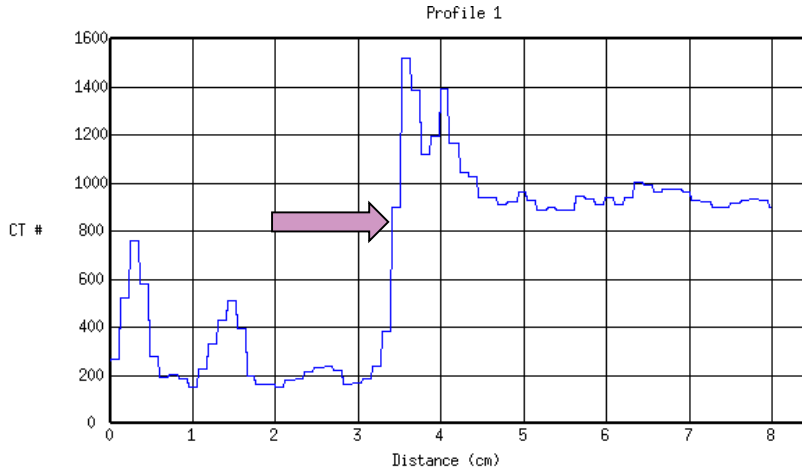
Emerging topics

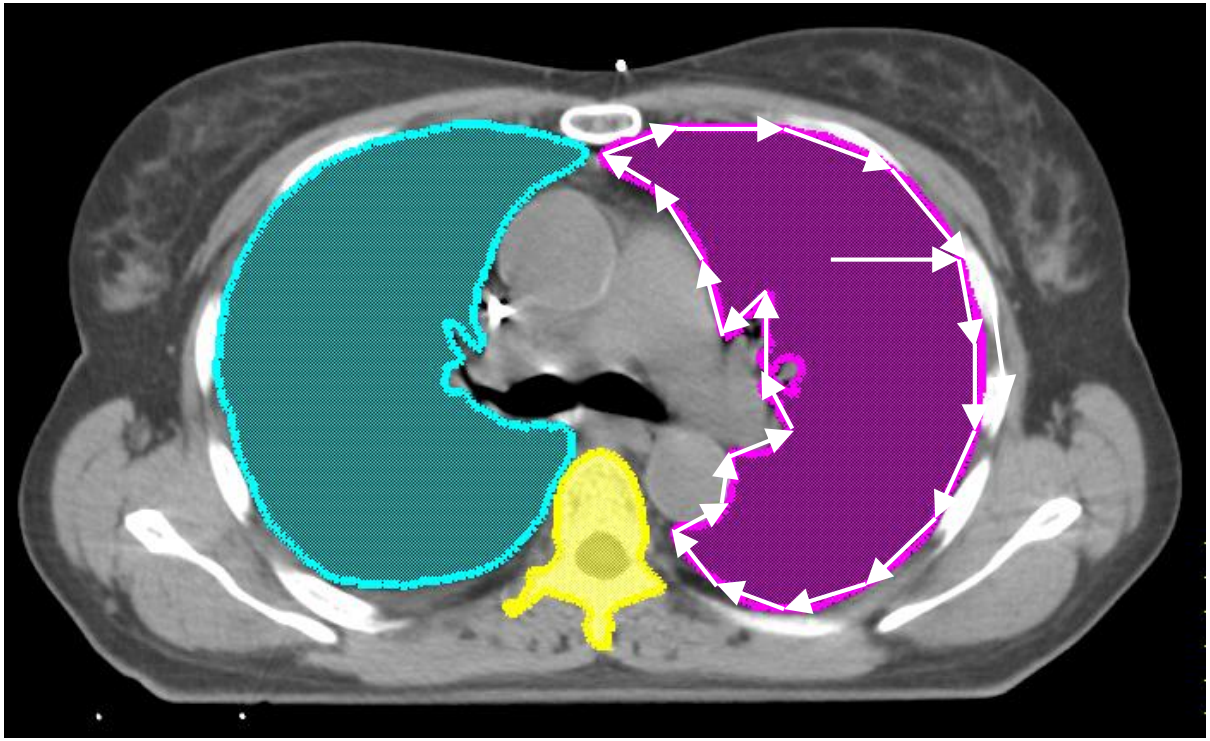
- Normal tissue segmentation
- Plan quality prediction & Automated planning
- Bridging the gap between surgery and radiation oncology

Automatic normal tissue segmentation









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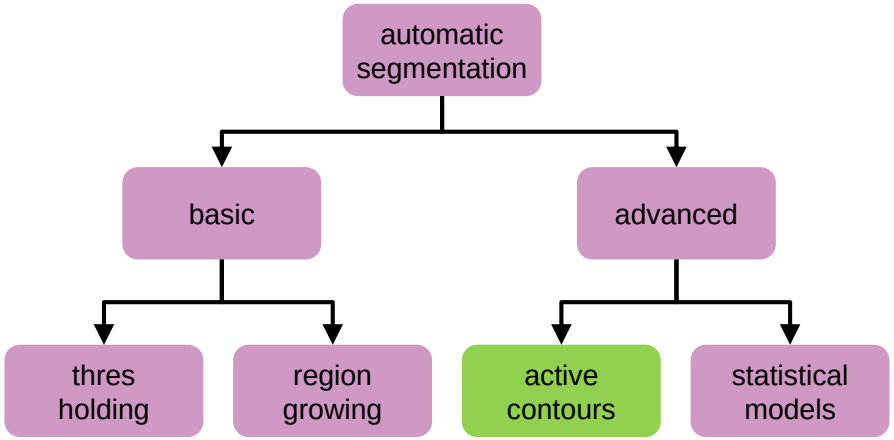
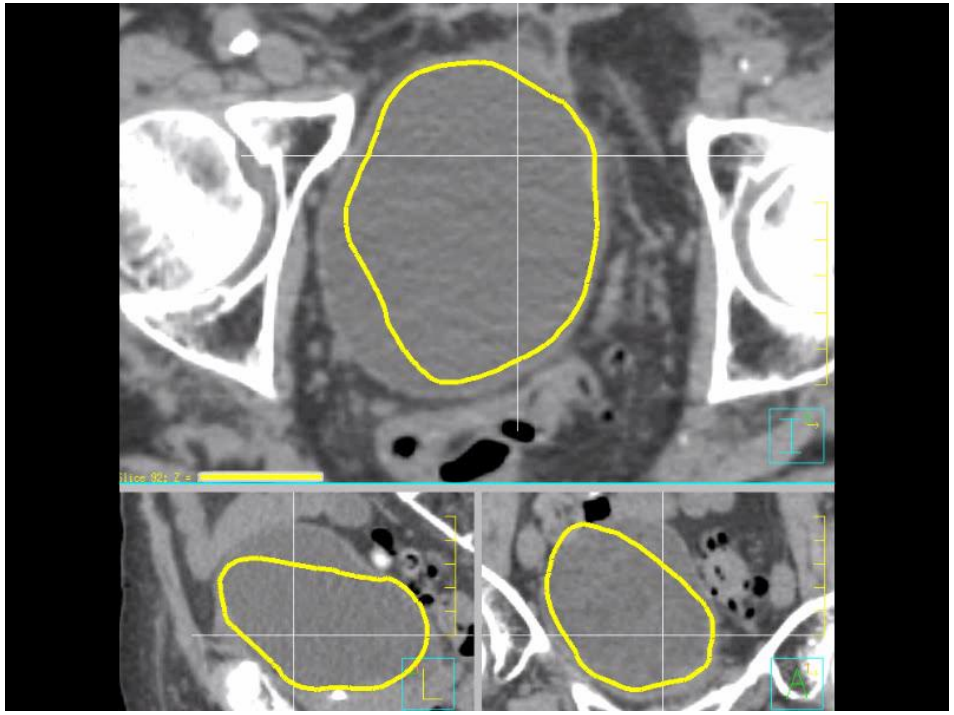
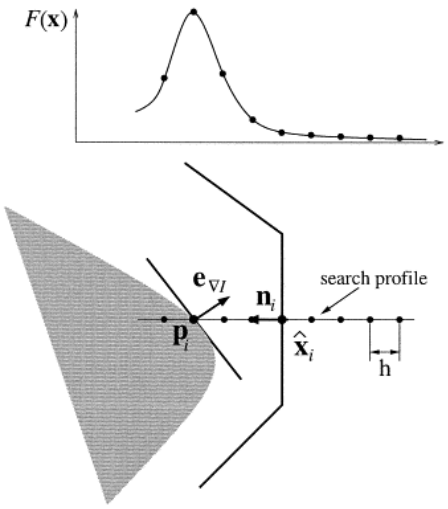
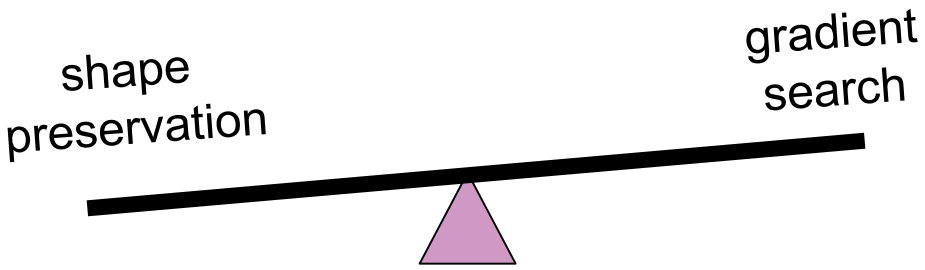


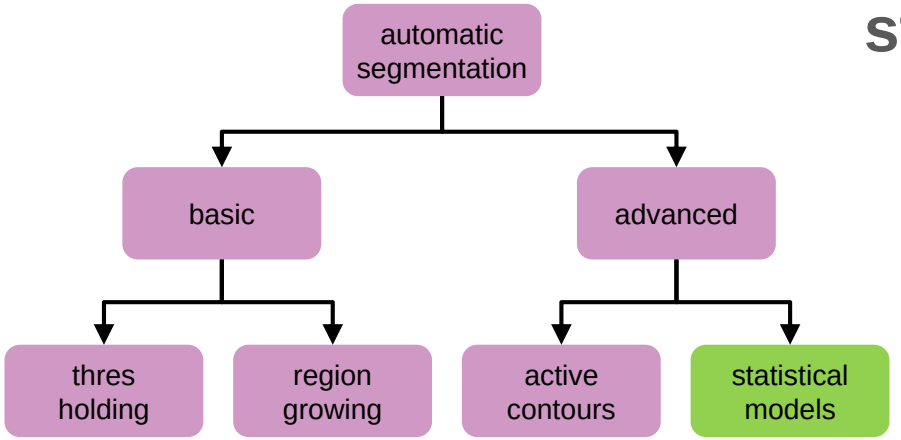


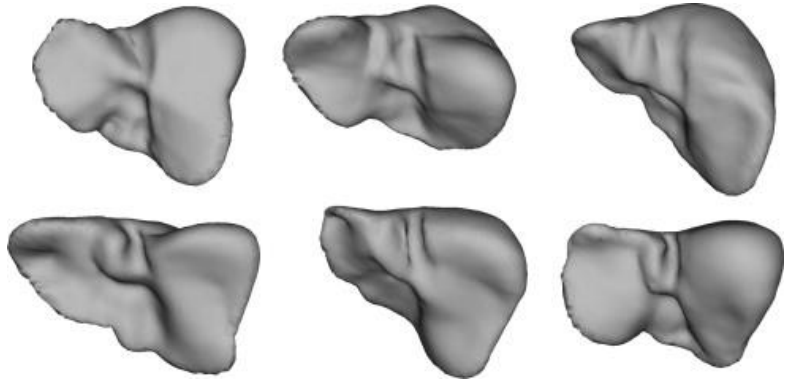


Pekar *et al.* 2004 IJROBP 60(3)

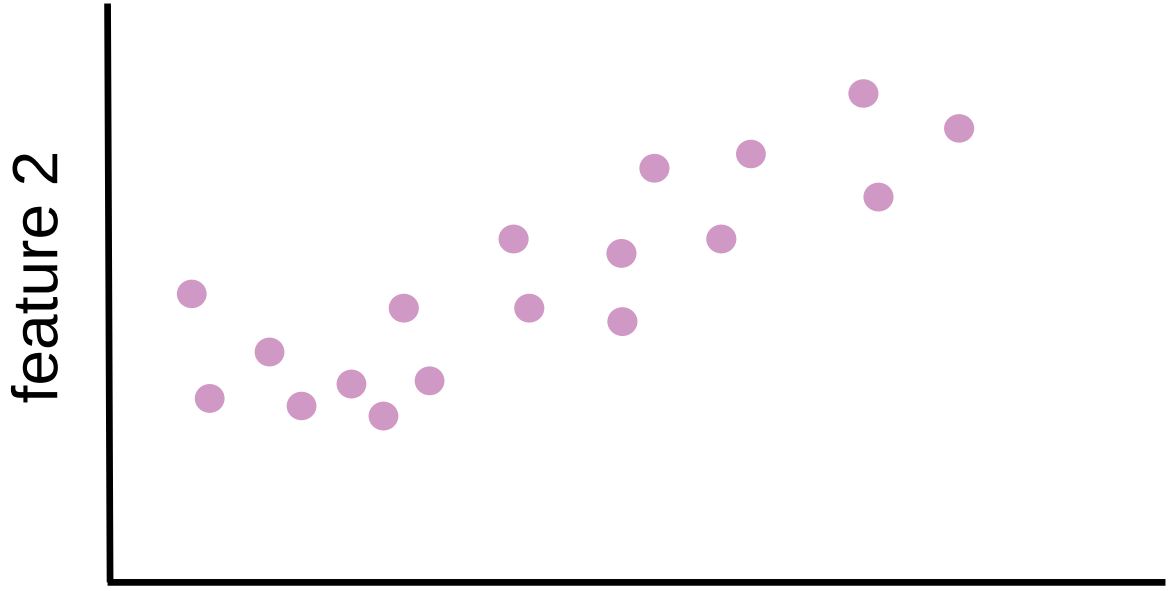


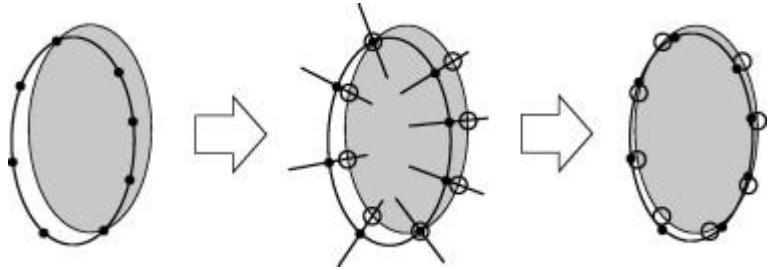
statistical shape models





principal modes liver





Heimann & Meizner Medical image analysis 13(4) 2009

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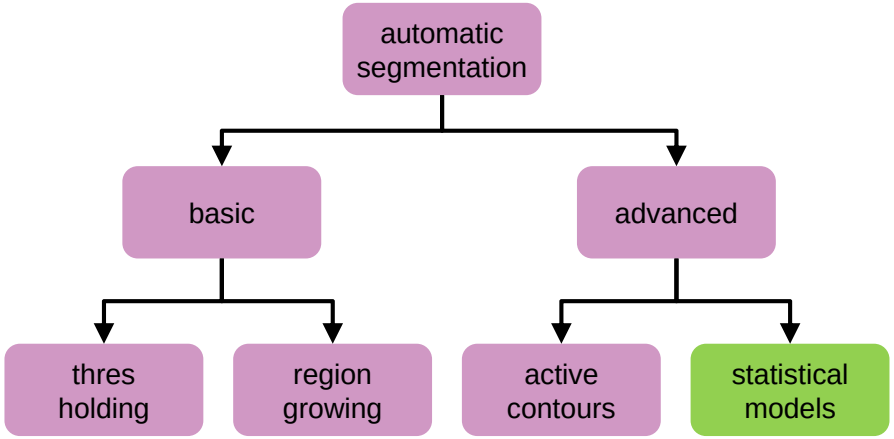
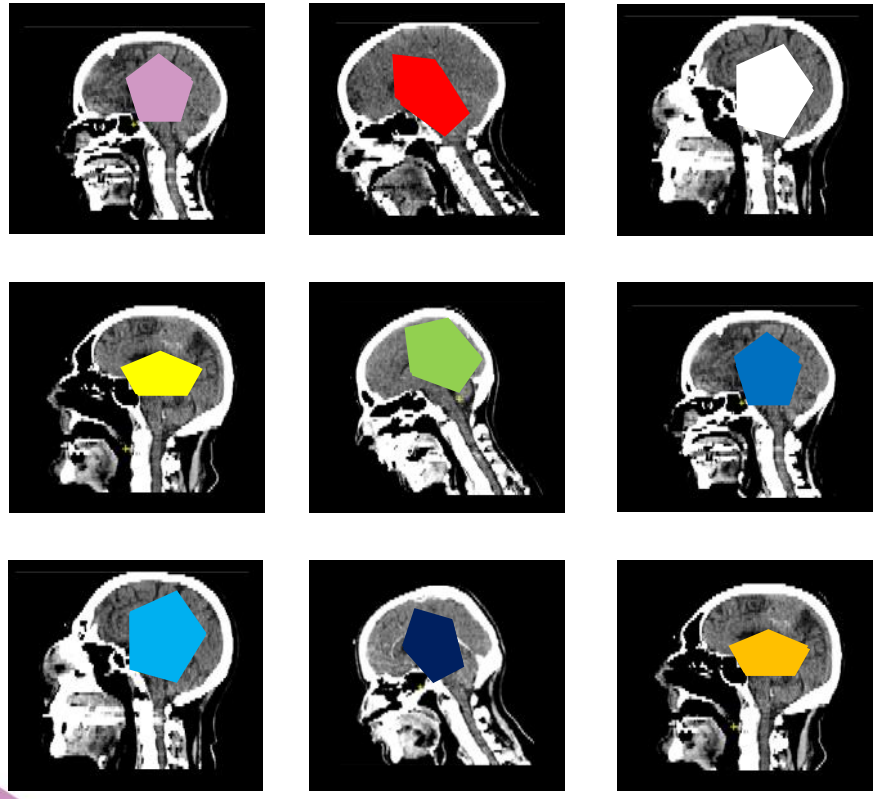
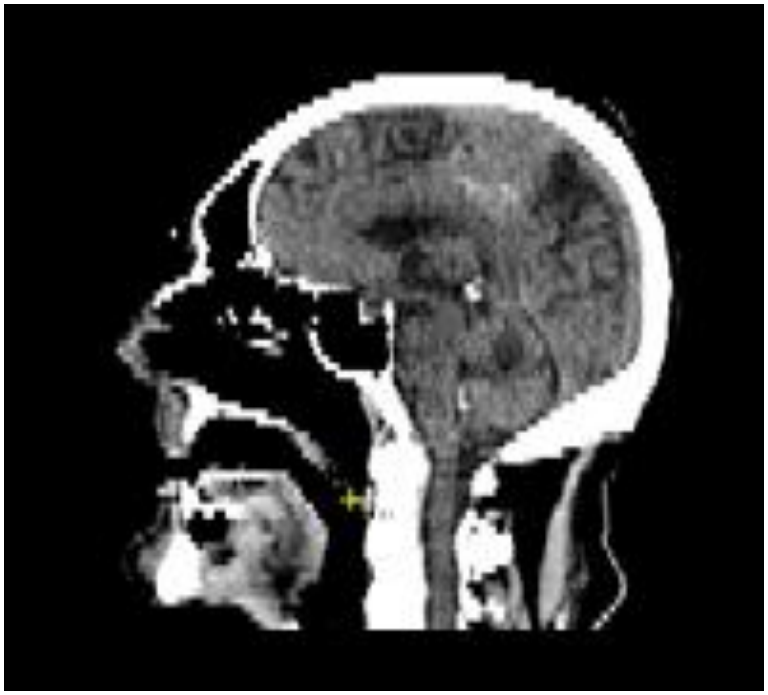
atlas based models





atlas set

non-rigid registration



remove outliers based on estimated performance (e.g. DICE)

Langerak *et al. IEEE Trans Med Imaging. 2010 Dec;29(12)*

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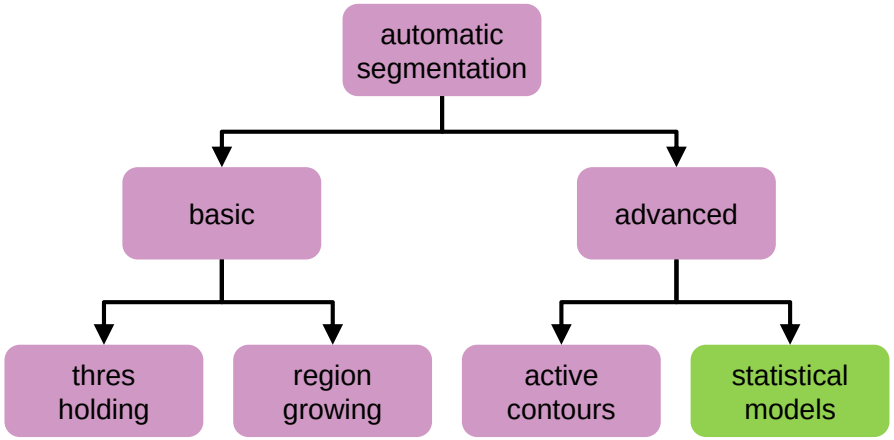
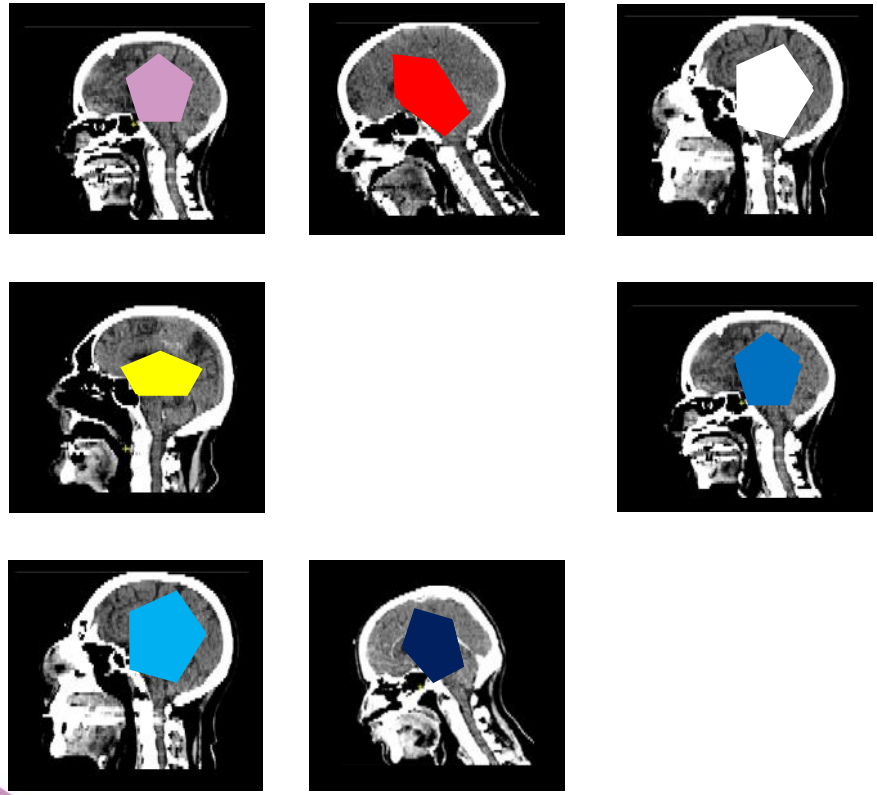
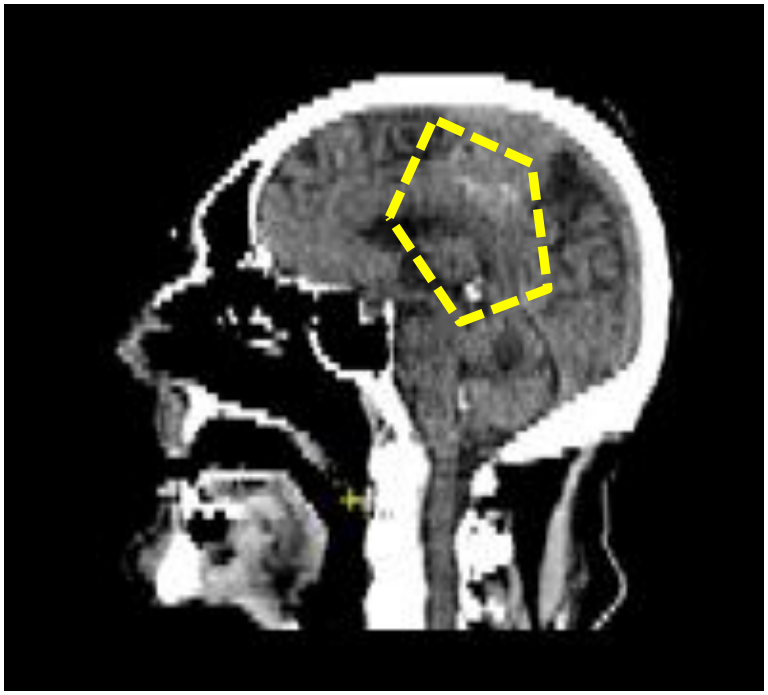
atlas based models





atlas set

non-rigid registration



majority vote

Langerak *et al. IEEE Trans Med Imaging. 2010 Dec;29(12)*

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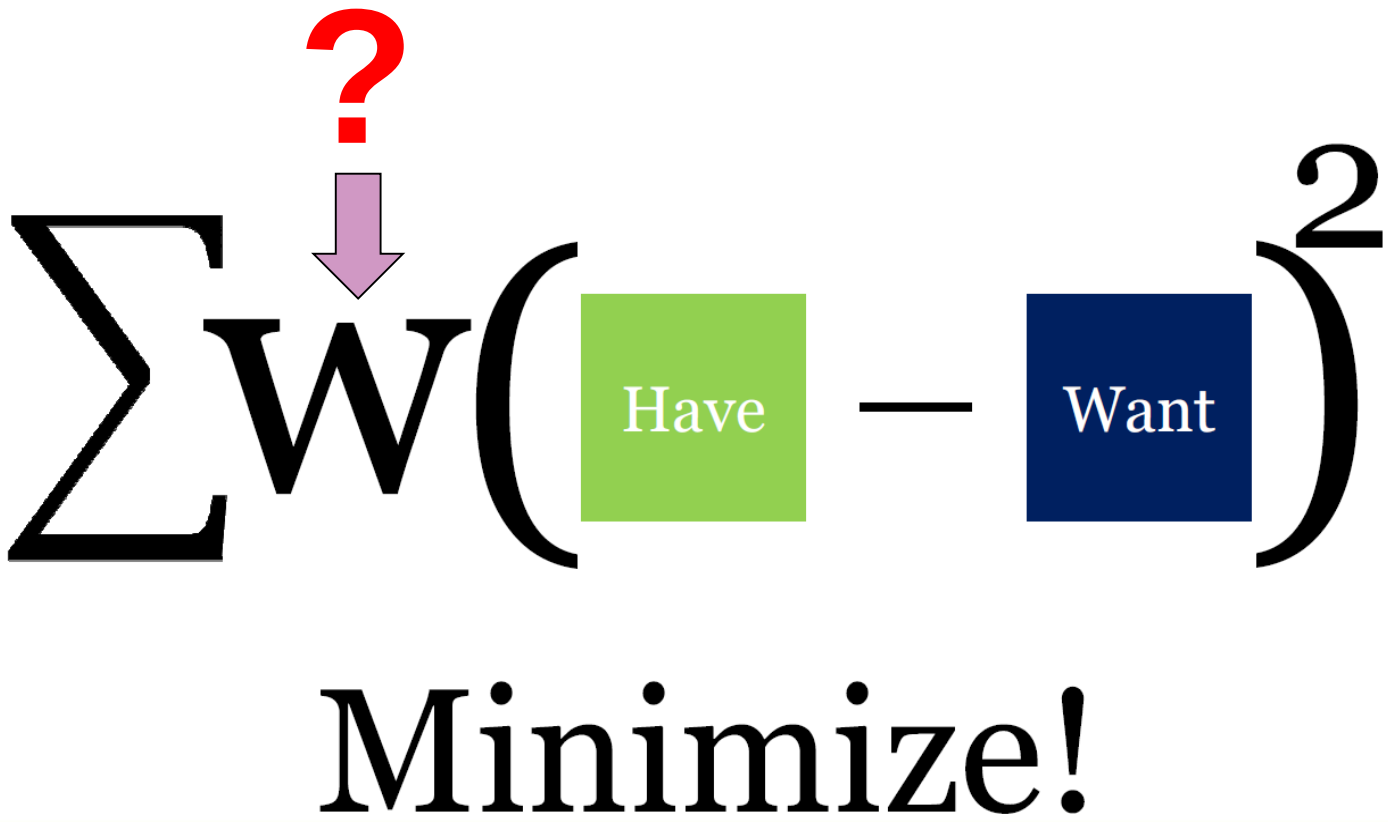
Summary

- Many methods available!
- Statistical models and atlas-based are the most suitable for normal tissue segmentation.
- But… they require training data or atlas
- Manual validation of experts is still used as golden truth

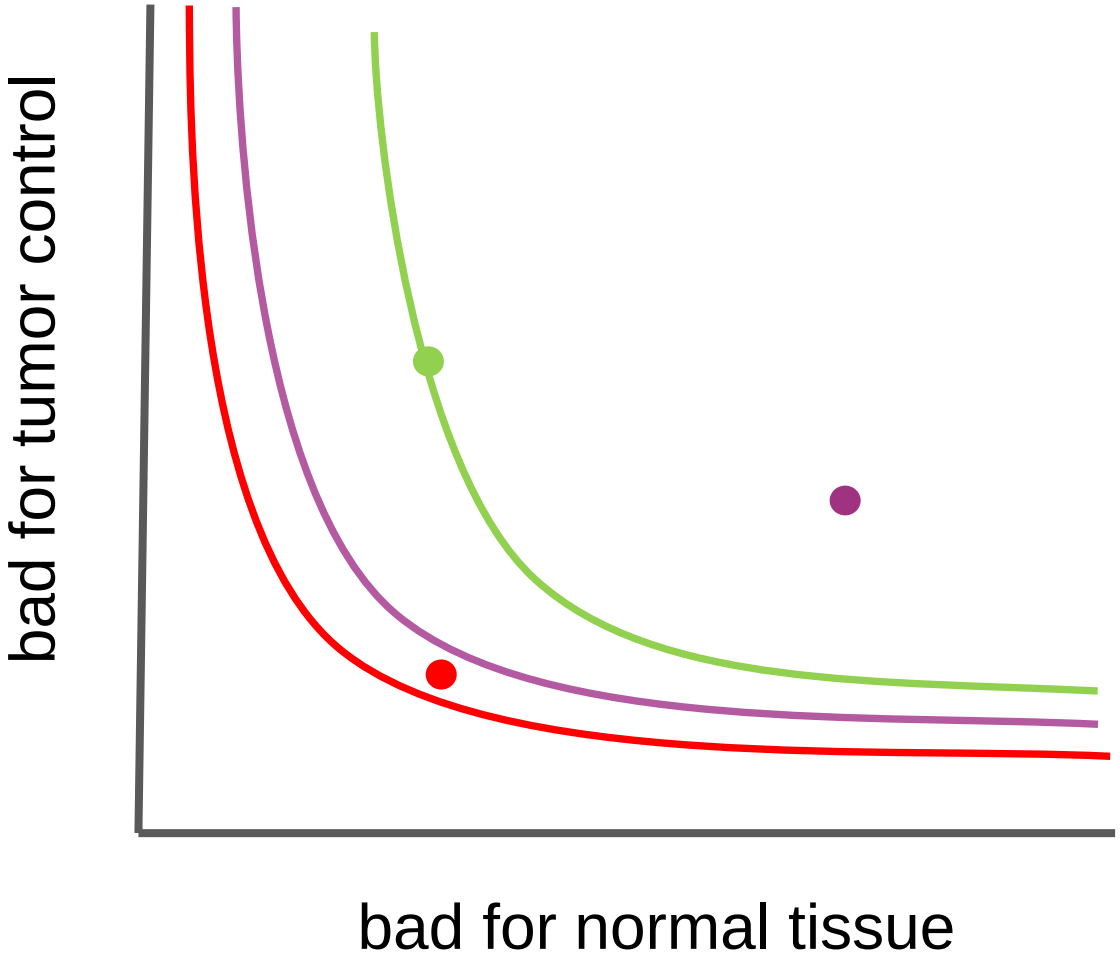
Templates and Automated Plan Generation



Sebastian Breedveld
Treatment planning workshop
ESTRO 2014 Vienna

ESTRO School

Templates and Automated Plan Generation



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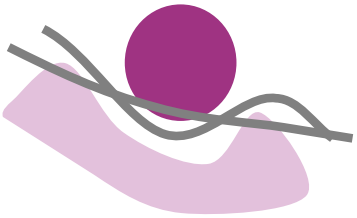
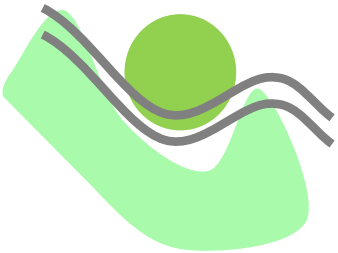
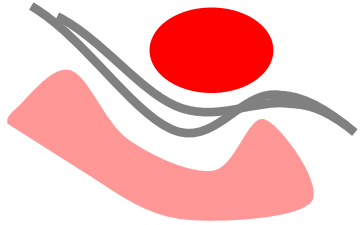


pat 2



pat 3



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How to create a good set of objectives?

Knowledge-based

large database
find similar case
extract objectives
reproduce plan

Automated planning

automate decision making
wish-list
define and *prioritize* objectives
iteratively navigate towards
and over pareto surface

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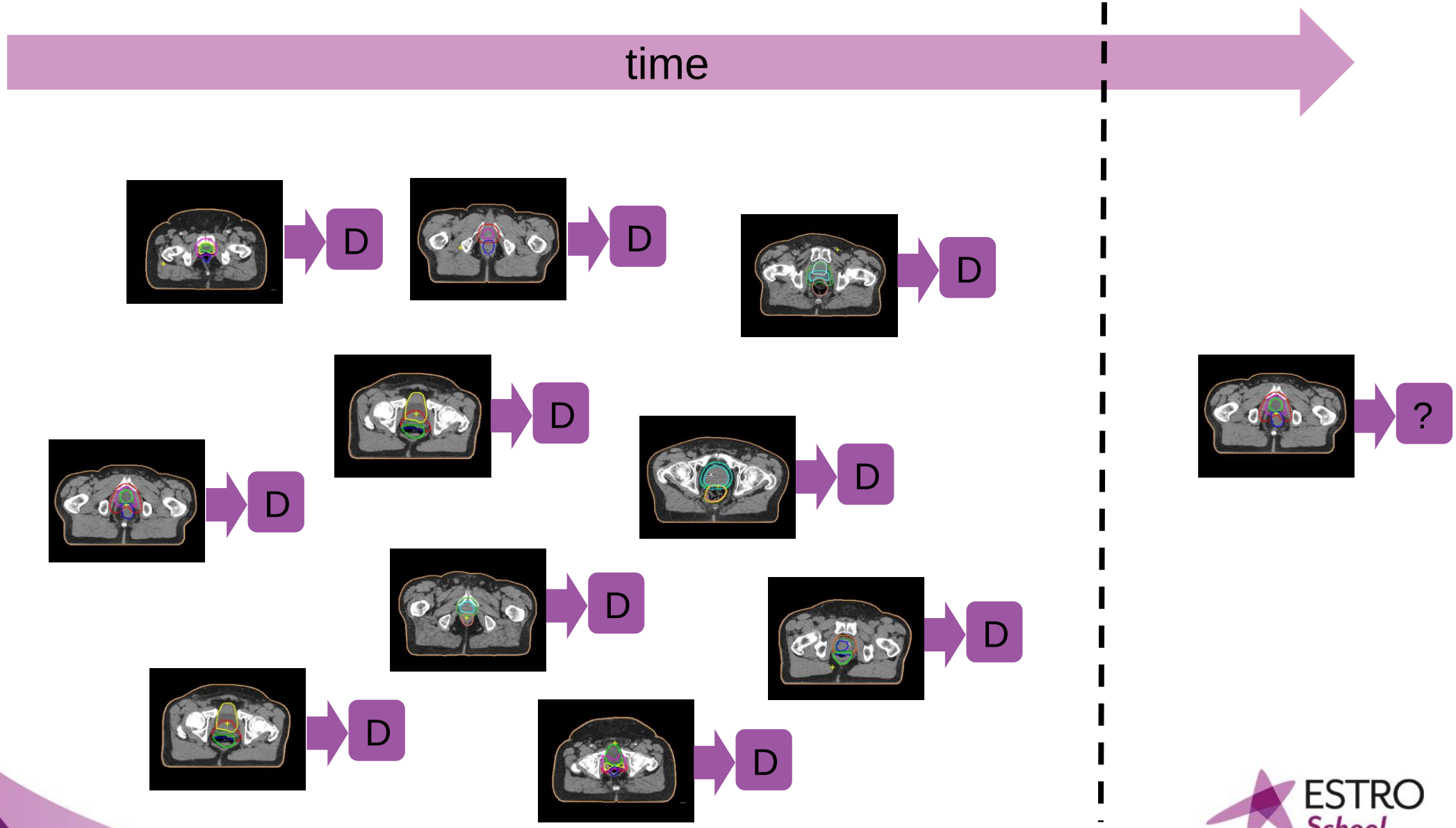
Knowledge-based approach



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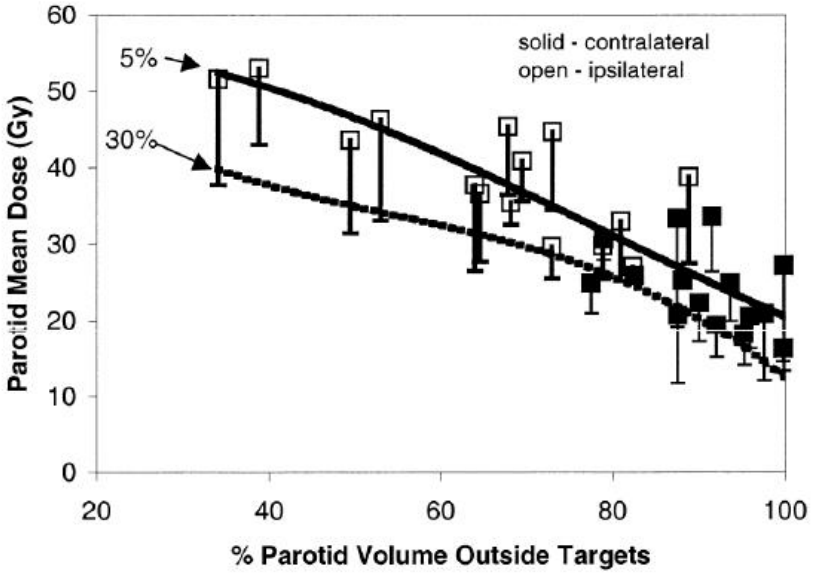
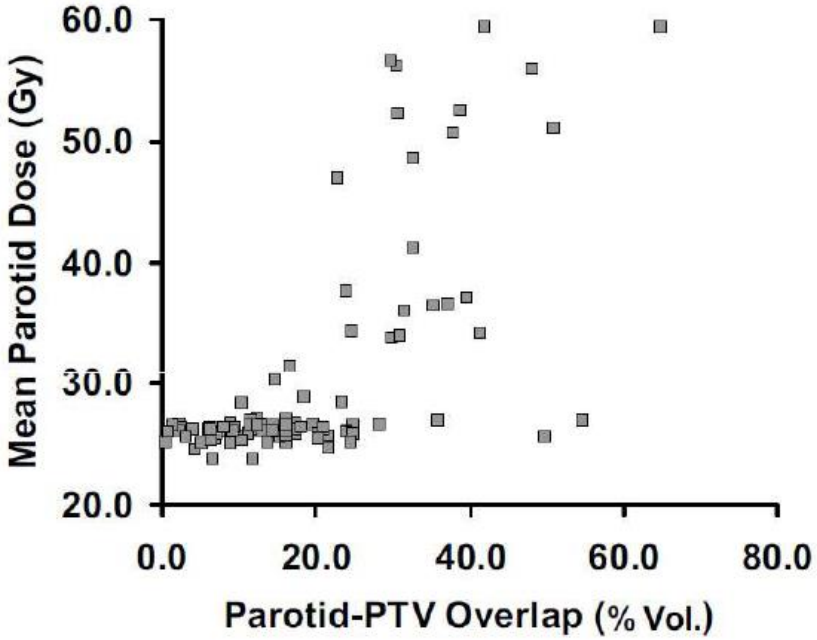
geometric quantification = dosimetric quantification

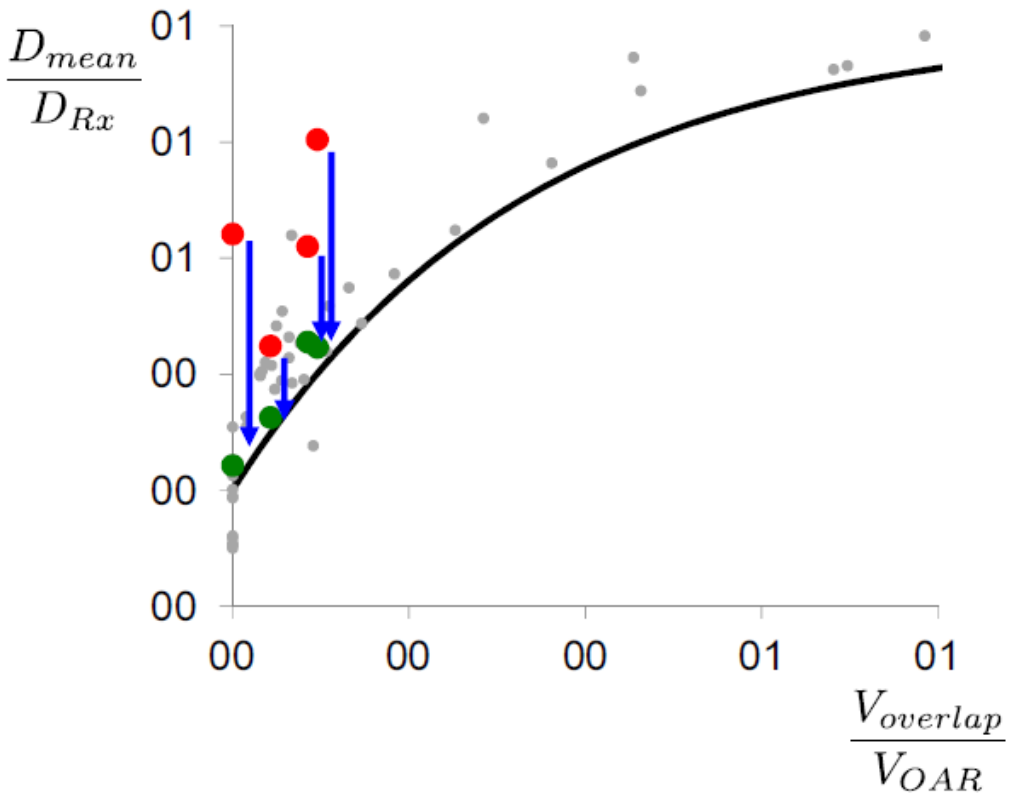


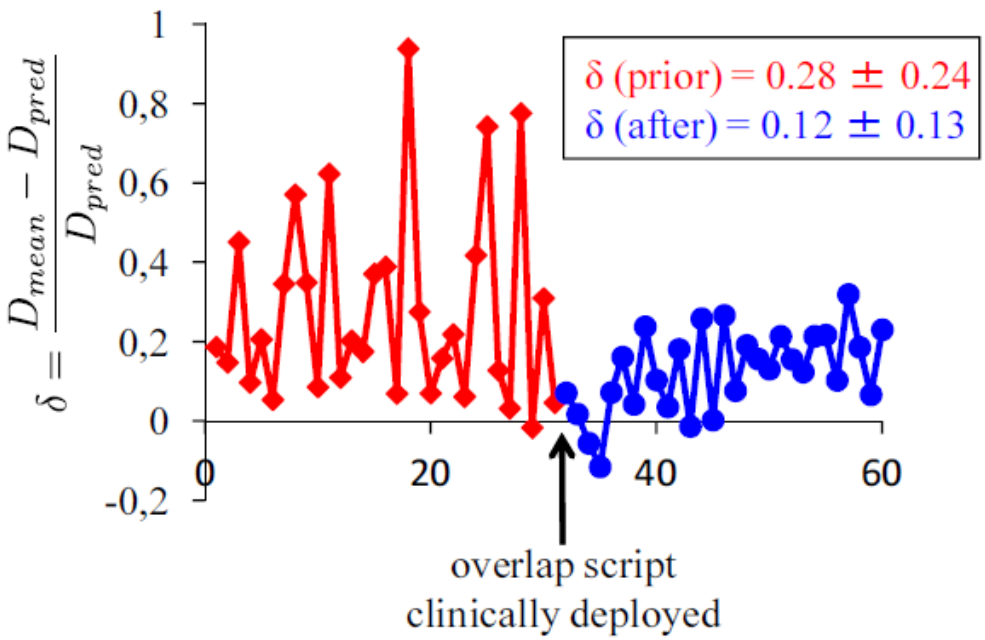
Vineberg, K. A. *et al*. Is uniform target dose possible in IMRT plans in the head and neck? *Int J Radiat Oncol Biol Phys* 52 (5):1159-72 (2002)



Hunt, M.A. *et al.* Geometric factors influencing dosimetric sparing of the parotid glands using IMRT, *Int J Radiat Oncol Biol Phys* 66 (1):296-304 (2006)

catch and correct suspected outliers





KL Moore *et al.*, IJROBP 81 (2010)

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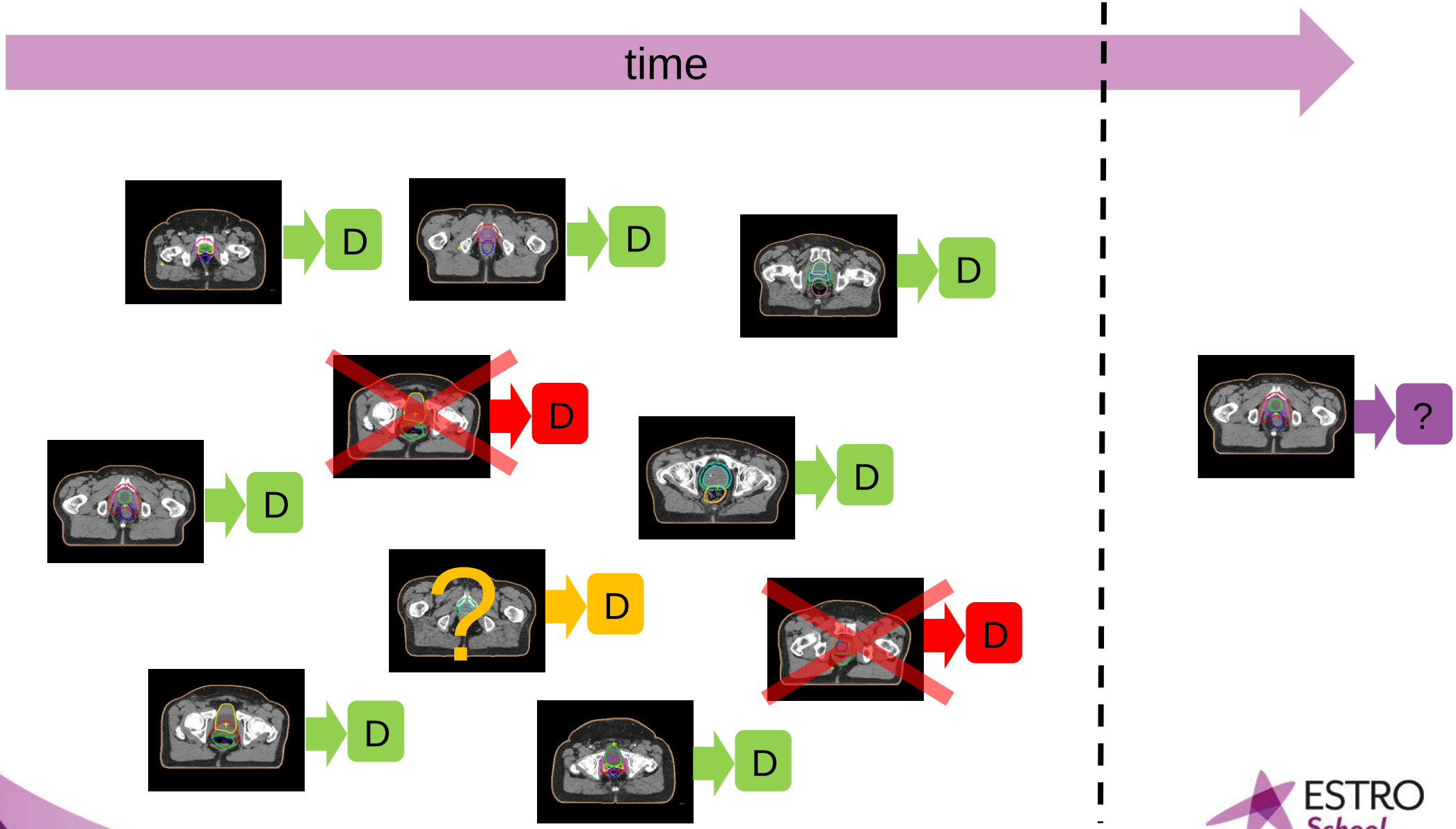
Knowledge-based approach



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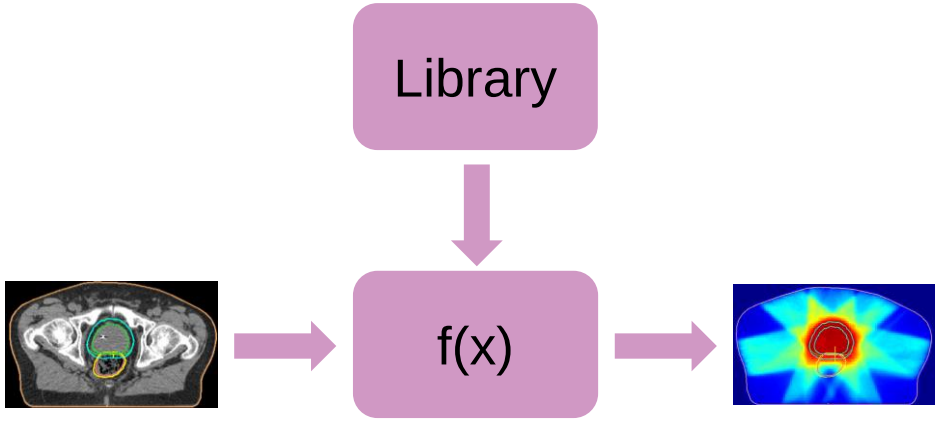
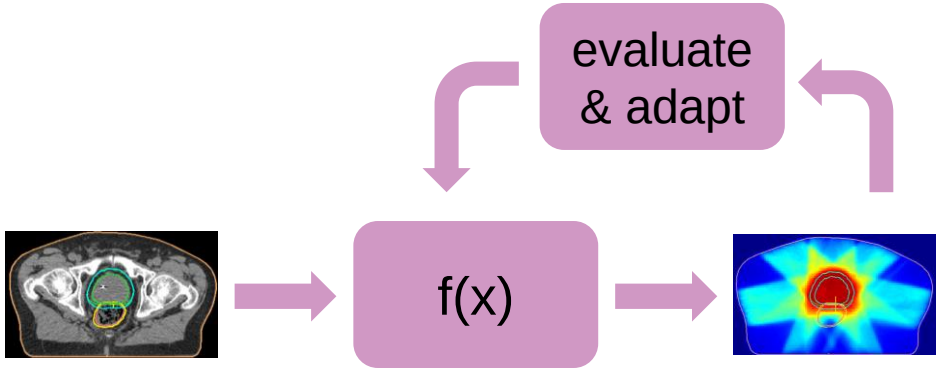
extract objectives
reproduce plan



Automated planning

automate decision making
wish-list
define and *prioritize* objectives
iteratively navigate towards
and over pareto surface



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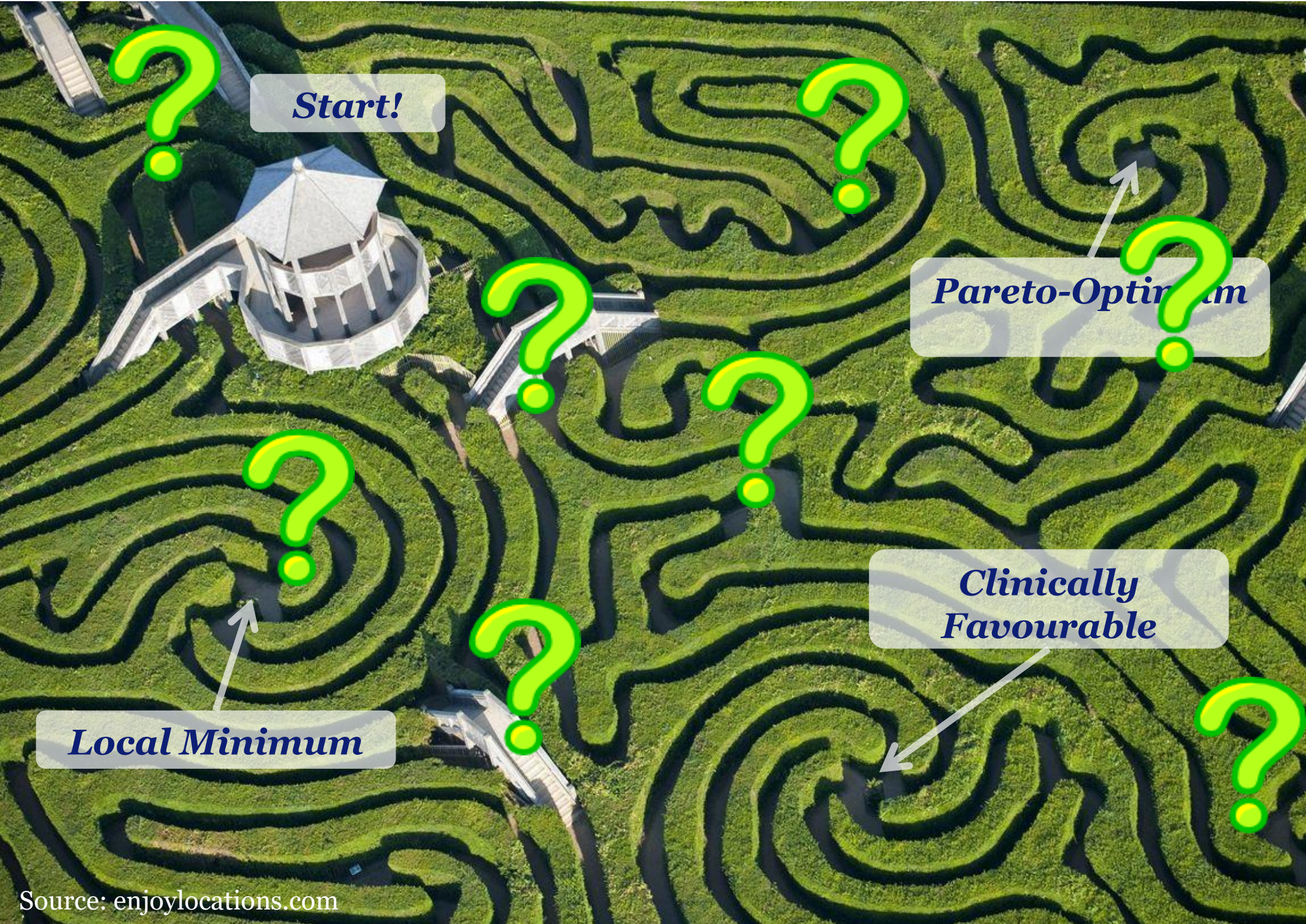
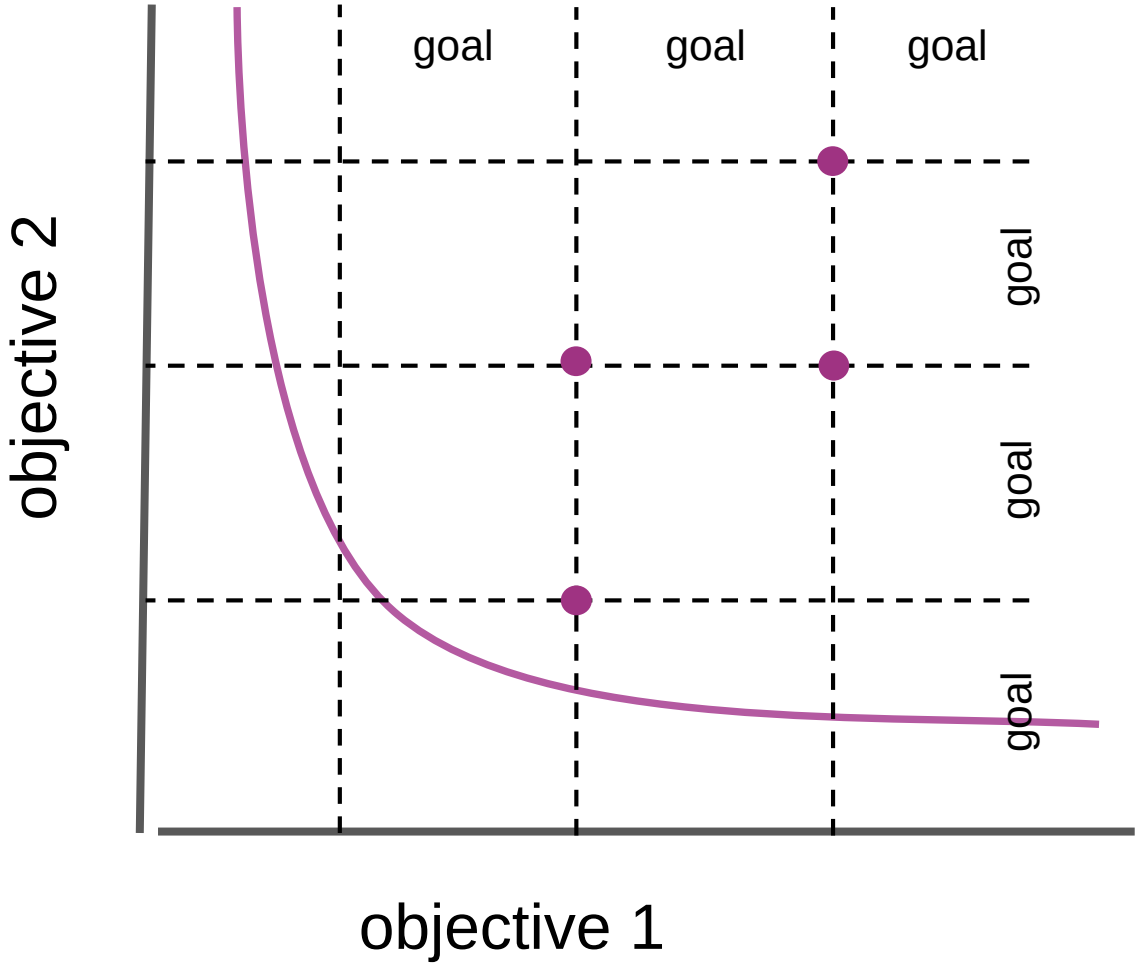
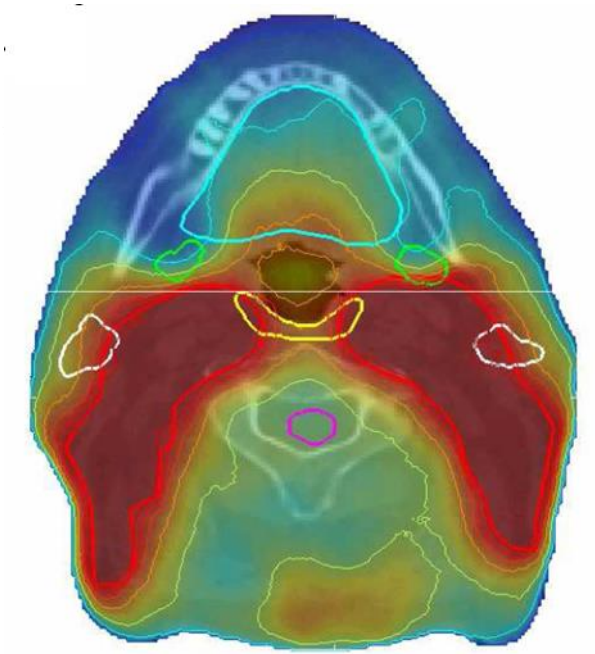


Source: enjoylocations.com

Wish-list





target dose OK

lower dose submandibular glands <39Gy

improve conformality

lower dose submandibular glands <20Gy

lower dose parotid glands <10Gy

Breedveld *et al.* PMB 54 2009

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Automated planning

- may take longer, but can run overnight immediately after the contouring process
- may result in improved plan quality (computer doesn’t mind ‘drinking another cup of coffee’)
- does general require an extensive hierarchical list of priorities
- output can be used as an input for manual optimization
- reduces the interobserver variability

Bridging the gap between surgery and radiation oncology

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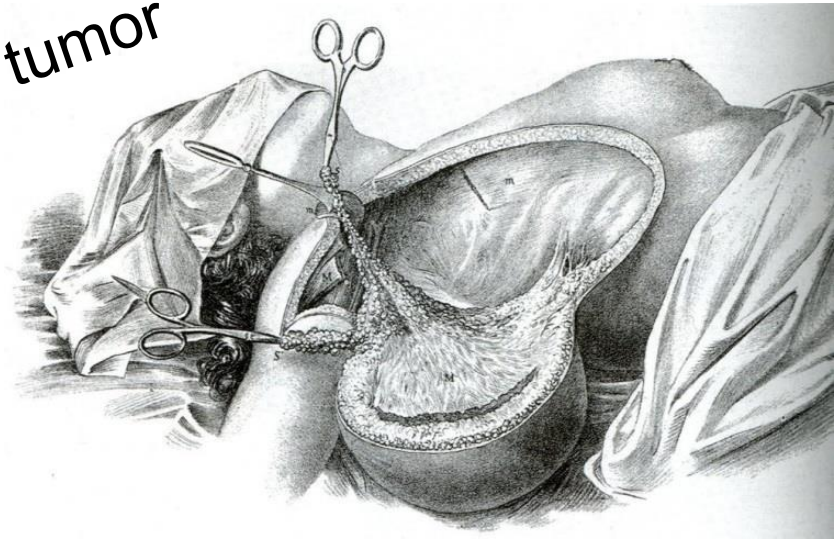
A brief history of Radiation Oncology

surgery the mainstay in
eradicating the primary tumor



1882

William Halsted

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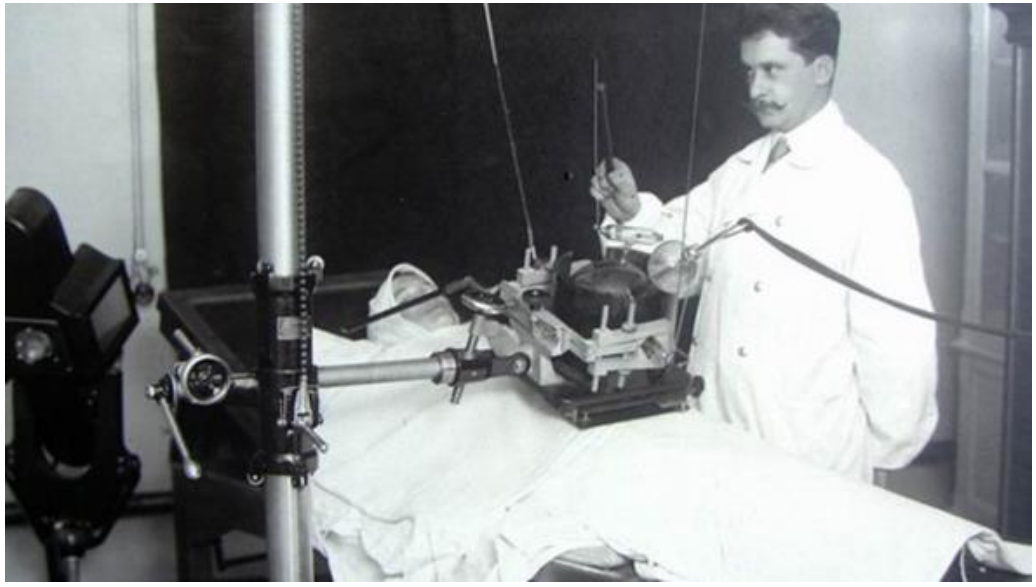
A brief history of Radiation Oncology

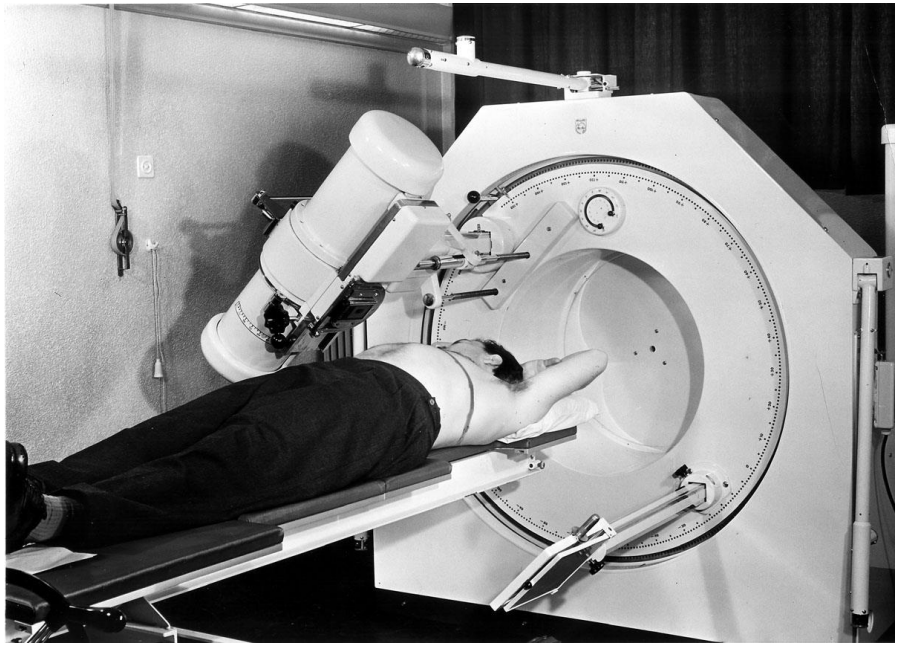
80-100 kV



1914

A brief history of Radiation Oncology

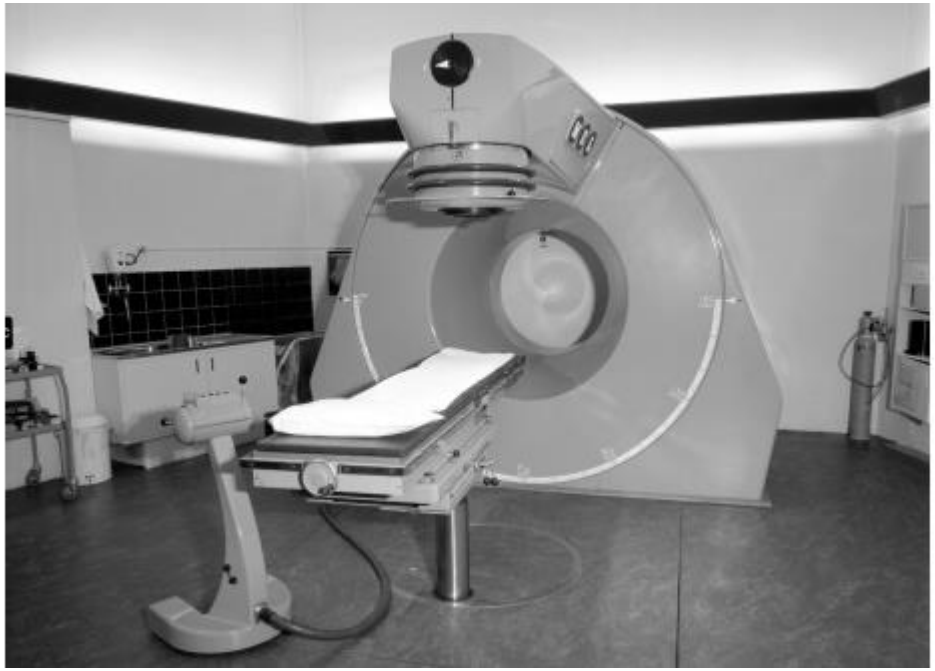
250 kV



1954

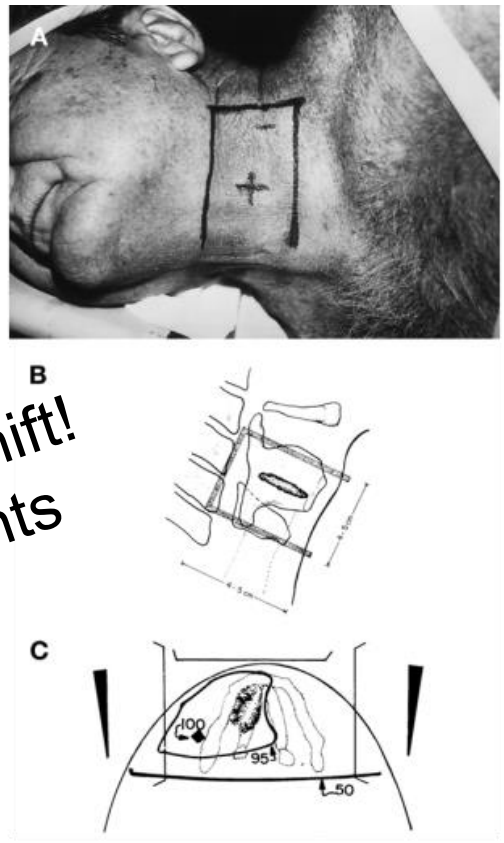
A brief history of Radiation Oncology

8 MV



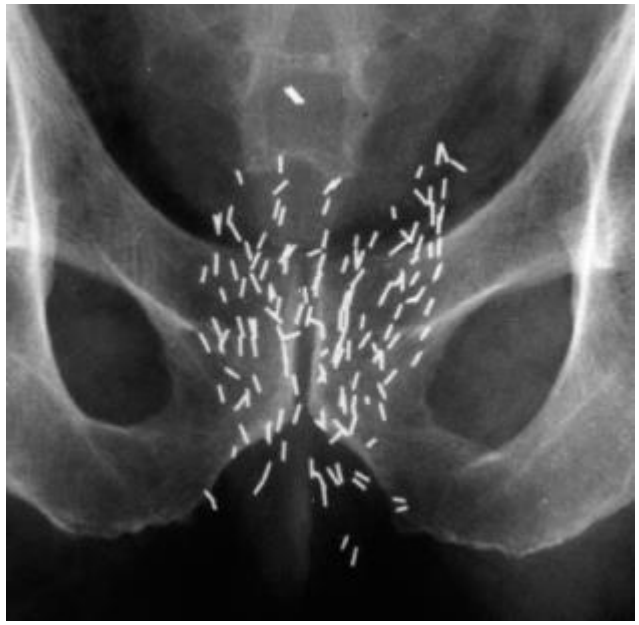
1964

A brief history of Radiation Oncology



William M. Mendenhall et al. JCO 2001;19:4029-4036

first paradigm shift!
RT curing patients



Drs. Blasko, Grimm and Ragd (Seattle)

Department of Veterans Affairs
Laryngeal Cancer Study Group

80's

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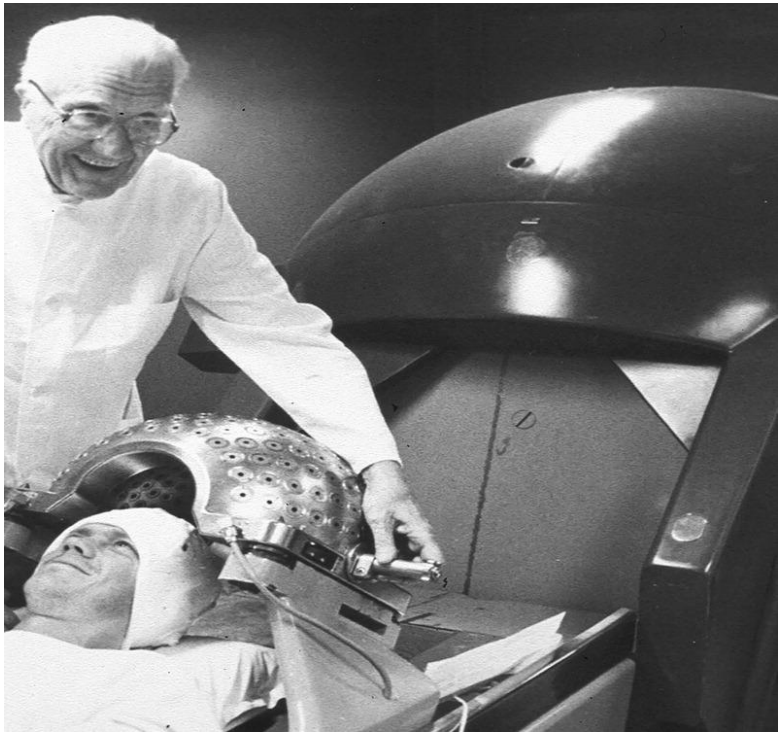
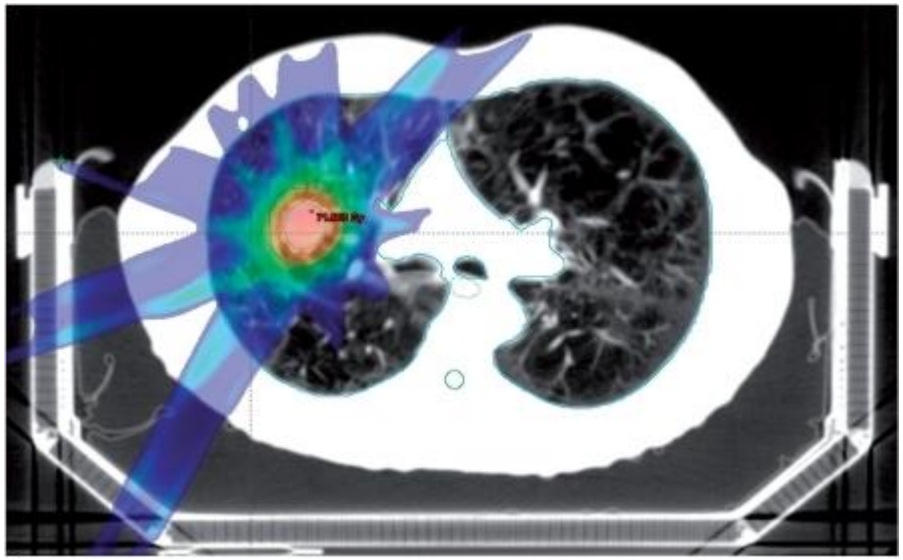
A brief history of Radiation Oncology



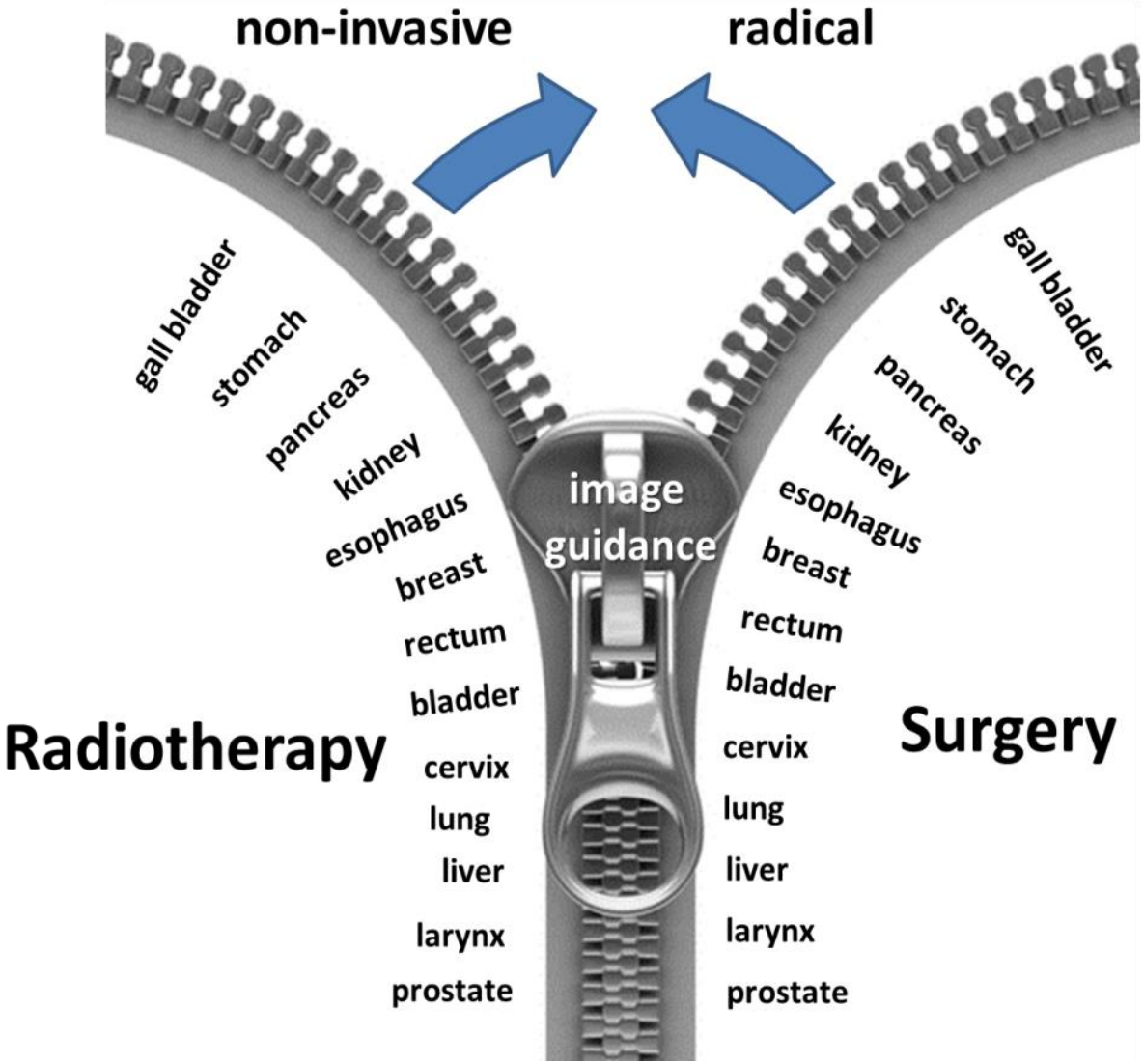
80’s

A brief history of Radiation Oncology



90’s

Image guidance is key!

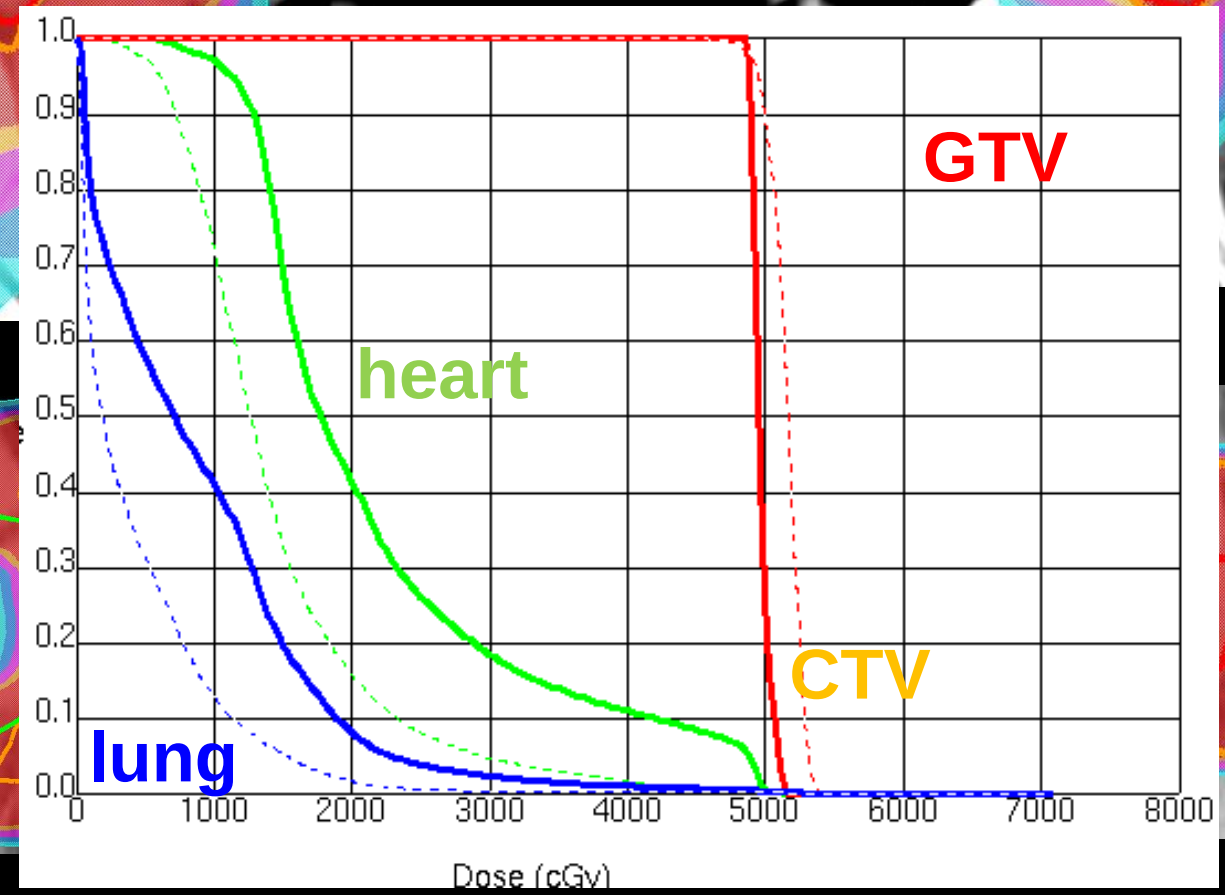


Esophageal cancer

contemporary RT

MRL

GTV=8 cm³
CTV=63 cm³
PTV=290 cm³

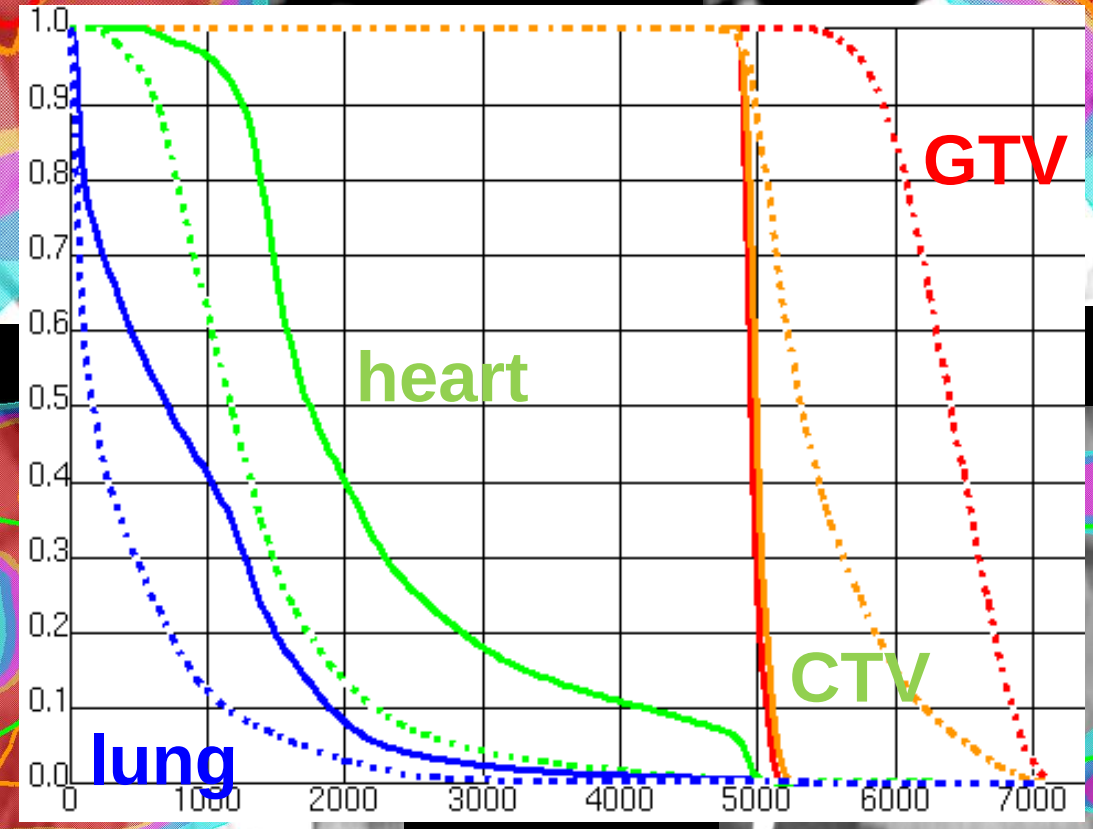


Esophageal cancer

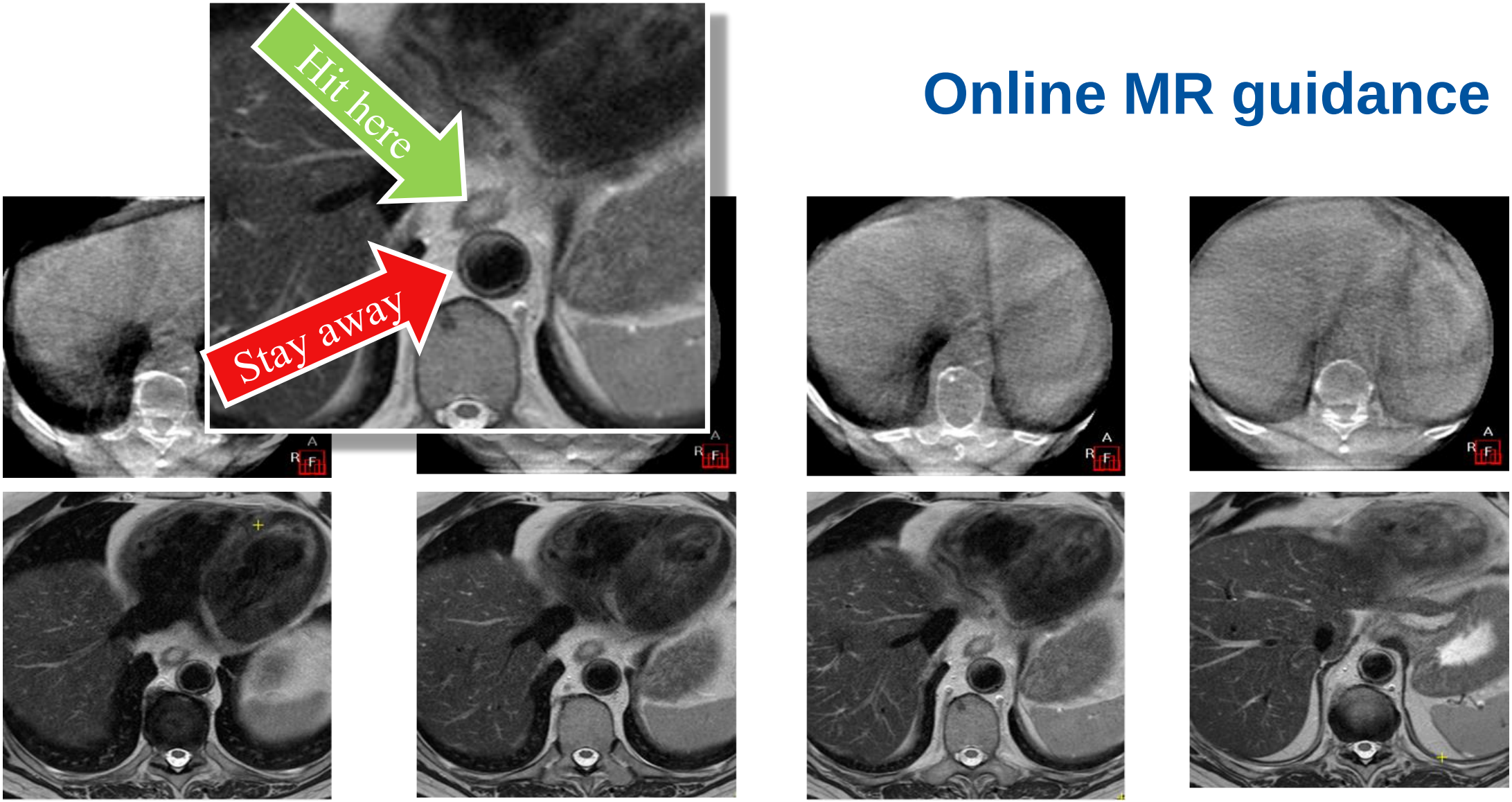
contemporary RT

reinvented RT

GTV=8 cm^3
CTV=63 cm^3
PTV=290 cm^3



Online MR guidance



With online MR guidance we see GTV, “CTV” and risk organs

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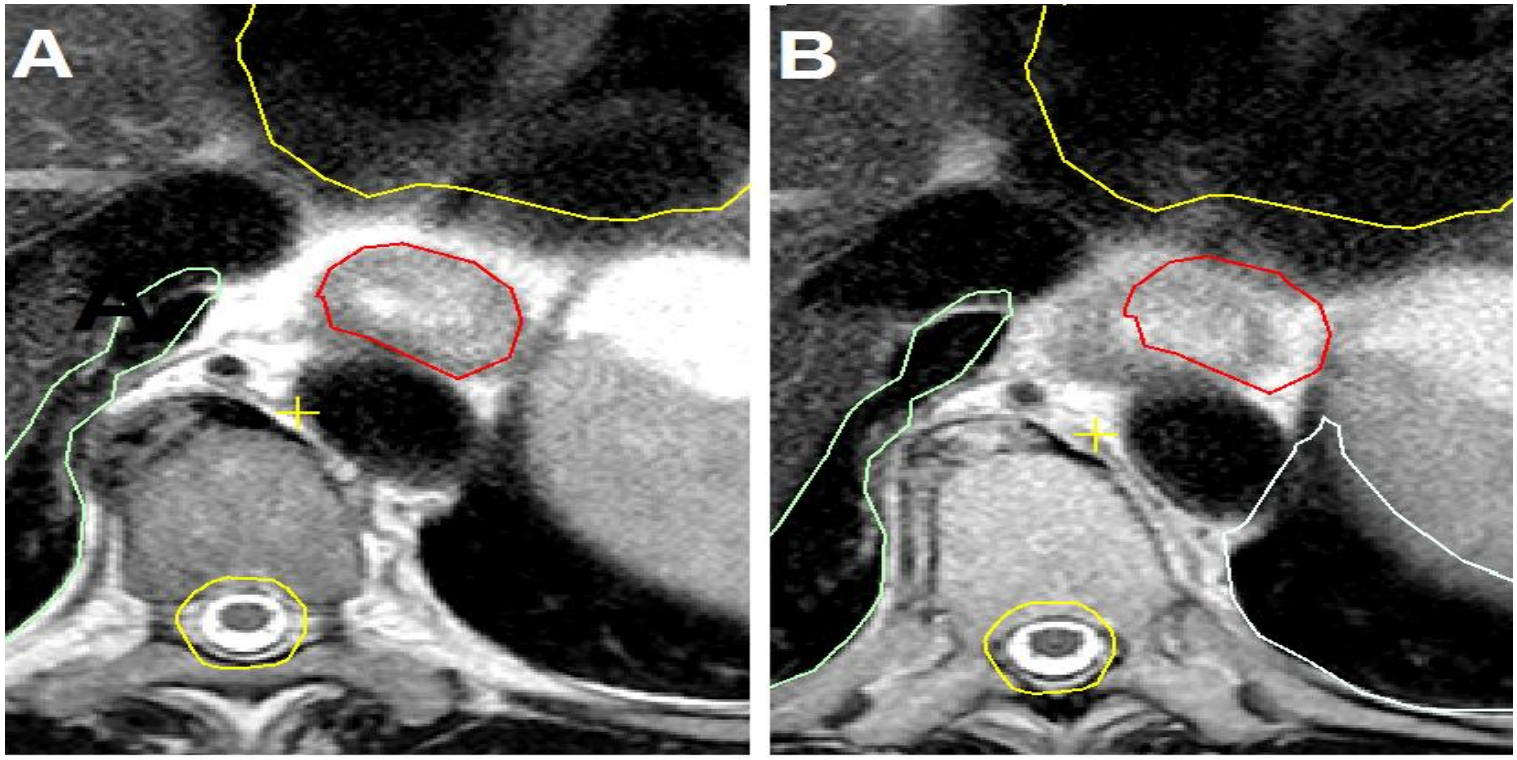
1 MRI guidance for identifying changes in anatomy



Day 1 **Day 4**

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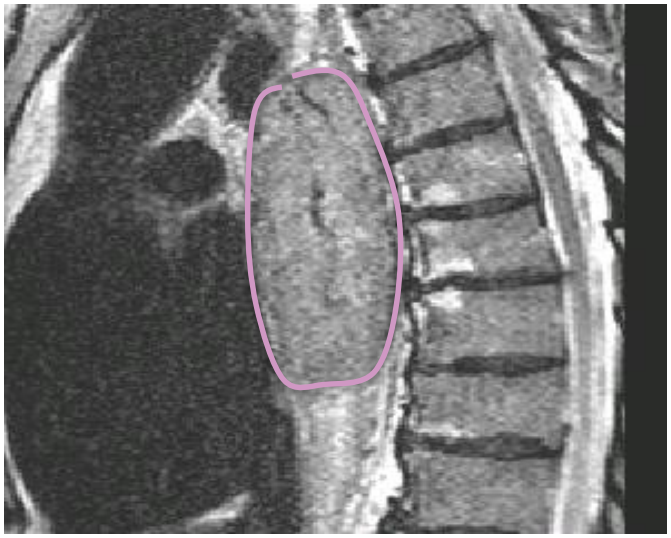
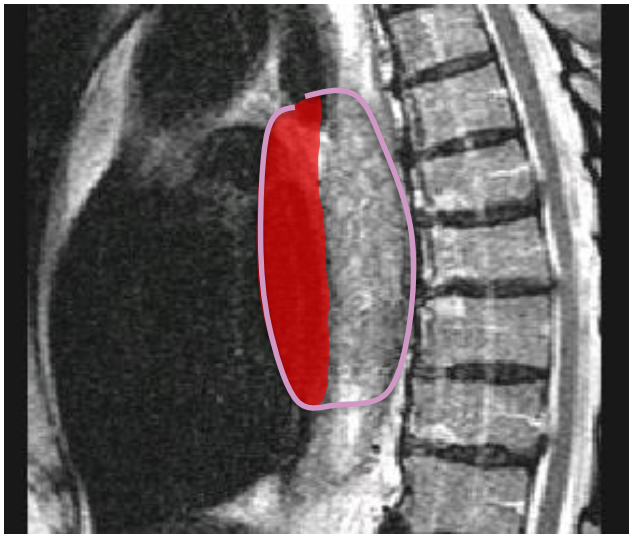
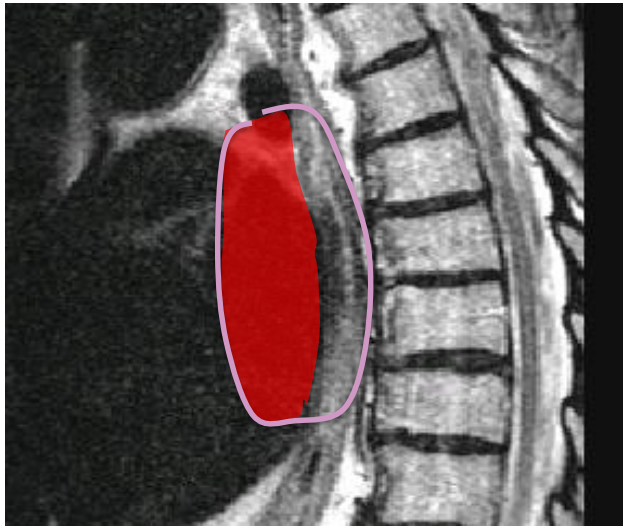
2 MRI guidance for identifying tumor shrinkage



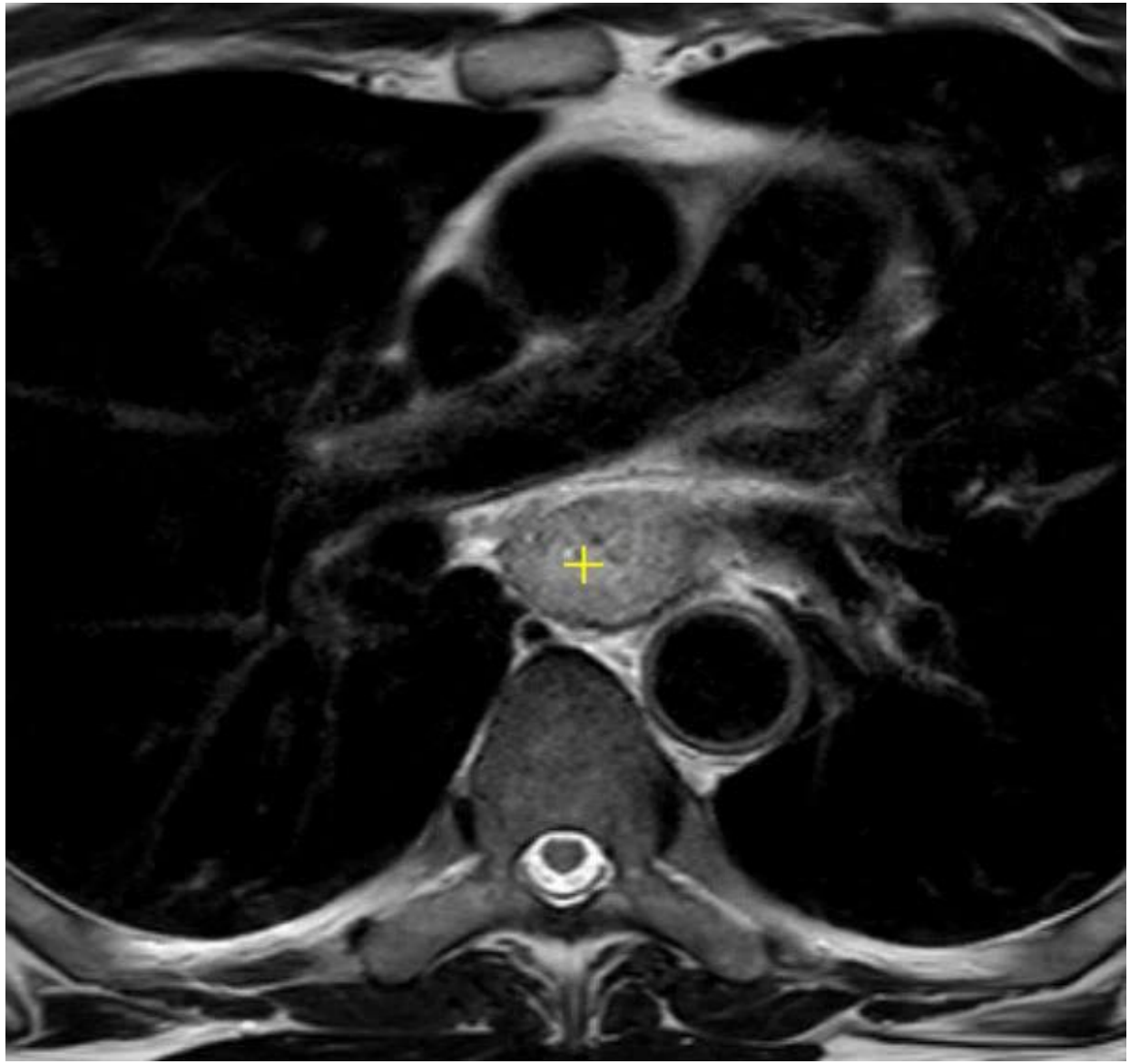
Day 0

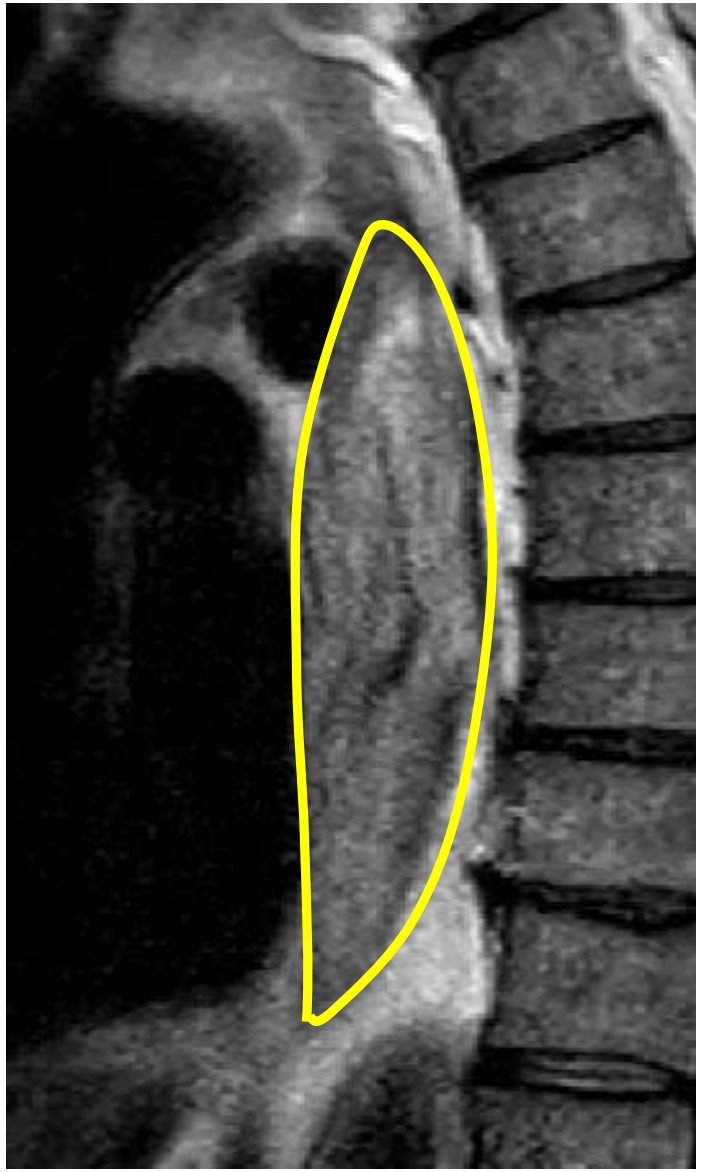


Day 10



Day 20





First patient with weekly repeat imaging

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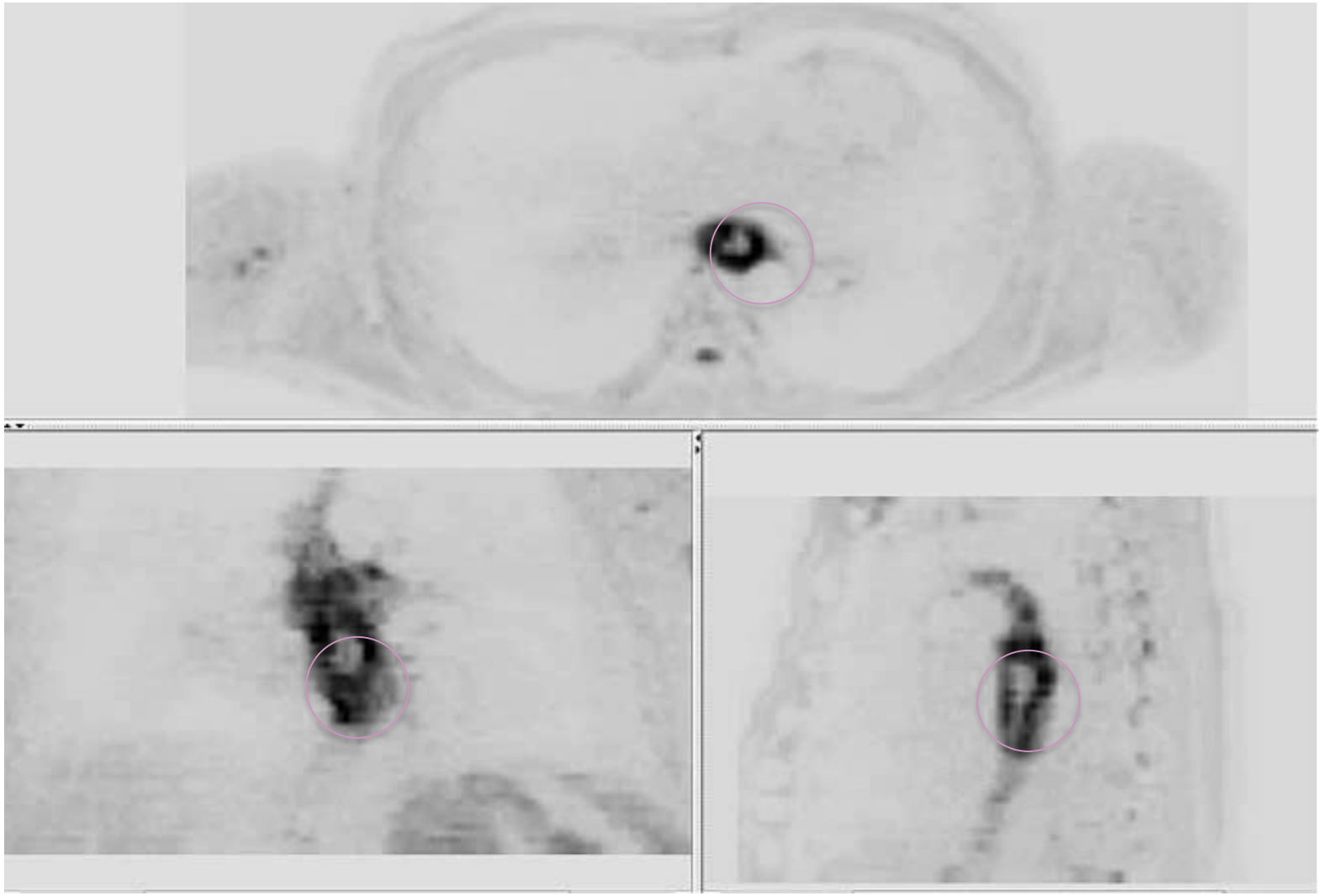
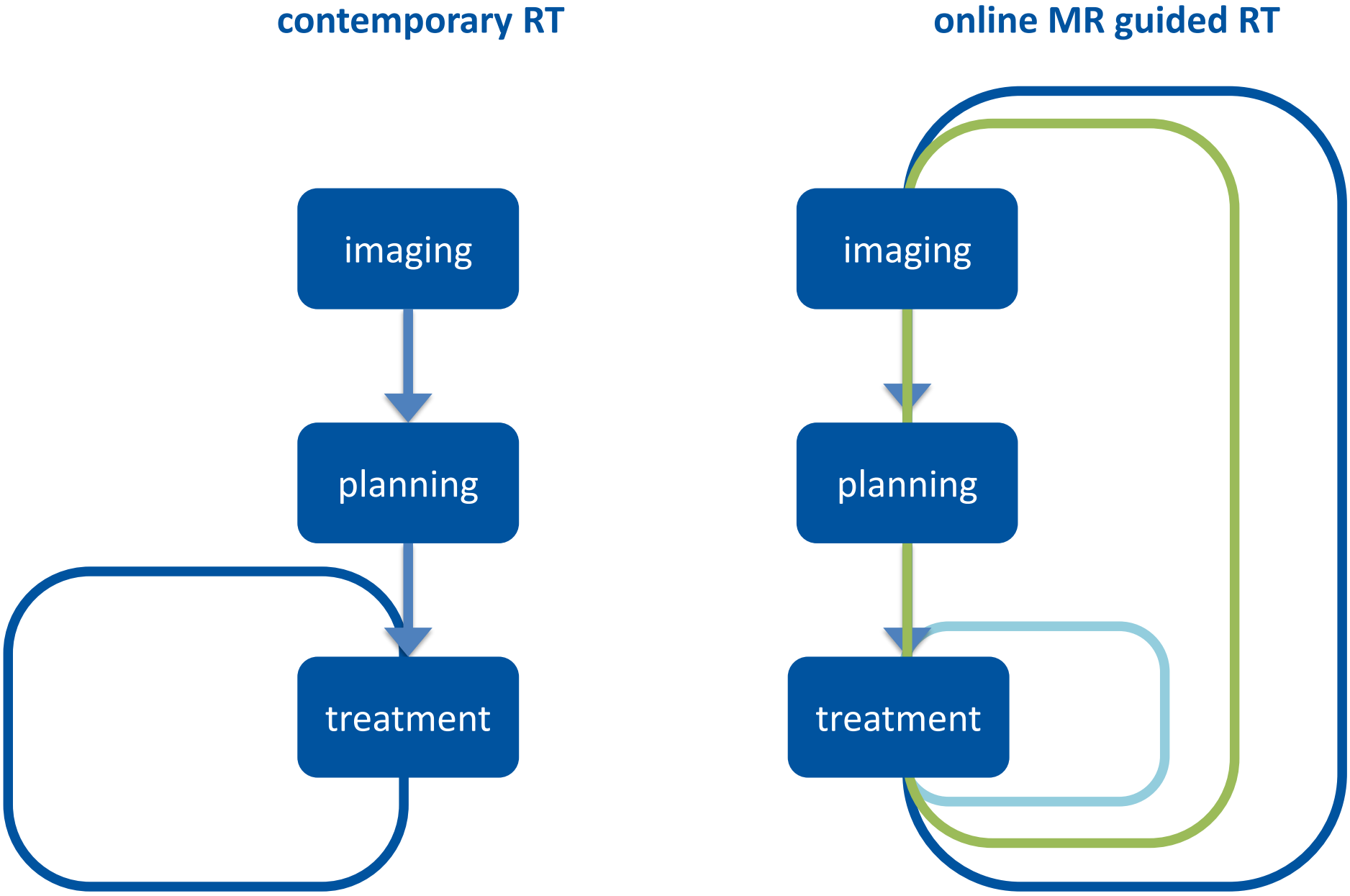
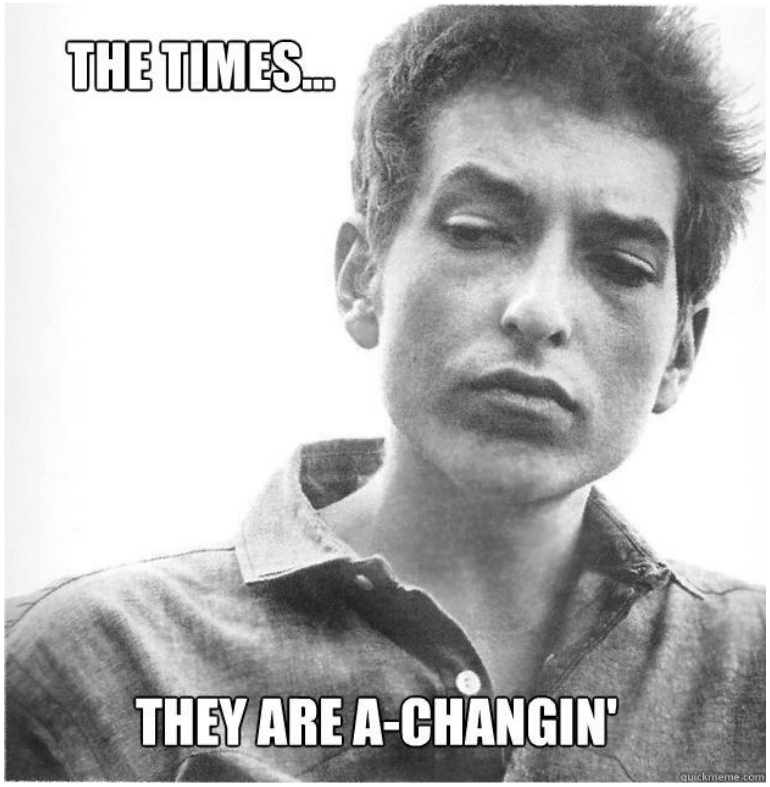
functional changes over time




contemporary RT
online MR guided RT
imaging
planning
treatment
imaging
planning
treatment

the times they are a changin’



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WWW.ESTRO.ORG/SCHOOL

The doctor's perspective

Neil
Burnet

Manchester Cancer Research Centre,
University of Manchester and Christie Hospital,
Manchester, UK

ATP
Athens 2018

Summary

- Small dose differences make a difference (clinically)
- Multi-criteria optimisation (MCO) – improved individualisation
- Keep talking – dialogue = 2 way conversation

- Protons
- Normal tissue response
  - More data needed on normal tissue toxicity dose response
  - Dose accumulation in normal tissues
  - Biological variation in normal tissue sensitivity
  - Could we convolve a ***biological*** measure of individual normal tissue radiosensitivity with the ***physical*** dose plan

Small dose differences matter

- ‘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
  - Individual patients
  - Society

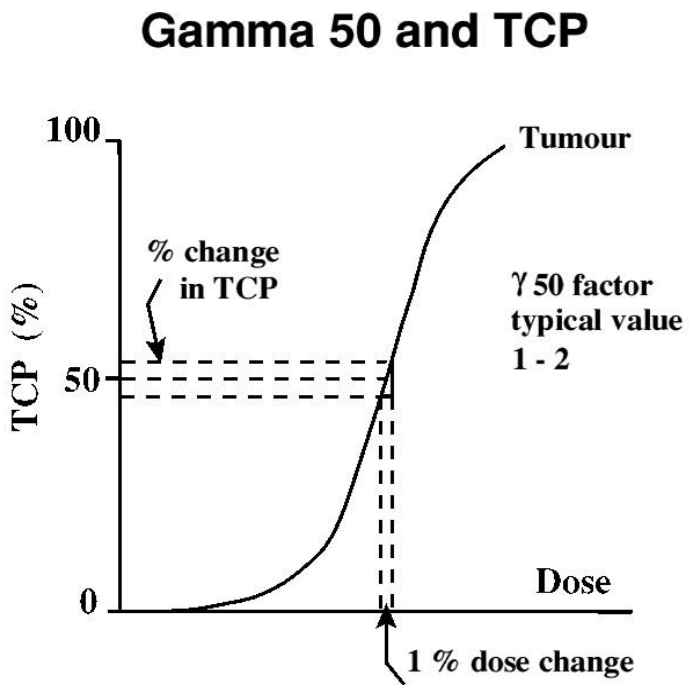
Mike on his bike

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 TCP of 5 - 10%



Use the best tools for the job !

- “If you want to treat a complex shape … like this shell … then you need IMRT”

Jason and Lucy discussing RT techniques …

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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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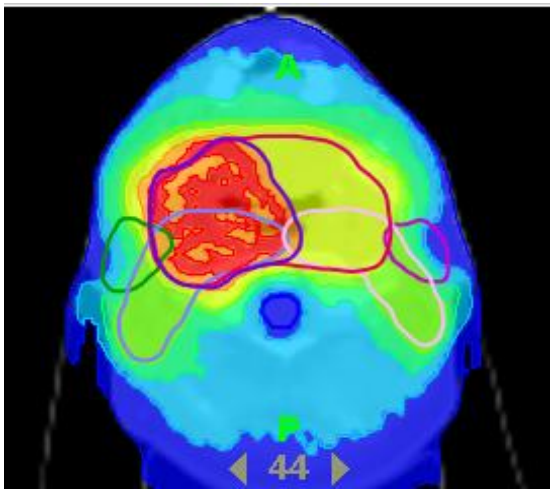
Multi-criteria optimisation (MCO)

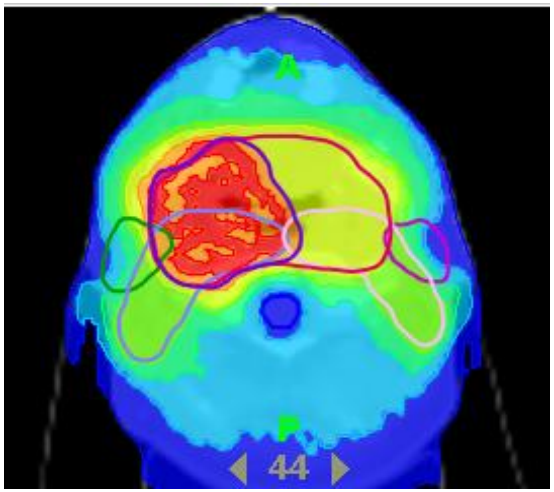


Multi-criteria optimisation (MCO)

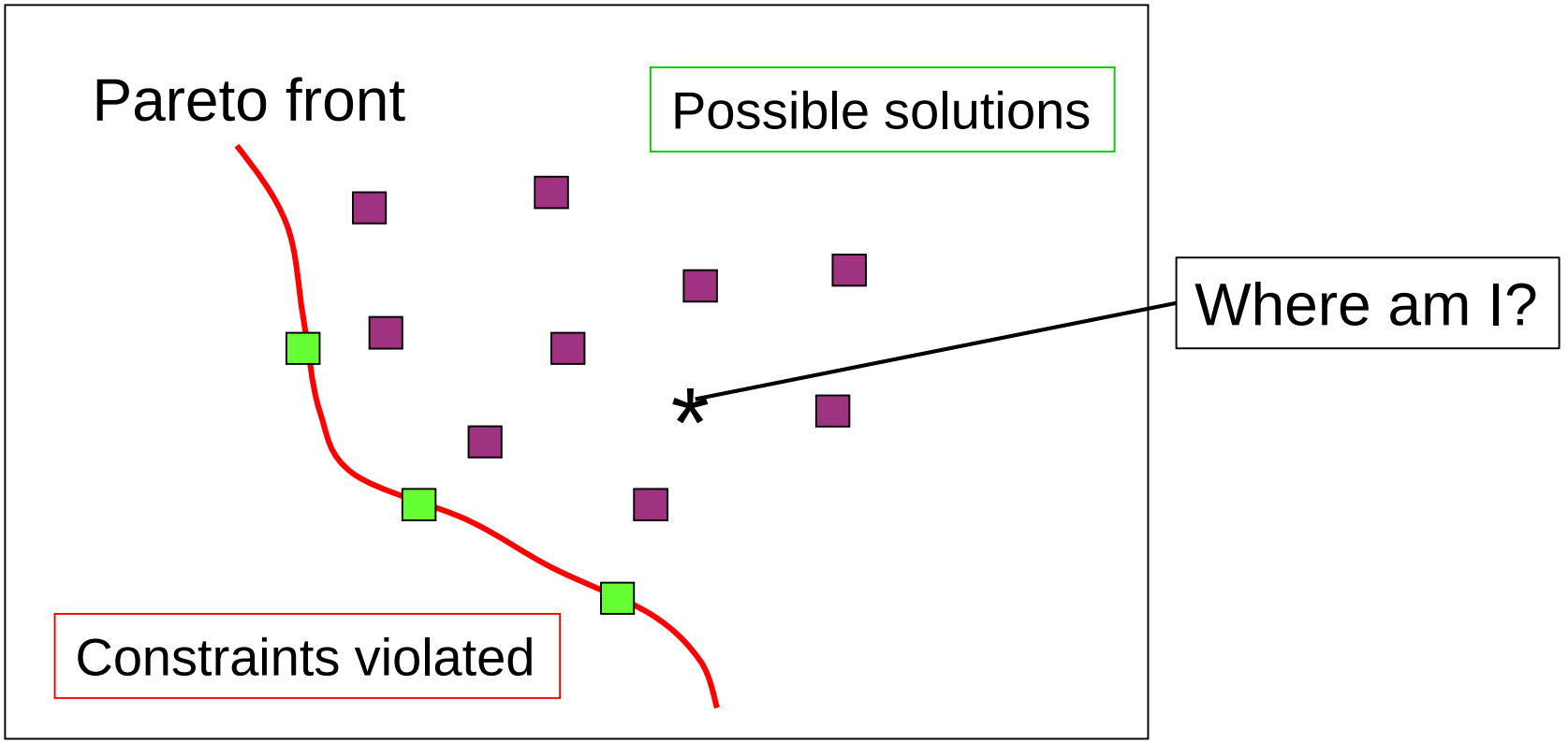
- Multi-criteria (MCO) – prospect of improved individualisation

- Pareto optimisation is basis for IMRT
- Normally have 1 plan from within solution space
- MCO allows real-time examination of solution space

- This might allow (small) improvements in dose plan for individual patients

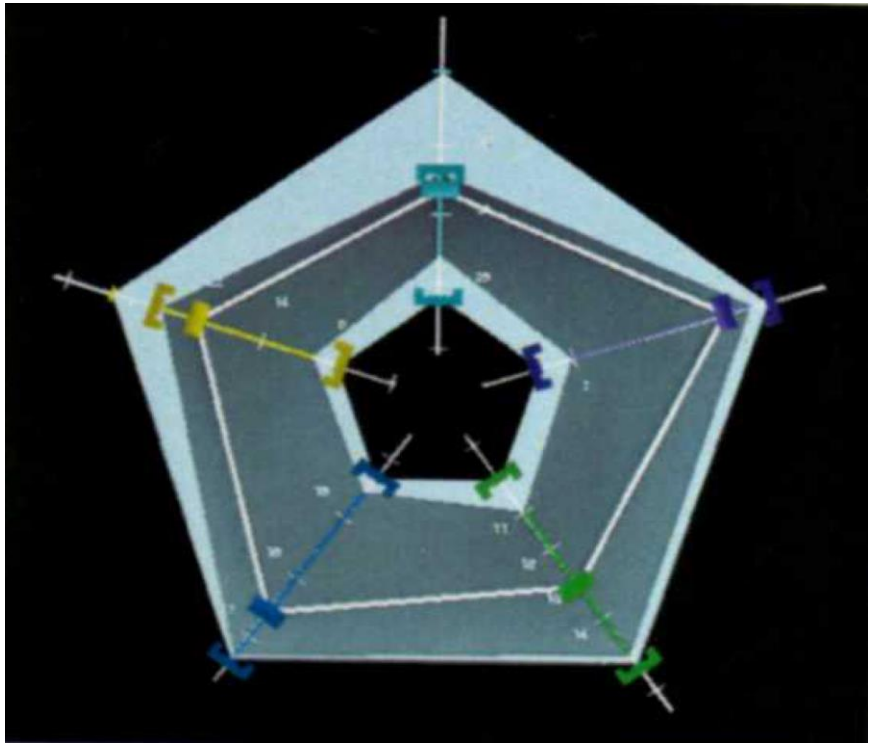


IMRT – Optimisation



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 available
- Full value not yet known, but appears useful



Courtesy of Fraunhofer Institute

Dialogue – a key component of happy planning

- Talk to your colleagues …

… and at least I always get an intelligent answer!

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Protons

Venetian cannon balls Rethymno Fortezza

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Protons

- PBT is harder to use than X-ray therapy
- Full of uncertainties

- 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

Clinical benefits of PBT

- **Reduce dose to normal tissues**
  - **Children**
    - Reduce growth impairment
    - Reduce second cancer risk (late)
    - Reduce organ doses
  - **Teenagers and young adults**
    - Same
  - **Older adults**
    - (2) & (3) – but at what age?
    - Dose escalate radio-resistant tumours

Clinical benefits of PBT

- **Reduce dose to normal tissues**
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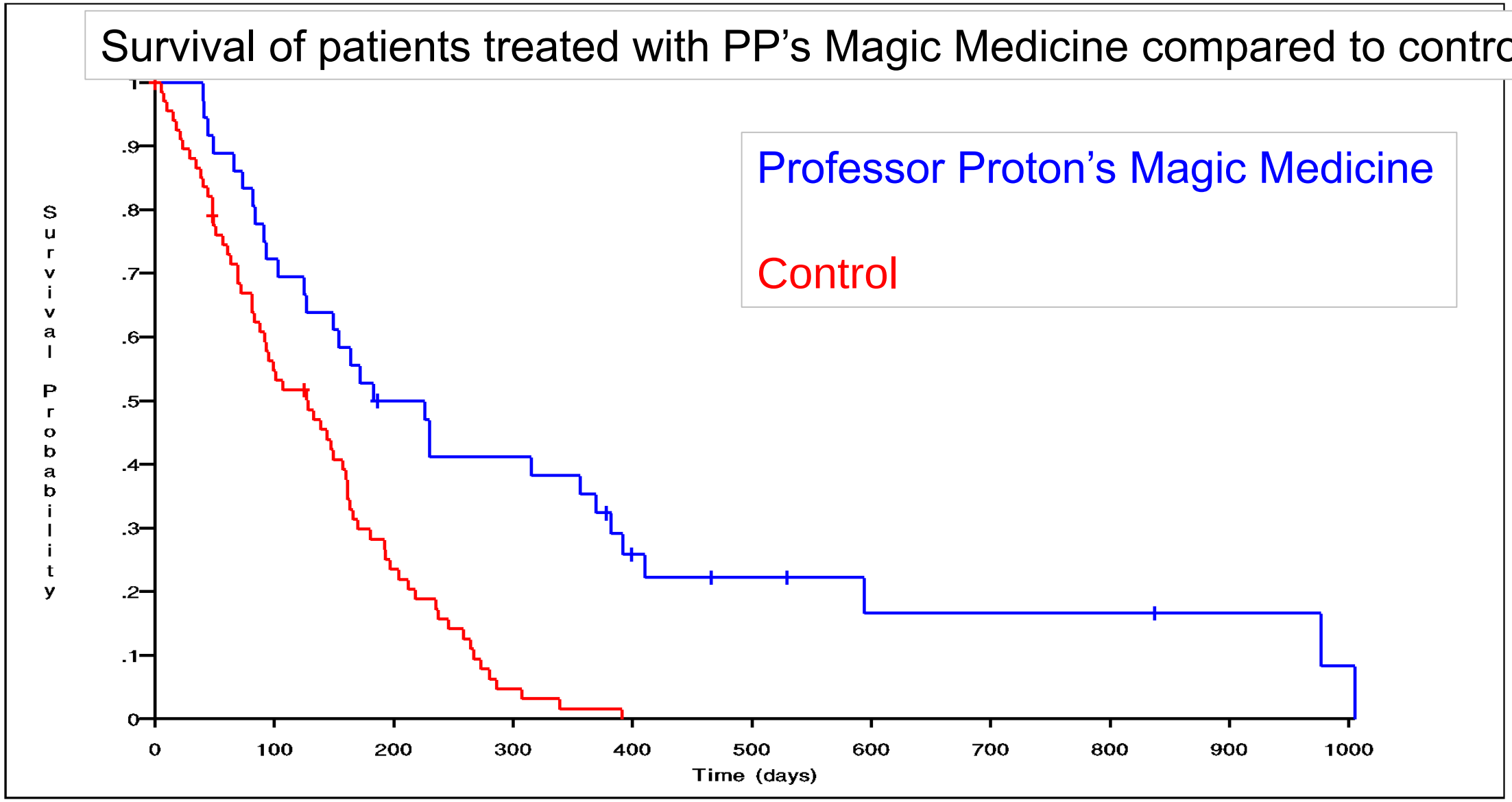
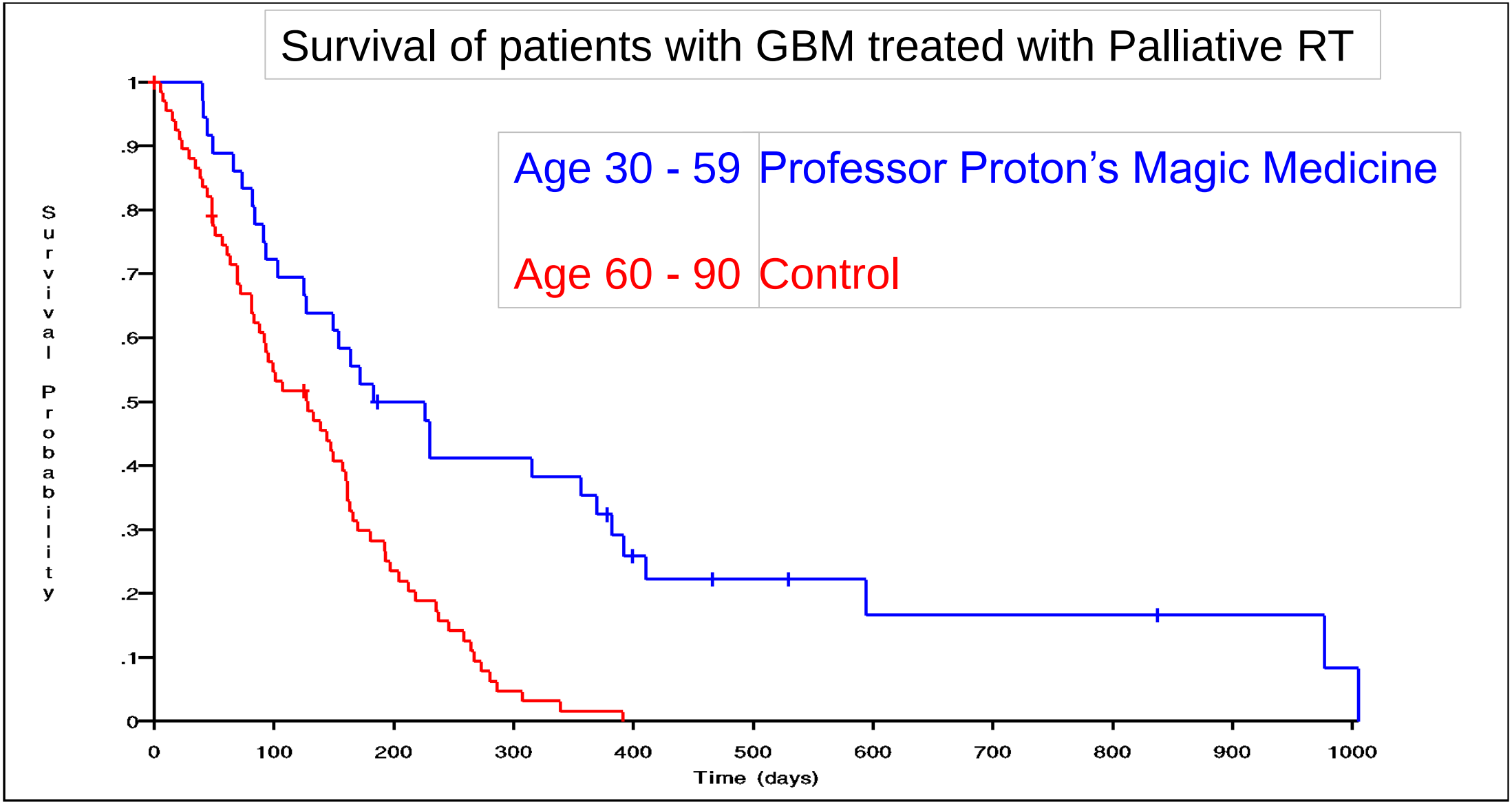
  - **Teenagers and young adults**
    - Same
  - **Older adults**
    - (2) & (3) – but at what age?
    - Dose escalate radio-resistant tumours

What about older adults?

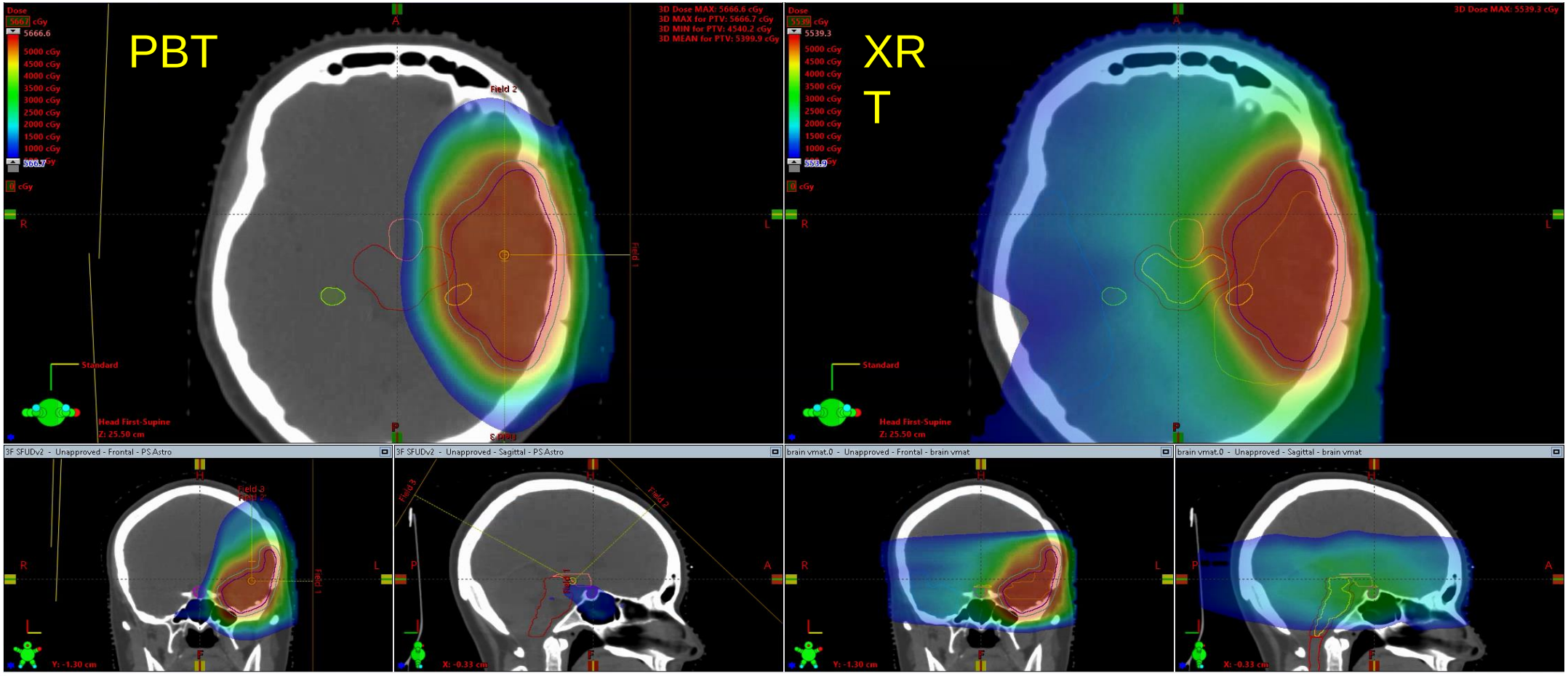
Patient selection



Patient selection



PBT compared to IMRT



- But what is the *clinical* difference?

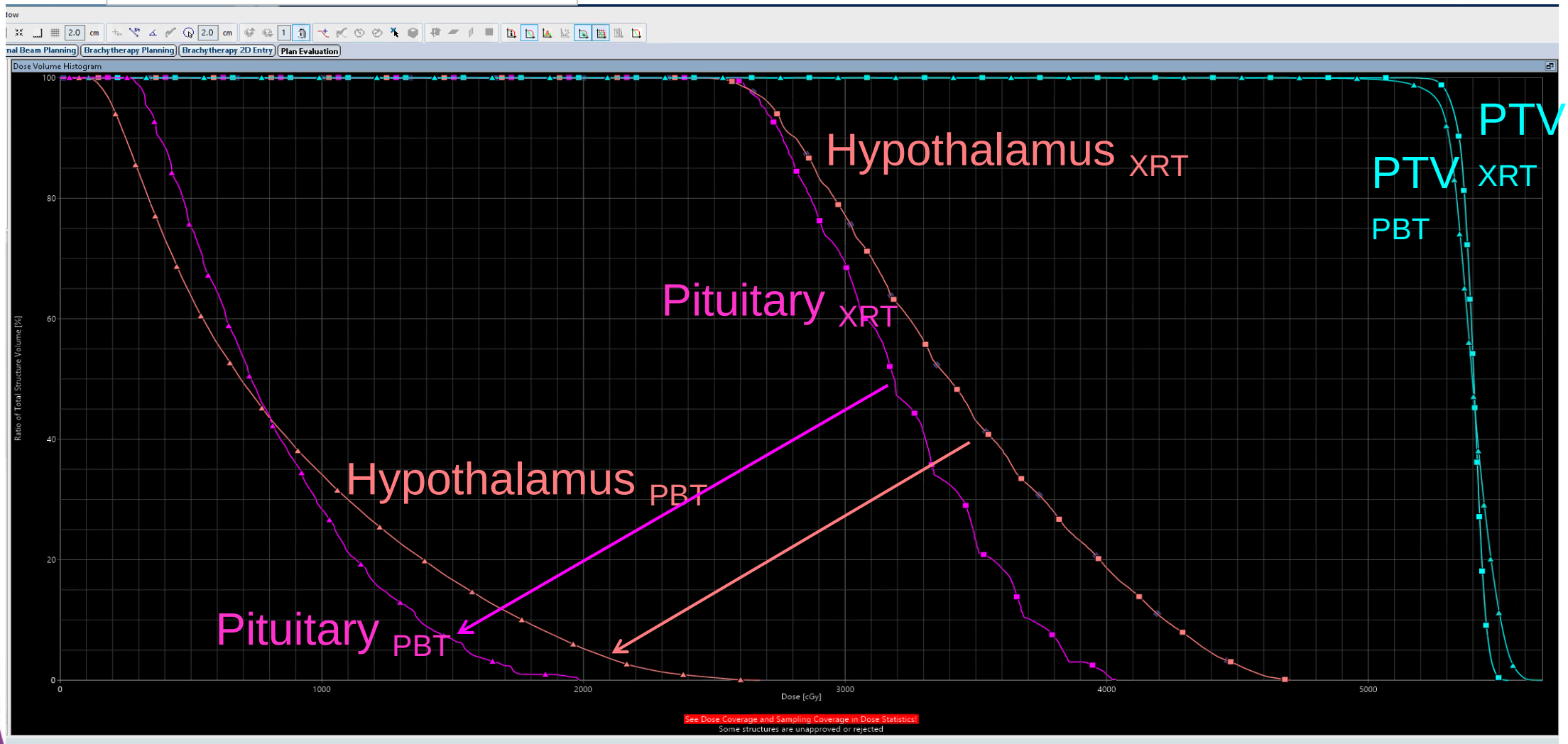
Thanks to Gillian Whitfield

3 field SFO proton plan

Rotational IMRT (VMAT) plan

Δ PBT

☐ XRT (VMAT IMRT)



- But what is the clinical difference? What are dose limits?

Thanks to Gillian Whitfield

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Hippocampal sparing

- Hippocampal sparing may spare memory

Hippocampus - ιππόκαμπος

Image courtesy of Google

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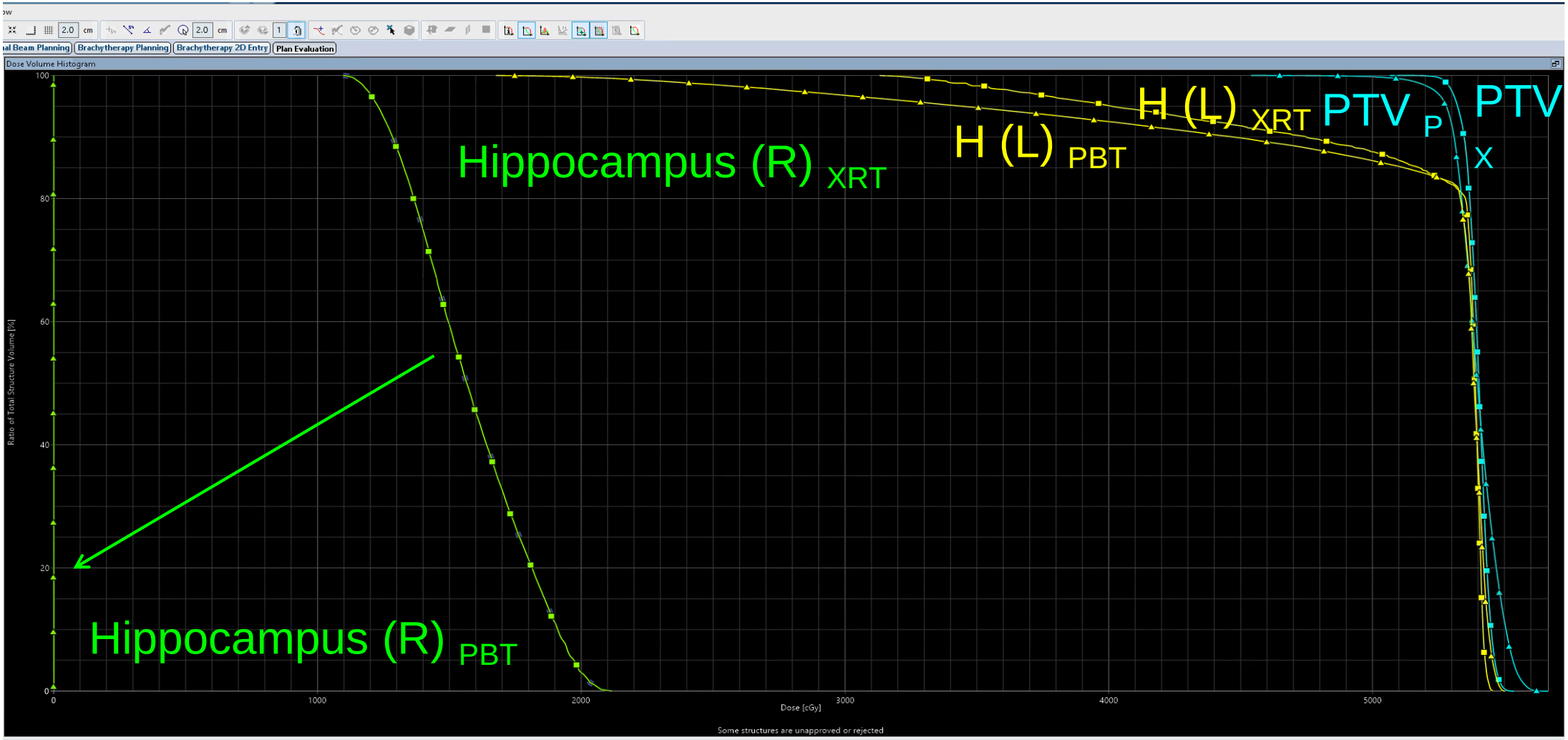


Approval Status	Plan	Course	Volume [cm³]	Dose Cover.[%]	Sampling Cover.[%]	Min Dose [cGy]	Max Dose [cGy]	Mean Dose [cGy]
Unapproved	brain vmat.0	VMAT						
Unapproved	brain vmat.0	VMAT						
Unapproved	brain vmat.0	VMAT						
Unapproved	brain vmat.0	VMAT	1.8	100.0	95.6	3133.3	5456.9	5231.7
Unapproved	brain vmat.0	VMAT	2.0	100.0	96.9	1097.6	2119.1	1583.4
Unapproved	3F SFUDv2	SKJ						
Unapproved	3F SFUDv2	SKJ						
Unapproved	3F SFUDv2	SKJ	23.2	100.0	99.9	0.0	5425.9	855.1

User: skelly Group: Physicist Site: Main

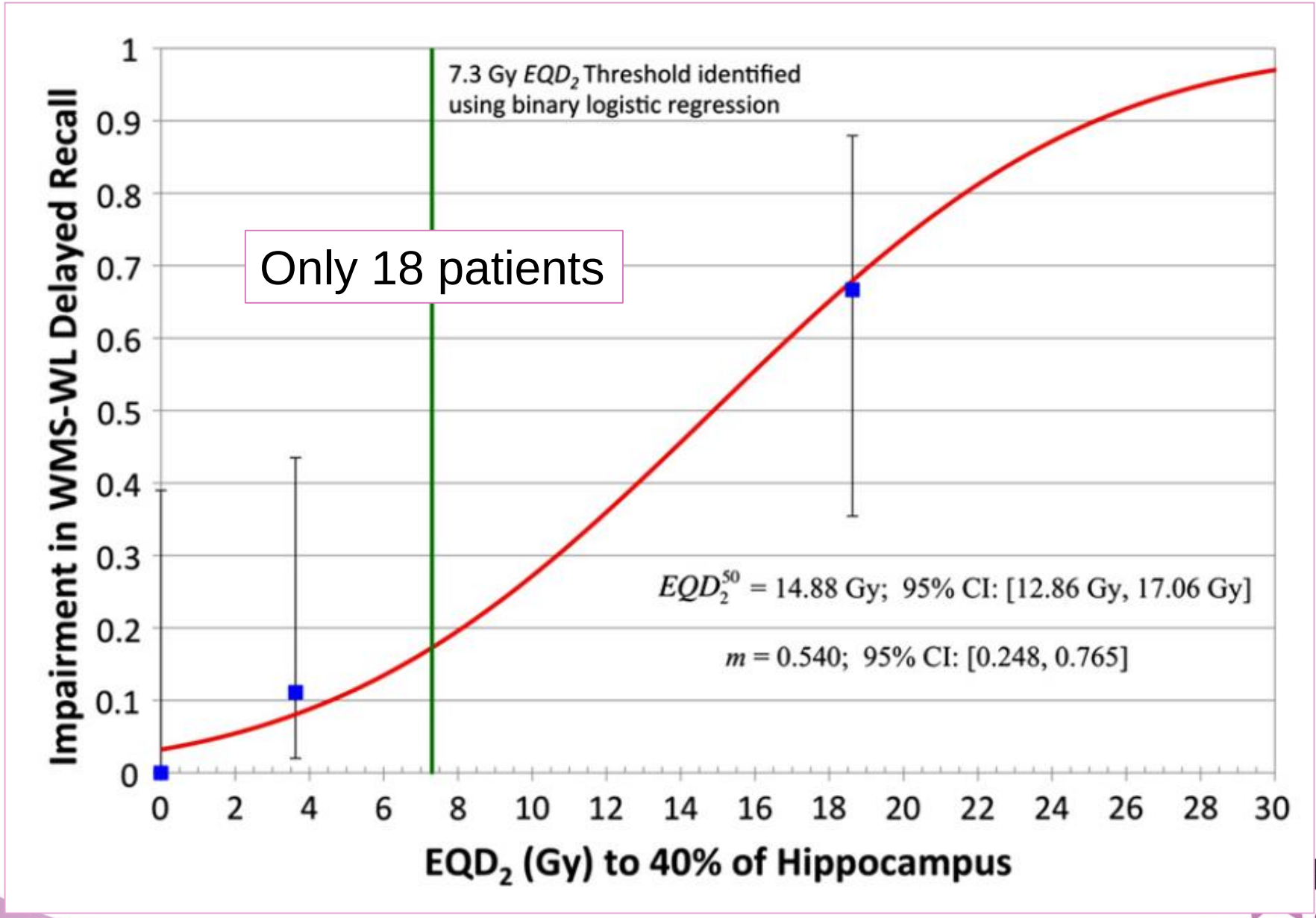
Normal tissue sparing

- The dosimetry benefit is obvious

- What *clinical benefit* does this confer?
  - Largely unknown
  - Needs investigation
  - Requires long follow up

- Connecting dose (dose difference) to clinical outcome (differences) is crucial

Gondi V. et al. IJROBP 2013; 85(2): 348-354



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

- NB variation
  - Physical
  - Biological

Normal tissue response data

- Spinal cord - need to avoid events which define tolerance threshold

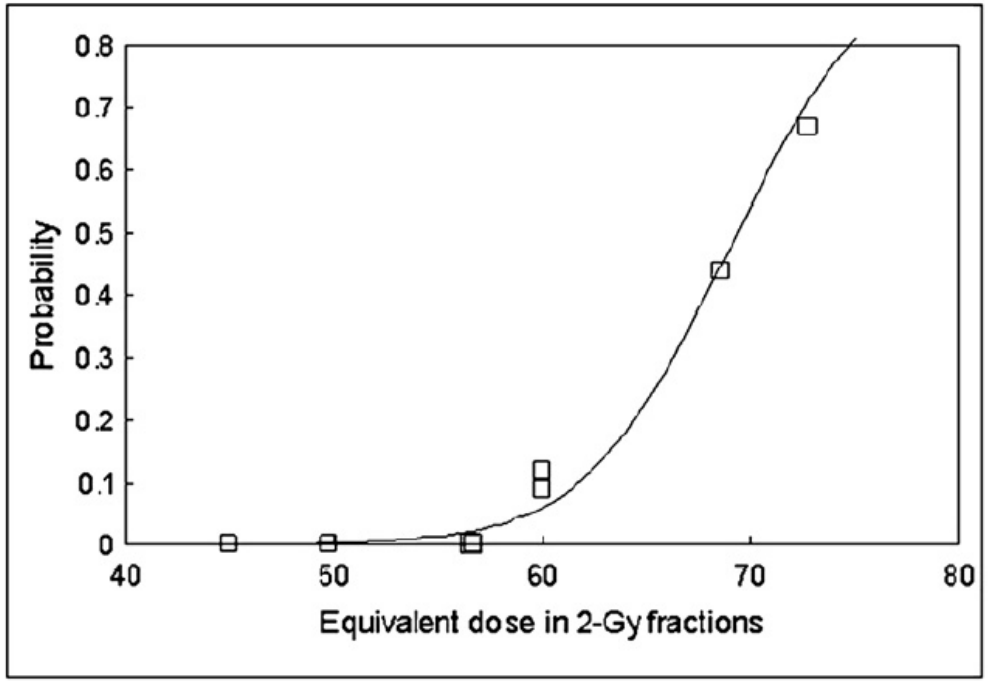


Fig. 1. The dose–response function for the myelopathy of the cervical spinal cord and data points (□) derived from Table 1. The probability of myelopathy was calculated from the data in Table 1, adjusted for estimated overall survival per (18).

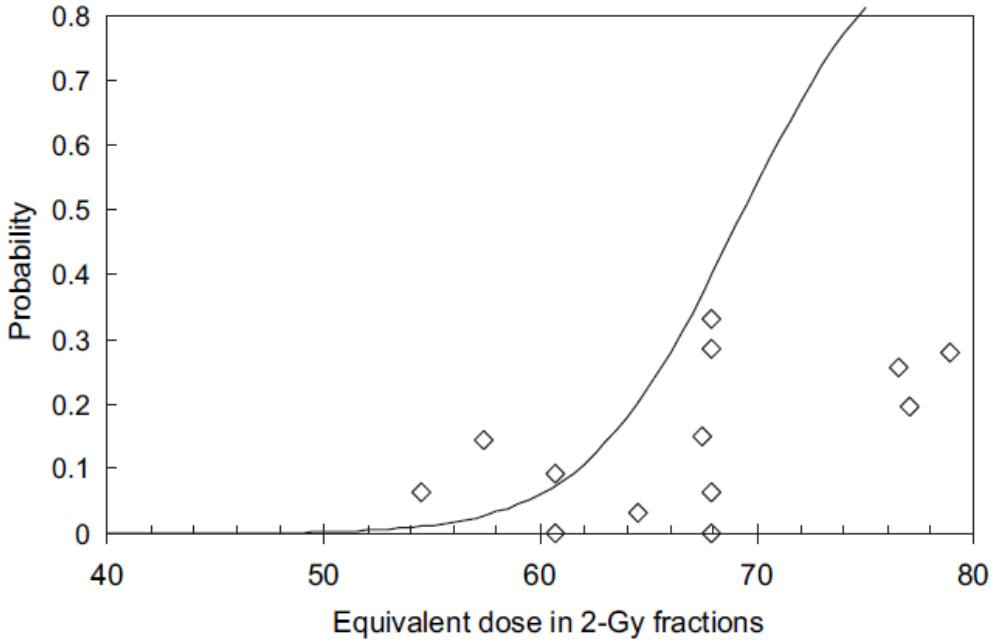


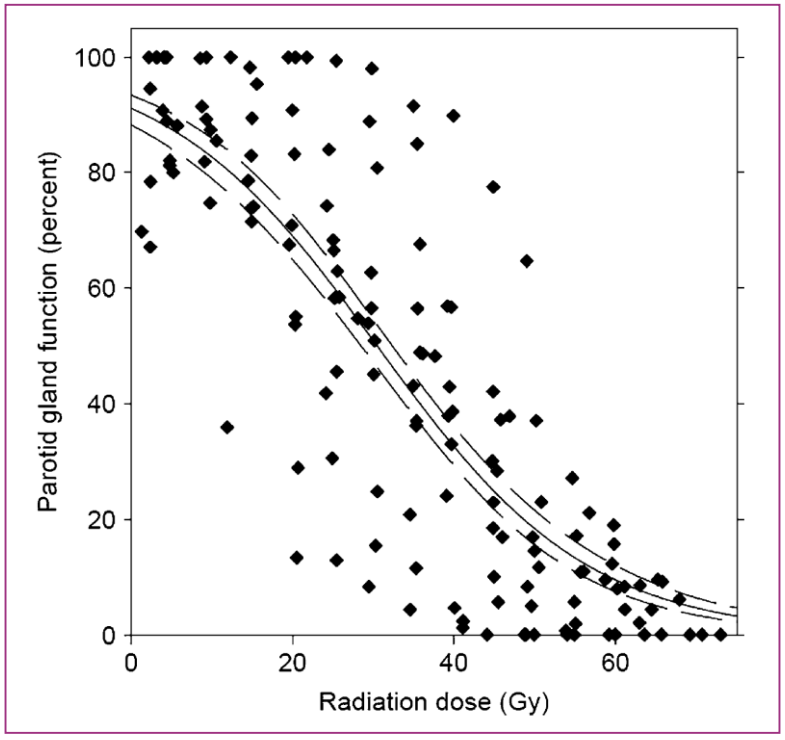
Fig. 2. The dose–response function for myelopathy of the cervical cord (solid line) and data points for the thoracic spinal cord (◇) derived from Table 2. The probability of myelopathy was calculated from the data in Tables 1 and 2, adjusted for estimated overall survival per (18).

- 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 …

Normal tissue response data

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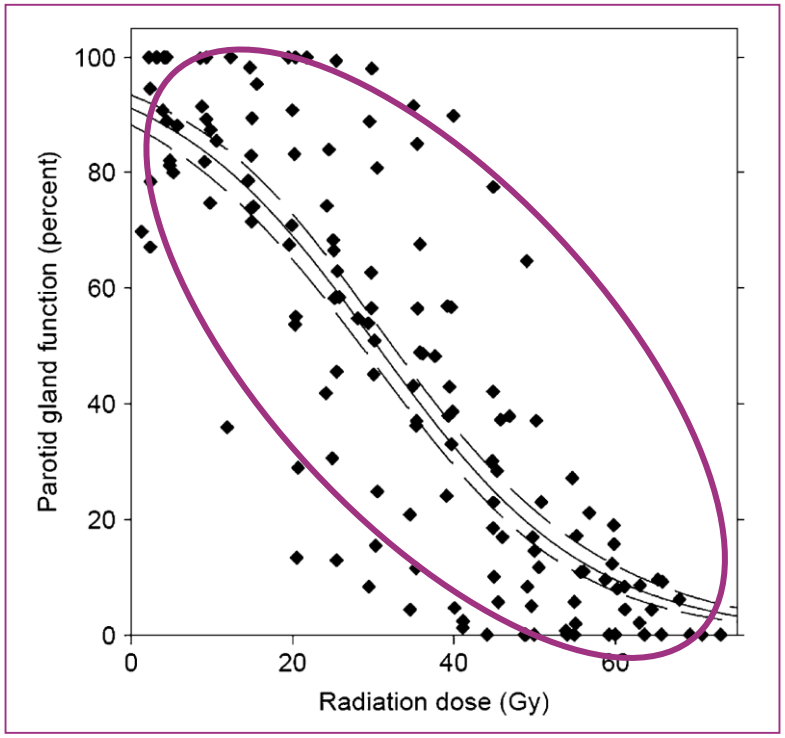


- Parotid dose-response
- Scatter …

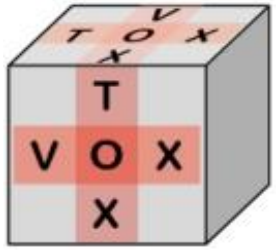
Dose accumulation – normal tissues

Dose accumulation – normal tissues

- 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 was trying to do just this
  - VoxTox – linking dose at the voxel level with toxicity
  - Consider rectal toxicity …



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CERN IdeaSquare Journal of Experimental Innovation, 2017; 1(1): 3
DOI: https://doi.org/10.23726/cij.2017.457

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]

- Description of a real multi-disciplinary research group
- Published as the first paper in the inaugural edition

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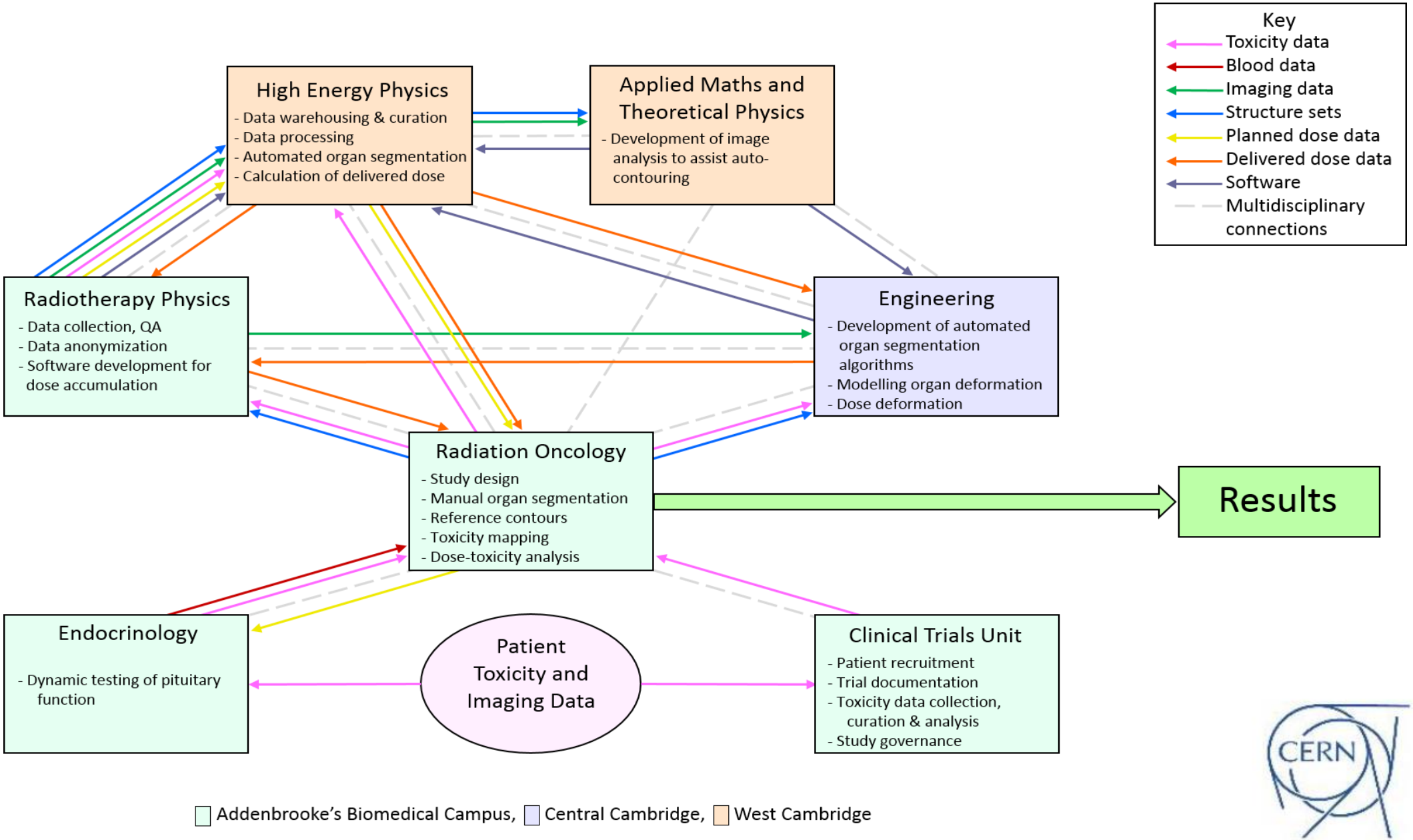
VoxTox multi-disciplinary relationships



CERN

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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 from accumulated dose-surface maps (DSMs) demonstrated stronger correlations with rectal bleeding and proctitis than planned DSMs.

- Very important for understanding NTCP better

108 patients, 4000 daily IG CT scans

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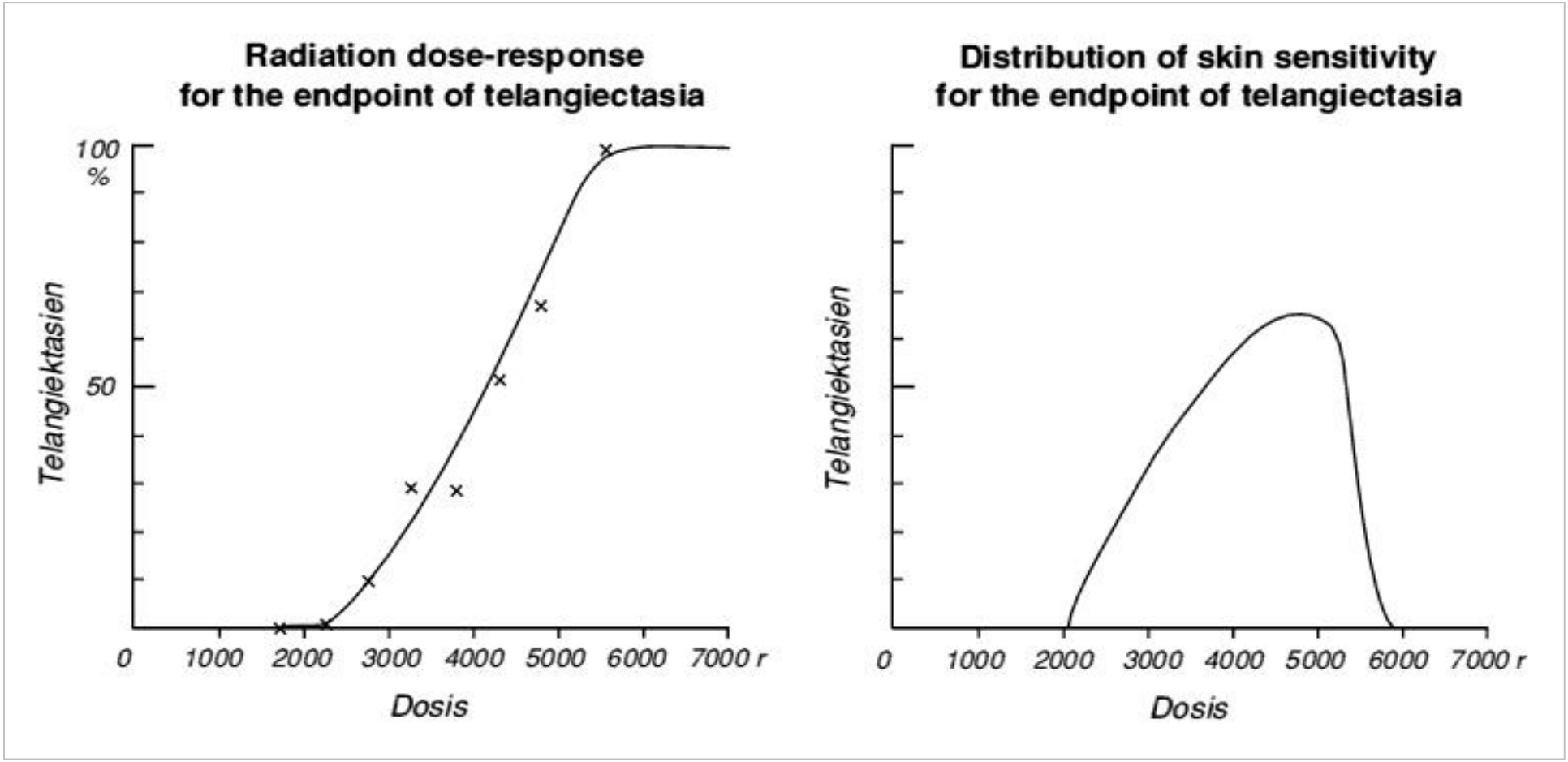
Individual variation in normal tissue sensitivity

Individual variation in normal tissue sensitivity

Holthusen H. Strahlentherapie 1936; 57: 254-69



- Matches clinical experience

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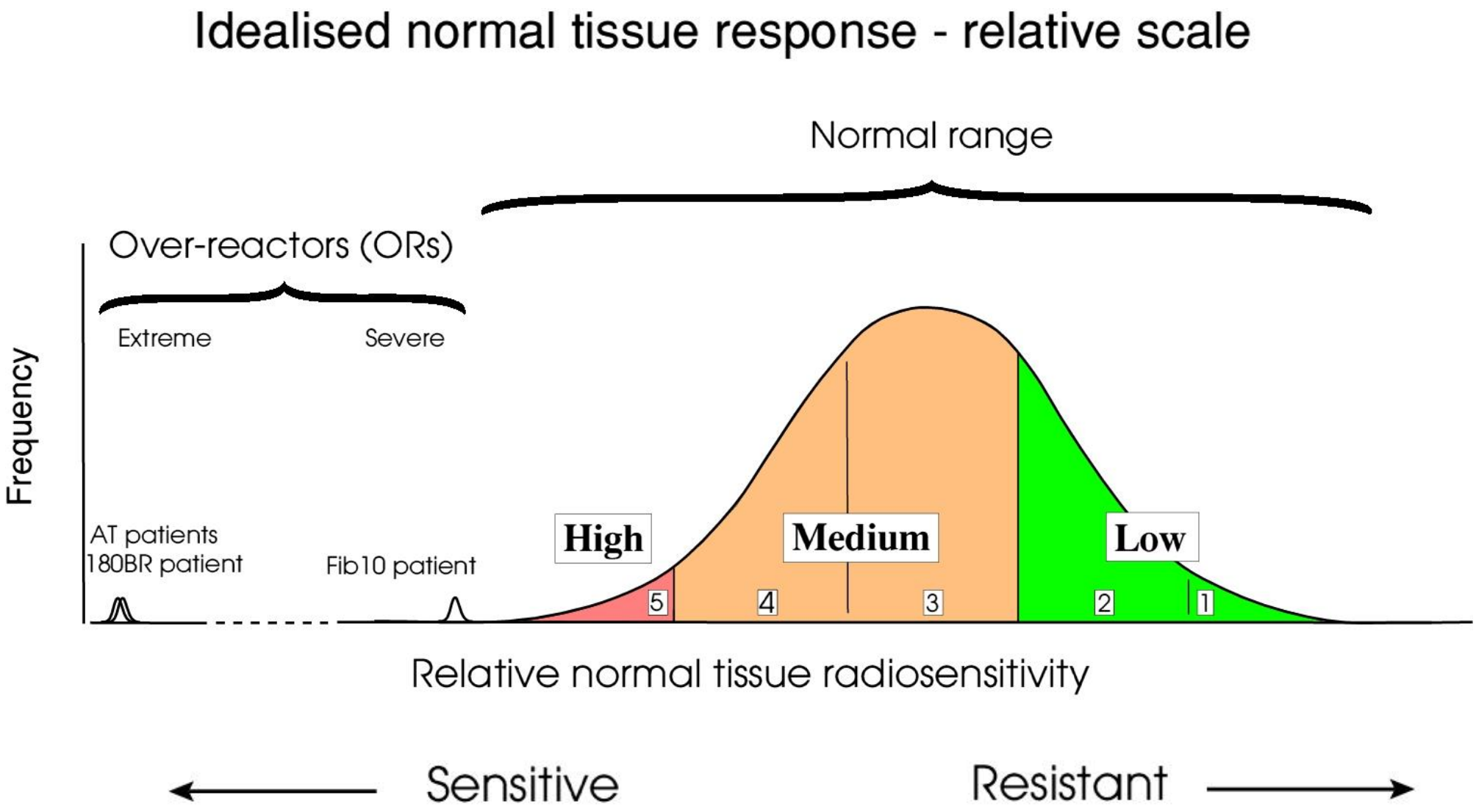
Individual variation in normal tissue sensitivity



Individual variation in normal tissue sensitivity

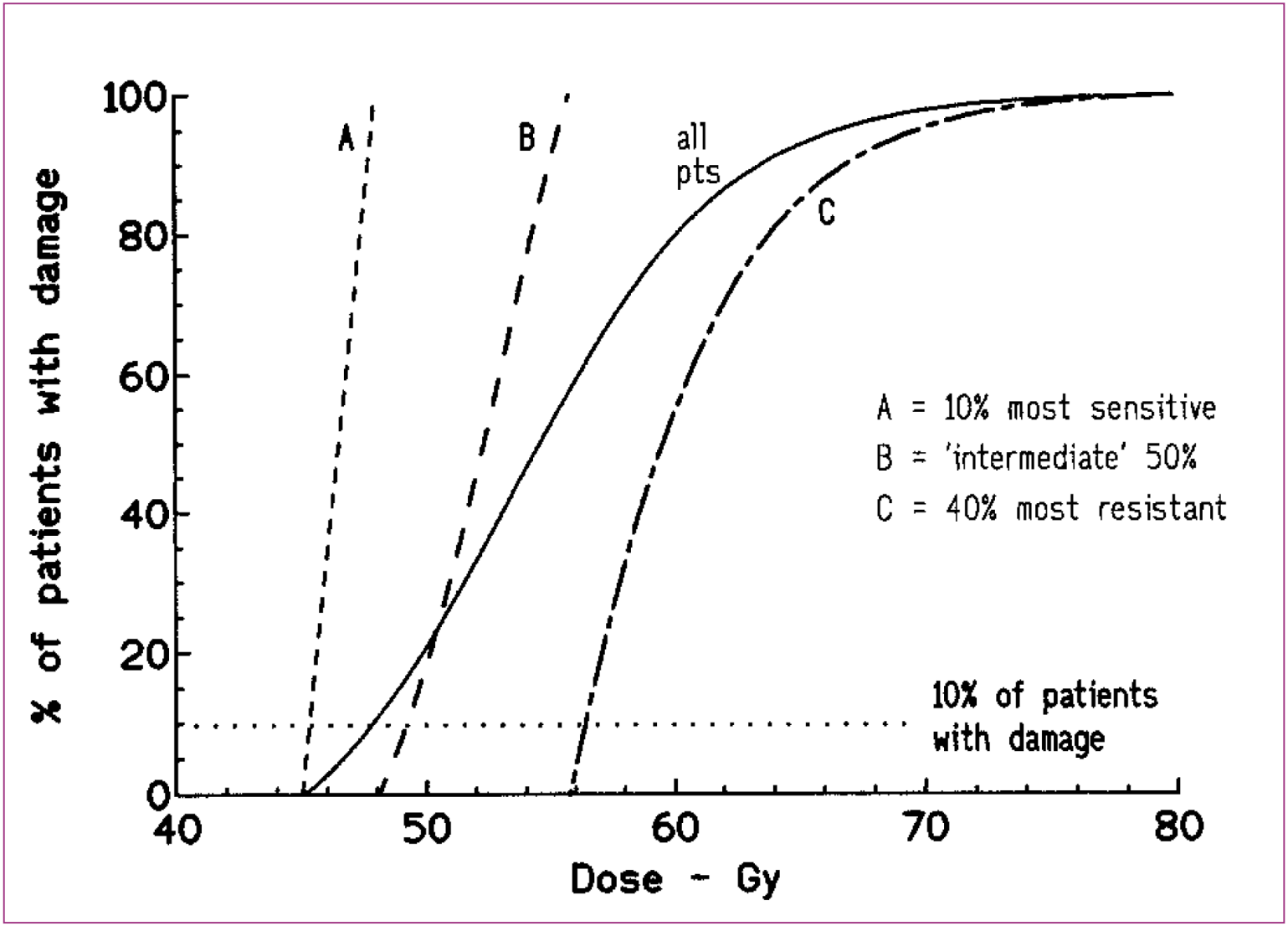
- Variation in response harder to observe with mega-voltage beams because of skin sparing

- 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



- Source data from Ingela Turesson, Göteborg

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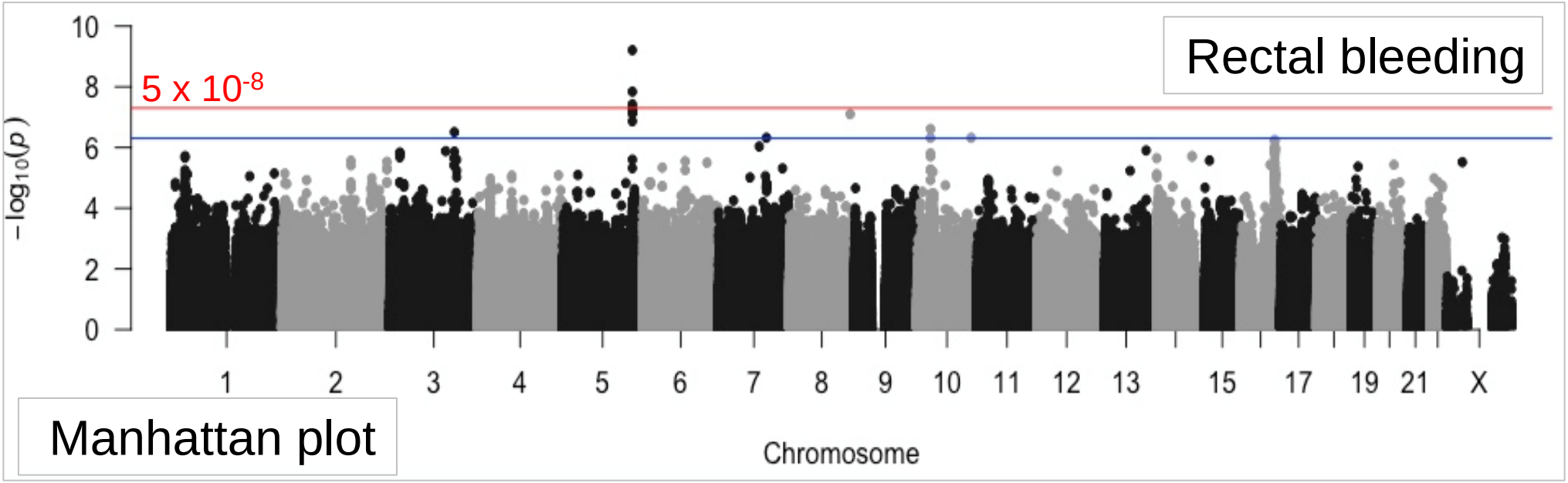
Individual variation in normal tissue sensitivity

- Definite evidence that *normal* genetic variation is linked to variation in tissue response or toxicity
- Major developments in last 4 years
- Not yet ready for clinical application

RAPPER

- Clinical data and DNA on ~10,000 patients



- Definite polymorphisms linked with variation in toxicity
- Relevant for PBT
- But … tissue specific

Individual variation in normal tissue sensitivity

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

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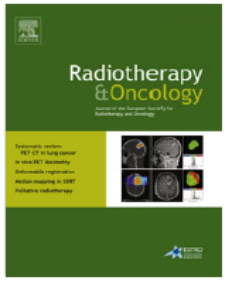
journal homepage: www.thegreenjournal.com



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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Bridging to clinical application

Hellenistic bridge at Eleftherna

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Convolving individual radiosensitivity & individual dose accumulation

- Could we put together a ‘signature’ of individual normal tissue radiosensitivity and an individual estimate of dose accumulation (D_A) ?

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

- Also important to better understand dose-response

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
- There is always still the biology

- 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**

First IG-IMRT patient - 31st October 2007


Thank you for listening