Martini-Klinik
Prostatakrebszentrum

Technische Universität Hamburg

5th Annual LLU Algorithm Workshop

Radiobiological Modelling in Radiation Therapy (of Prostate Cancer)

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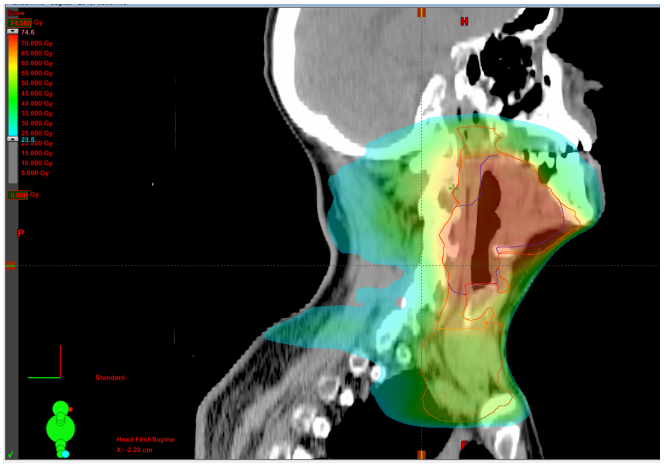
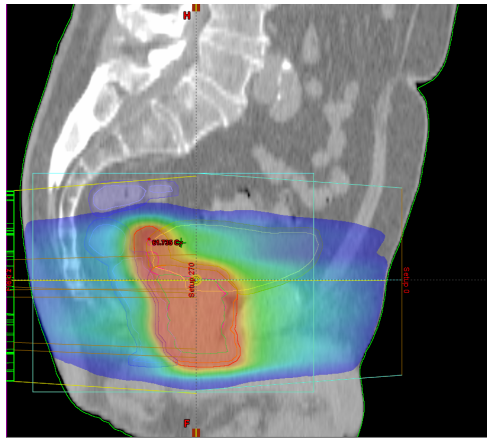
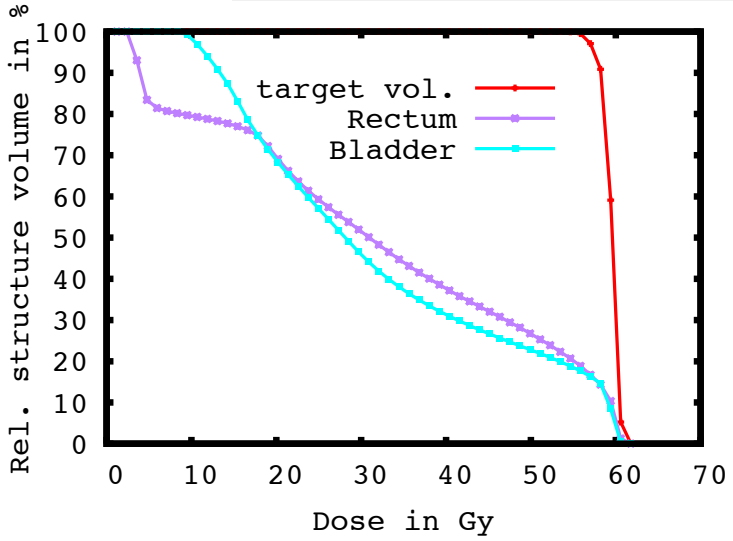
Radiotherapy: balance between cure and toxicity

Conventional treatment plan evaluation

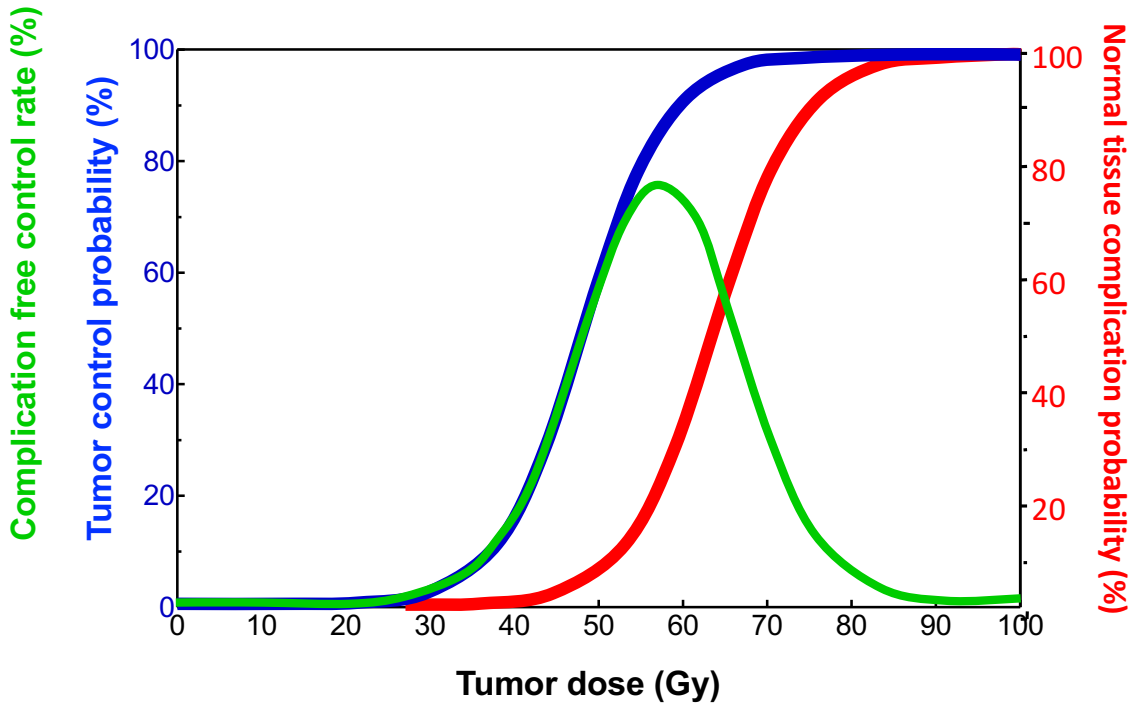
- 3D dose distribution
- Dose-Volume histograms





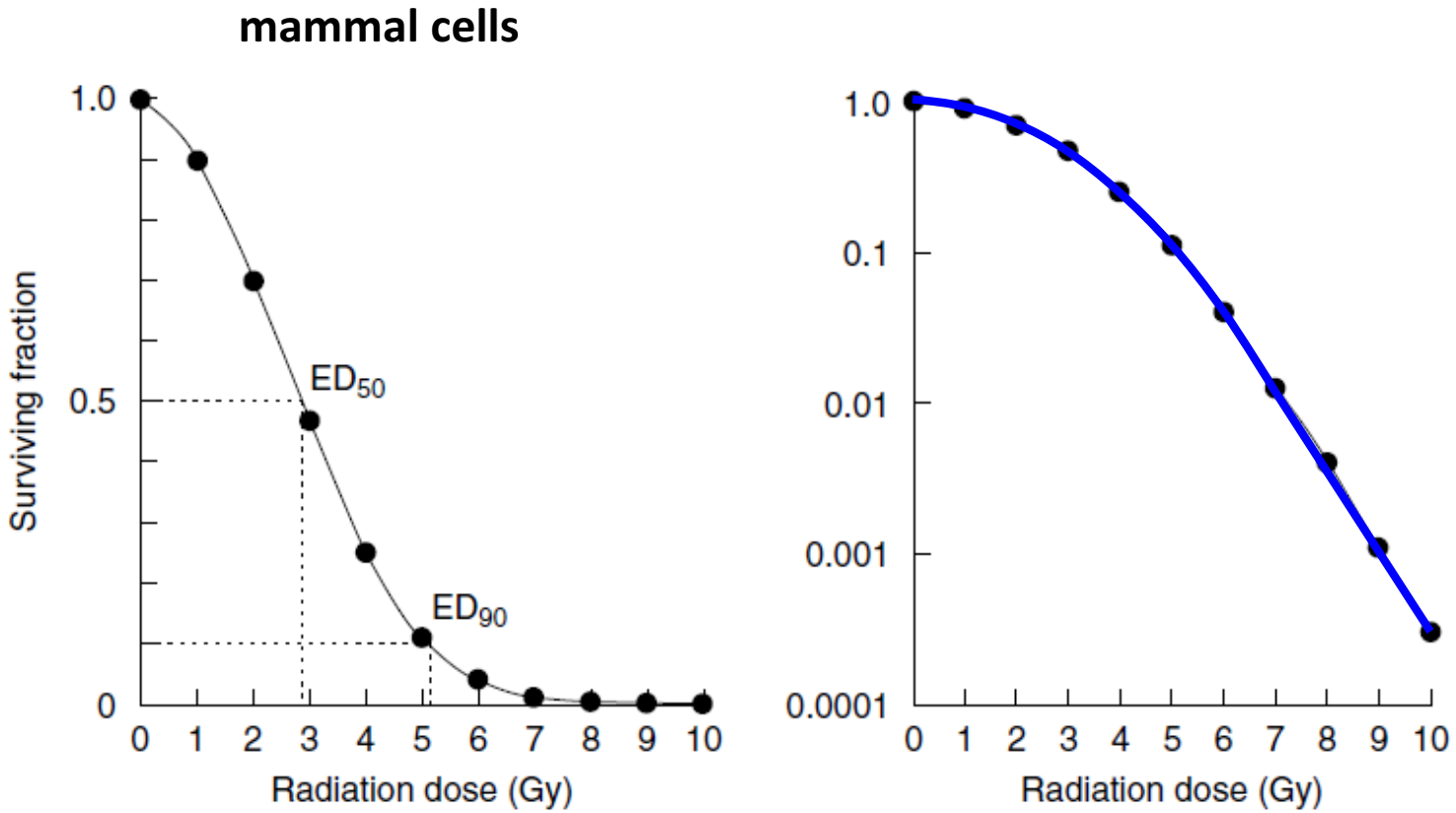


Why does radiotherapy work? The therapeutic window



Curves typically obtained from experimental (clinical) data → mathematical or mechanistic models to describe them

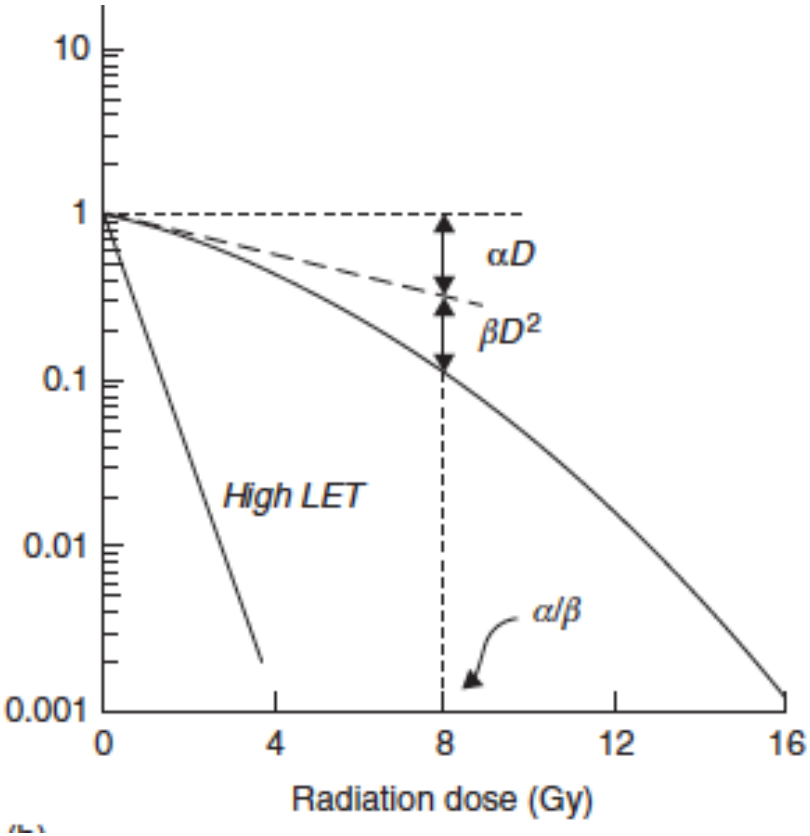
Cell survival and LQ model



$$SF = \exp(-\alpha D - \beta D^2)$$

Source: M. Joiner and A. van der Kogel (Eds.), “Basic Clinical Radiobiology”, Edward Arnold (2009)

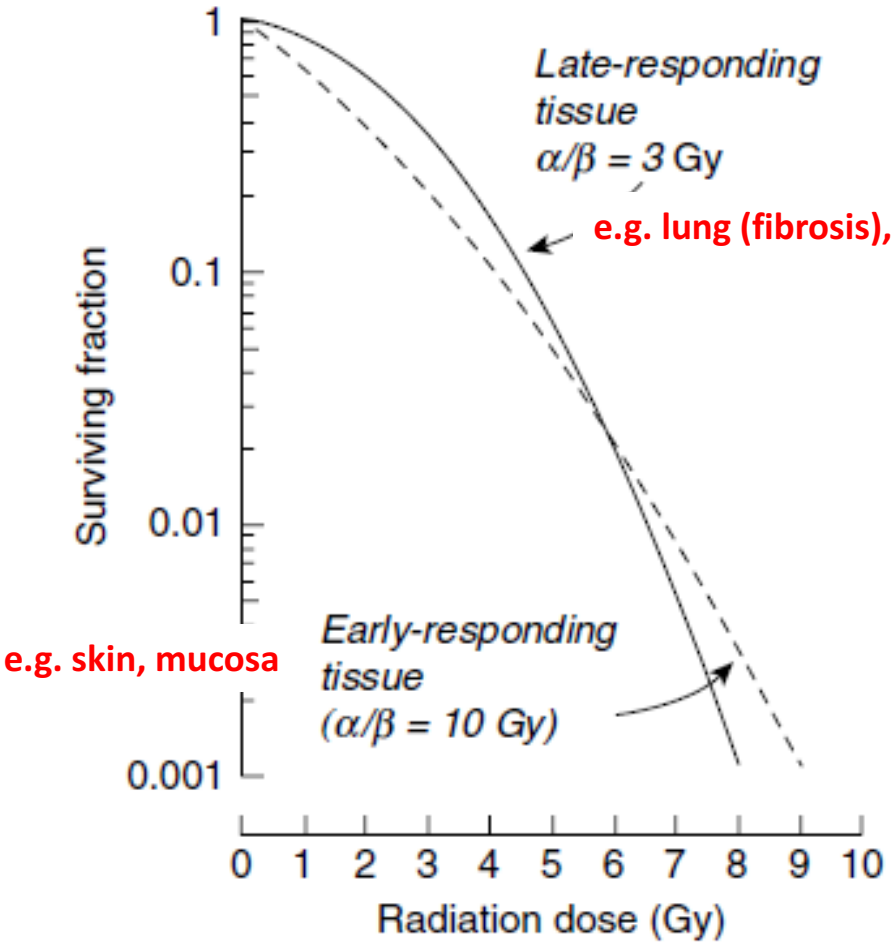
Cell survival and LQ model



$$SF = \exp(-\alpha D - \beta D^2)$$

Source: M. Joiner and A. van der Kogel (Eds.), “Basic Clinical Radiobiology”, Edward Arnold (2009)

α/β for tumor and normal tissue



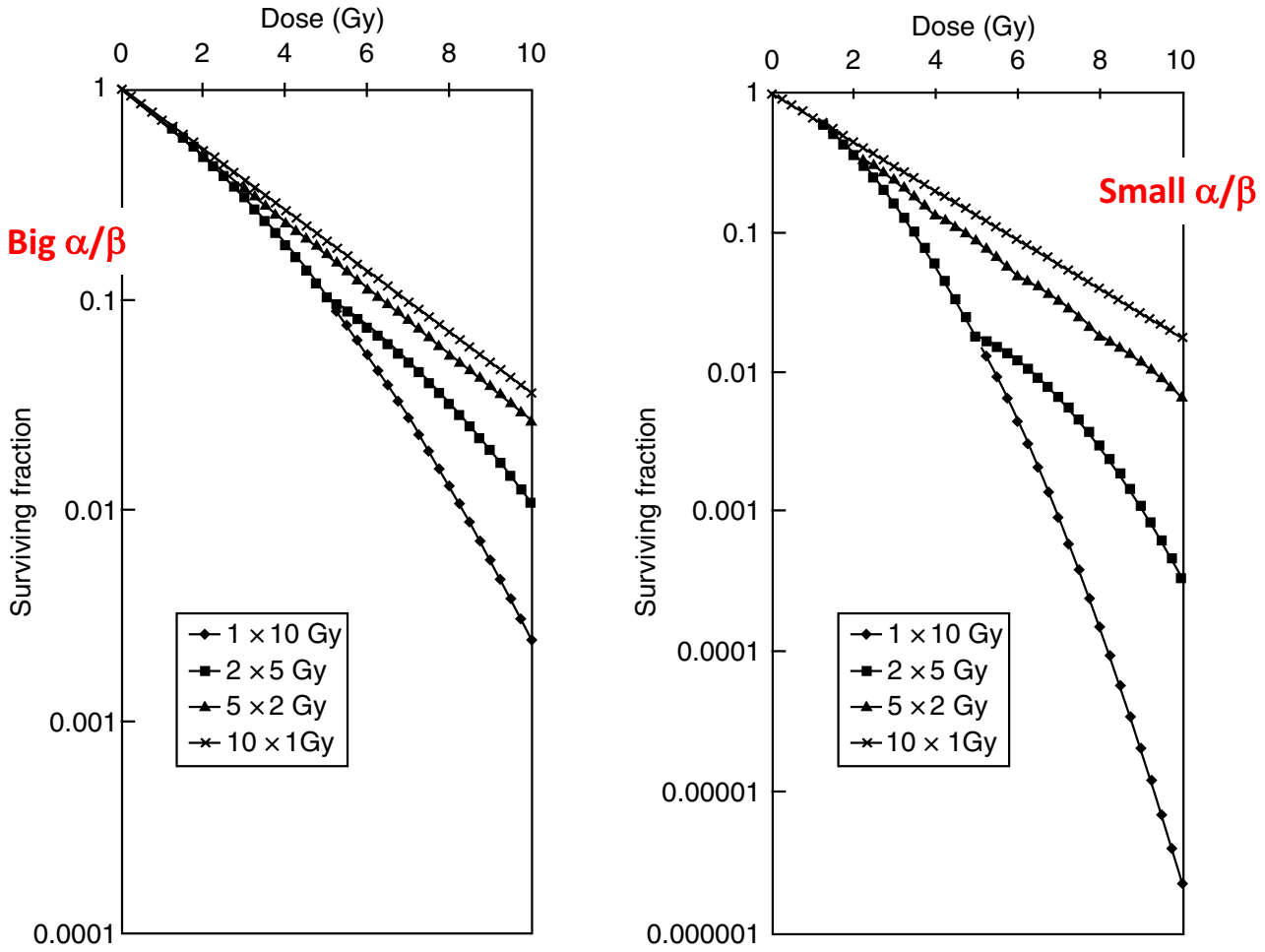
for most tumors:
α/β = 10 Gy

BUT:

- **Prostate ≈ 1.5 Gy**
- **Breast ≈ 4.6 Gy**
- **Oesophagus ≈ 4.9 Gy**
- **Melanoma ≈ 0.6 Gy**
- **Liposarcoma ≈ 0.4 Gy**

Source: P. Mayles, A. Nahum, J.-C. Rosenwald (Eds.), *Handbook of Radiotherapy Physics*, Taylor & Francis (2007)

Fractionation and α/β



Source: P. Mayles, A. Nahum, J.-C. Rosenwald (Eds.), *Handbook of Radiotherapy Physics*, Taylor & Francis (2007)

“Emerging” irradiation concepts

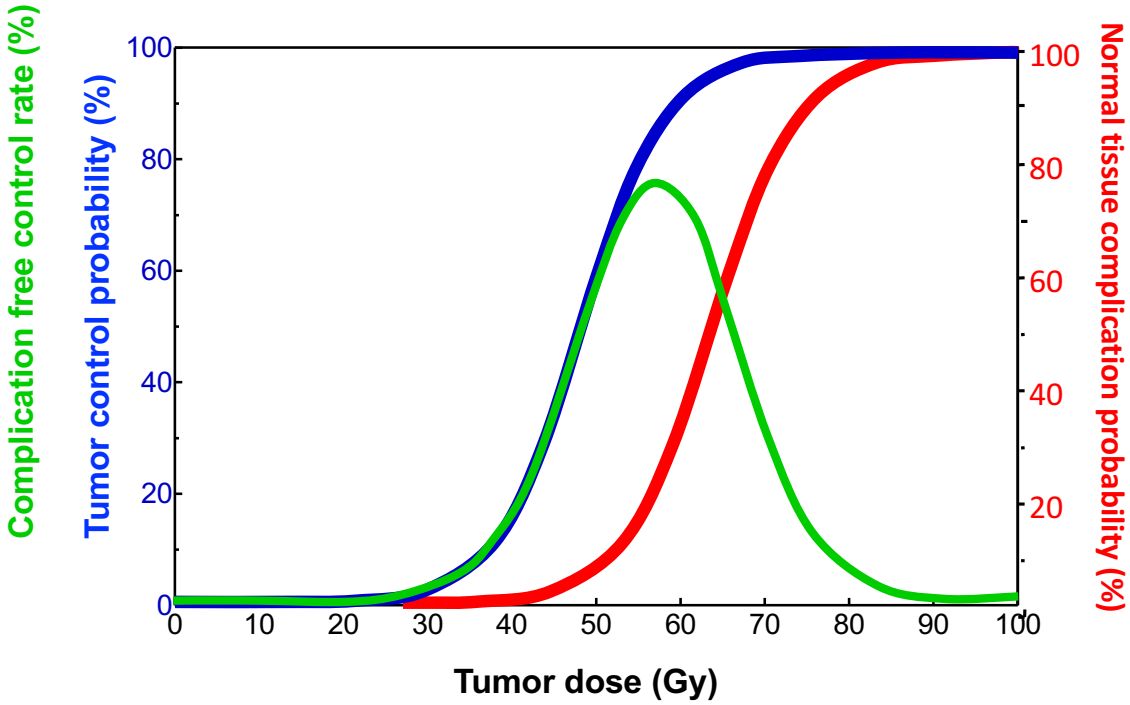
- dose escalation to the tumor
  - based on MRI or PET imaging → better identification of high-proliferation or hypoxic regions
- hypofractionation
- stereotactic body radiation therapy

Common issues:

- image guidance for margin reduction & motion management
- toxicity reduction / isotoxicity

Can we radiobiological models to this purpose?

e.g. for describing TCP or NTCP during the treatment planning process?



Curves typically obtained from experimental (clinical) data → mathematical or mechanistic models to describe them

Radiobiological models in radiotherapy

Several levels:

- Use of dose-response curves for determining the probability of tumor control or toxicity rate for a given treatment plan and fractionation scheme
- Use of dose-response curves for optimizing fractionation scheme and prescription dose on an individual basis
- Use of radiobiological models for optimizing the (biological) dose distribution on an individual basis

“Calculating” the TCP

Typically based on the linear-quadratic model of cell survival & Poisson statistics

$$TCP = \exp\left[-N_0 \exp(-\alpha D - \beta d D)\right]$$

Or, more sophisticated, considering population-based data → variation of α

$$TCP = \frac{1}{\sigma_\alpha \sqrt{2\pi}} \int_0^\infty \exp\left\{-\rho V \exp\left[-\alpha D(1 + d/(\alpha/\beta)\right]\right\} \exp\left[-\frac{(\alpha - \bar{\alpha})^2}{2\sigma_\alpha^2}\right] d\alpha$$

“Marsden-LQ Model”: see J Uzan & A E Nahum, Br. J. Radiol (2012) 85: 1279-1286

“Calculating” the NTCP

Lyman-Kutcher-Burman (LKB) model:

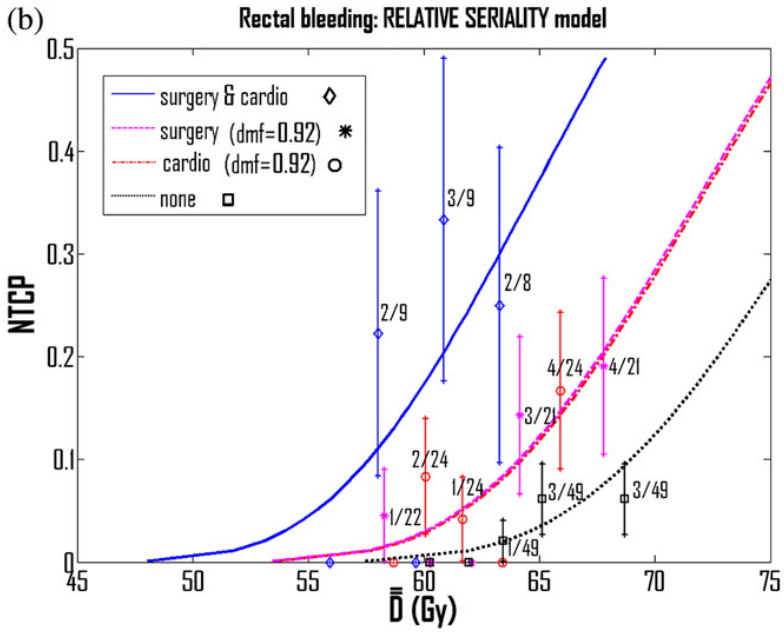
$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{(\mu-\mu_{50})/m\mu_{50}} \exp(-u^2/2)\,du$$

$$\mu = D_{eff} = \left(\sum_i v_i D^{1/n} \right)^n$$

Relative Seriality (RS) model:

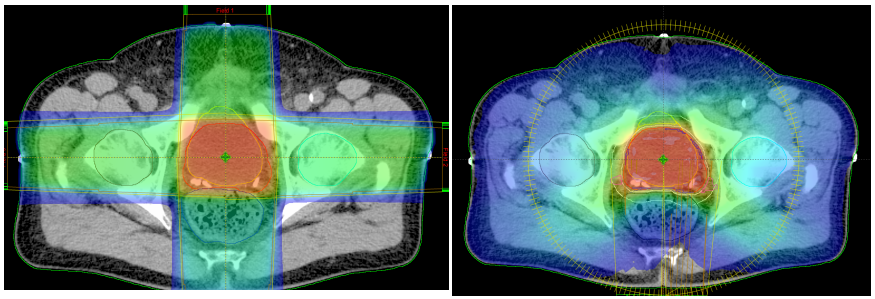
$$NTCP = \left(1 - \prod_{i=1}^{N} \left[1 - P(D_i)^s \right]^{v_i} \right)^{1/s}$$

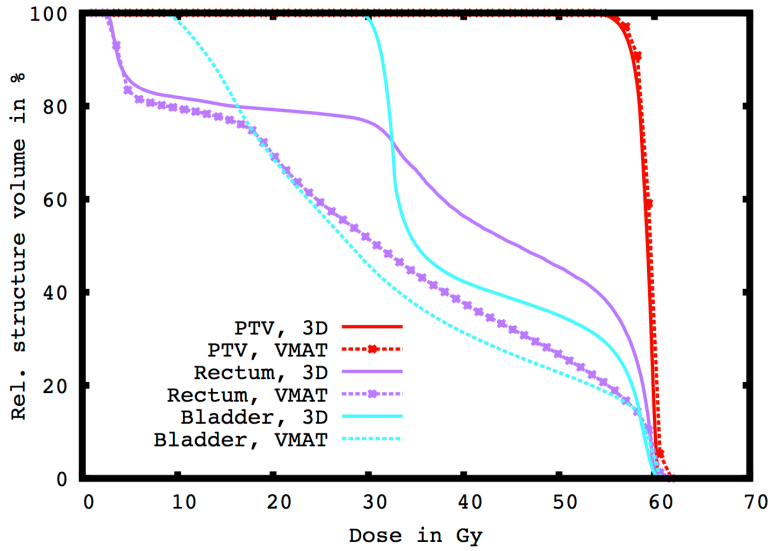
$$P(D_i) = 2^{-e^{e\gamma_s\left(1-\frac{D_i}{D_{50}}\right)}}$$



Source: Defraene et al. (2012)

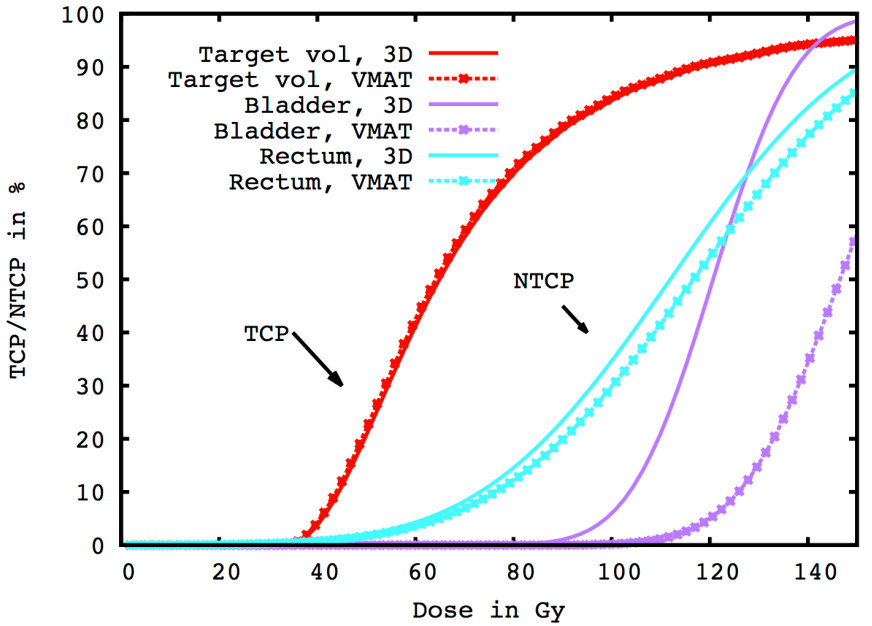
Determining the therapeutic window for prostate cancer





Physical values

MODELS



Biological Parameters

Fractionation: can we change the therapeutic window?

Prostate cancer → small α/β!

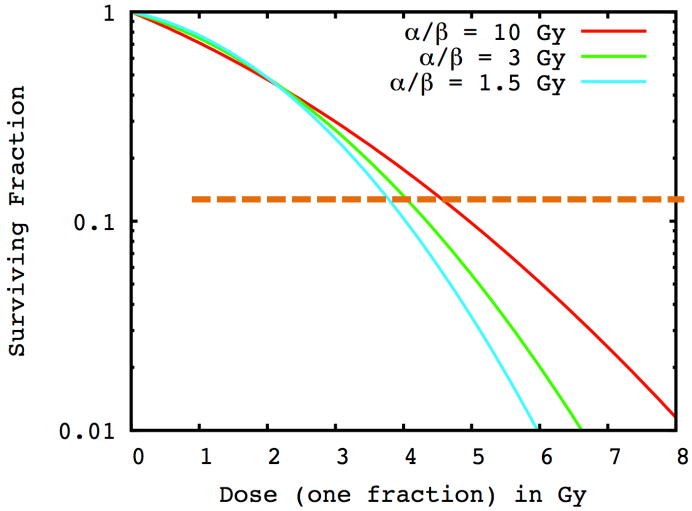
Organ	Endpoint	α/β (Gy)
Prostate	Tumor control	1,5-2,0
Rectum	Bleeding	3
Bladder	Late toxicity grade 3-4	6

Fractionation and iso-effectiveness

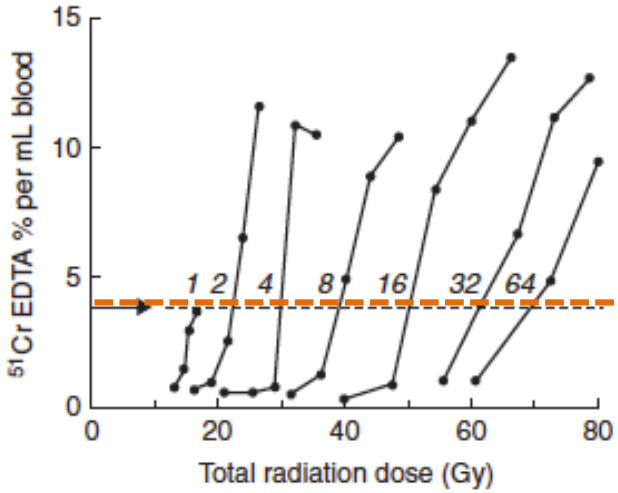
In this case "E" is 10% survival

$$E = nd(\alpha + \beta d)$$

n = number of fractions



In this case "E" is the evidence for late kidney toxicity in a mouse after fractionated radiotherapy



Quelle: M. Joiner and A. van der Kogel (2009)

Biological effective dose (BED)

$$BED \equiv E/\alpha = nd\left(1 + \frac{d}{\alpha/\beta}\right)$$

Quelle: J. Fowler (1989)

Iso-effectiveness for the tumor

example:

D_1 = 75 Gy with d_1 = 1.8 Gy for the tumor

α/β = 10 Gy

iso-effective dose for d_2 = 6 Gy?

D_2 = (1.8 +10)*75/(6+10)= 55.3 Gy

Iso-effect: same TCP

$$BED_1 = BED_2$$

$$\Downarrow$$

$$\frac{D_1}{D_2} = \frac{d_2 + \alpha/\beta}{d_1 + \alpha/\beta}$$

example:

D_1 = 75 Gy with d_1 = 1.8 Gy for Tumor

α/β = 1.5 Gy

Iso-effective dose for d_2 = 6 Gy?

D_2 = (1.8 +1.5)*75/(6+1,5)= 33 Gy

Iso-effectiveness for toxicity

$$BED_1 = BED_2$$

$$\Downarrow$$

$$\frac{D_1}{D_2} = \frac{d_2 + \alpha/\beta}{d_1 + \alpha/\beta}$$

example:

D_1 = 75 Gy with d_1 = 1.8 Gy

α/β = 3 Gy

iso-effective dose (e.g. late rectal bleeding) for d_2 = 6 Gy?

D_2 = (1.8 +3)*75/(6+3)= 40 Gy

Iso-effect: same NTCP

example:

D_1 = 75 Gy with d_1 = 1.8 Gy

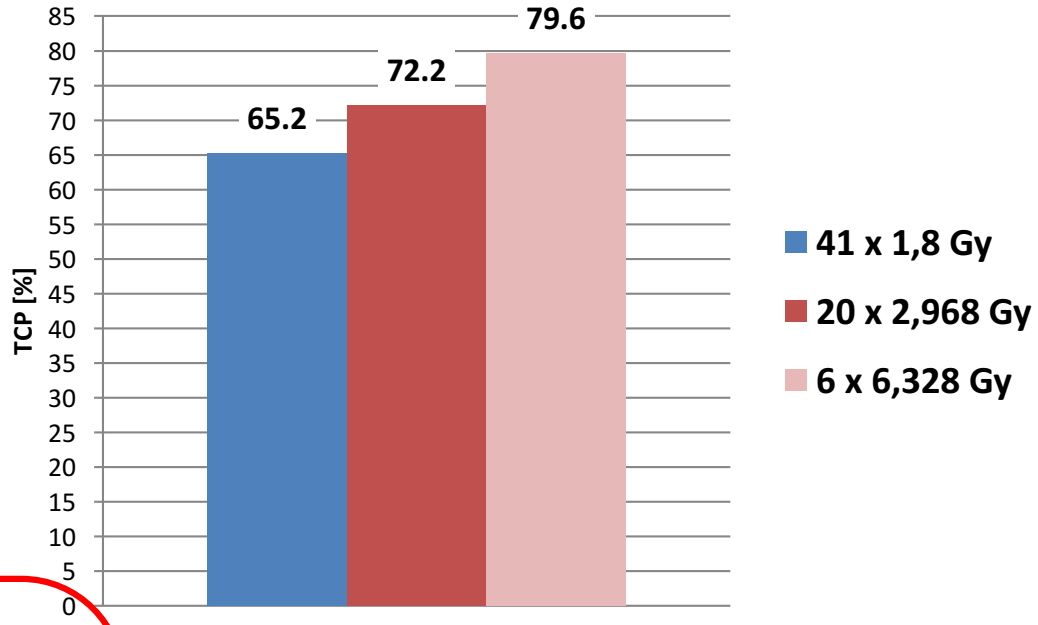
α/β = 6 Gy

Iso-effective dose (e.g. late bladder toxicity) d_2 = 6 Gy?

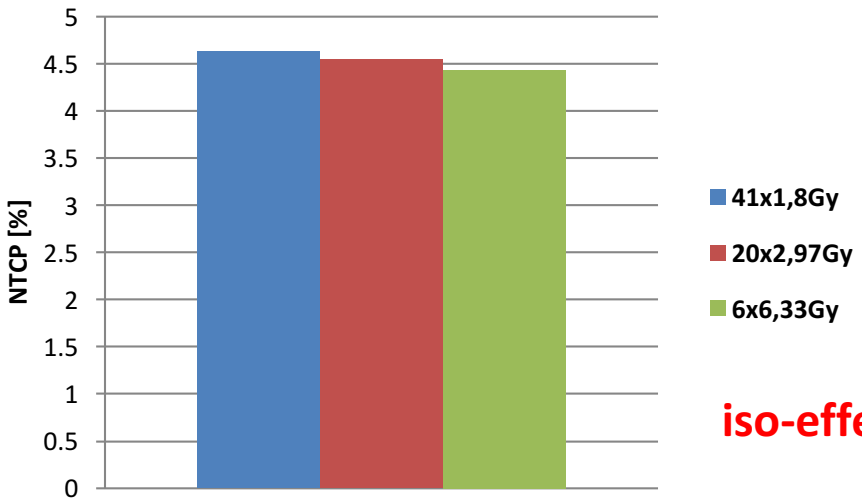
D_2 = (1.8 +6)*75/(6+6)= 48.8 Gy

Evaluating alternative fractionation schemes in prostate cancer radiotherapy

- Original scheme:
  41 x 1.8 Gy
- Alternative schemes:
  20 x 3.0 Gy
  6 x 6.3 Gy



higher TCP if α/β = 1.5 Gy



iso-effective with respect to late rectal bleeding

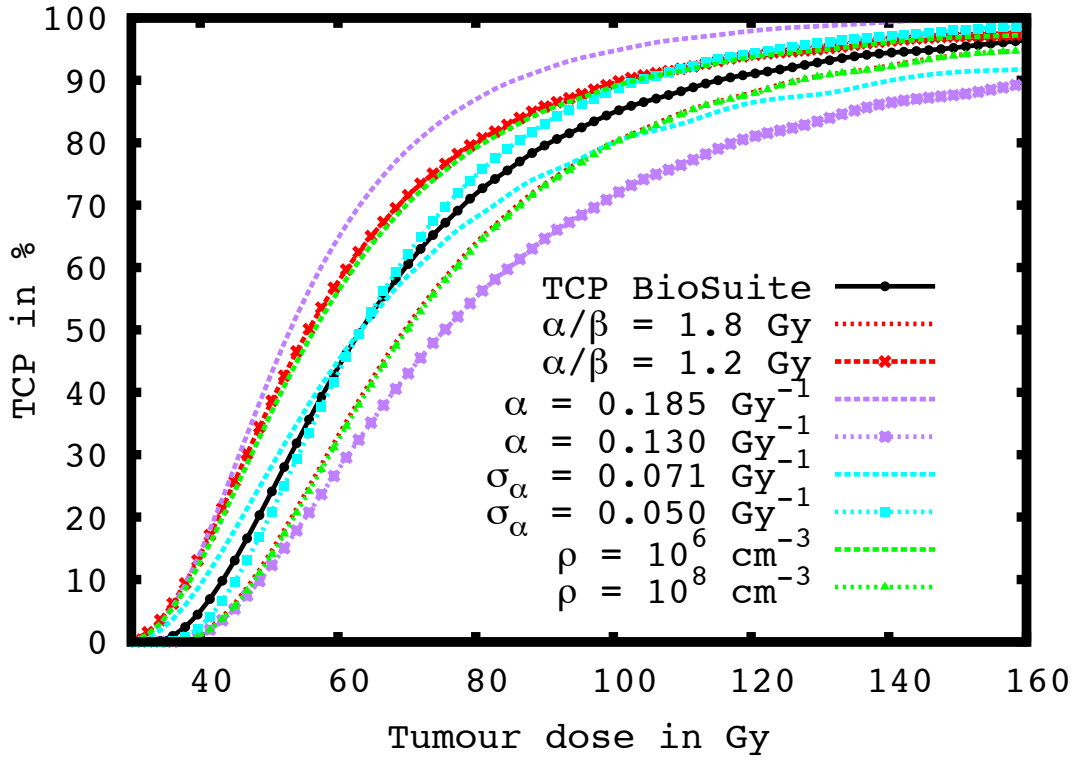
Are these models robust for predicting complications and tumor control rate?

Model parameters available from literature have quite large uncertainties

- What is the effect of such uncertainties on model predictions ?
  - Variation of the model parameter values within ± 20% of the reported values

Results for prostate cancer, Marsden-LQ model

$$TCP = \frac{1}{\sigma_\alpha \sqrt{2\pi}} \int_0^\infty \exp\left\{-\rho V \exp\left[-\alpha D(1 + d/(\alpha/\beta))\right]\right\} \exp\left[-\frac{(\alpha - \bar{\alpha})^2}{2\sigma_\alpha^2}\right] d\alpha$$



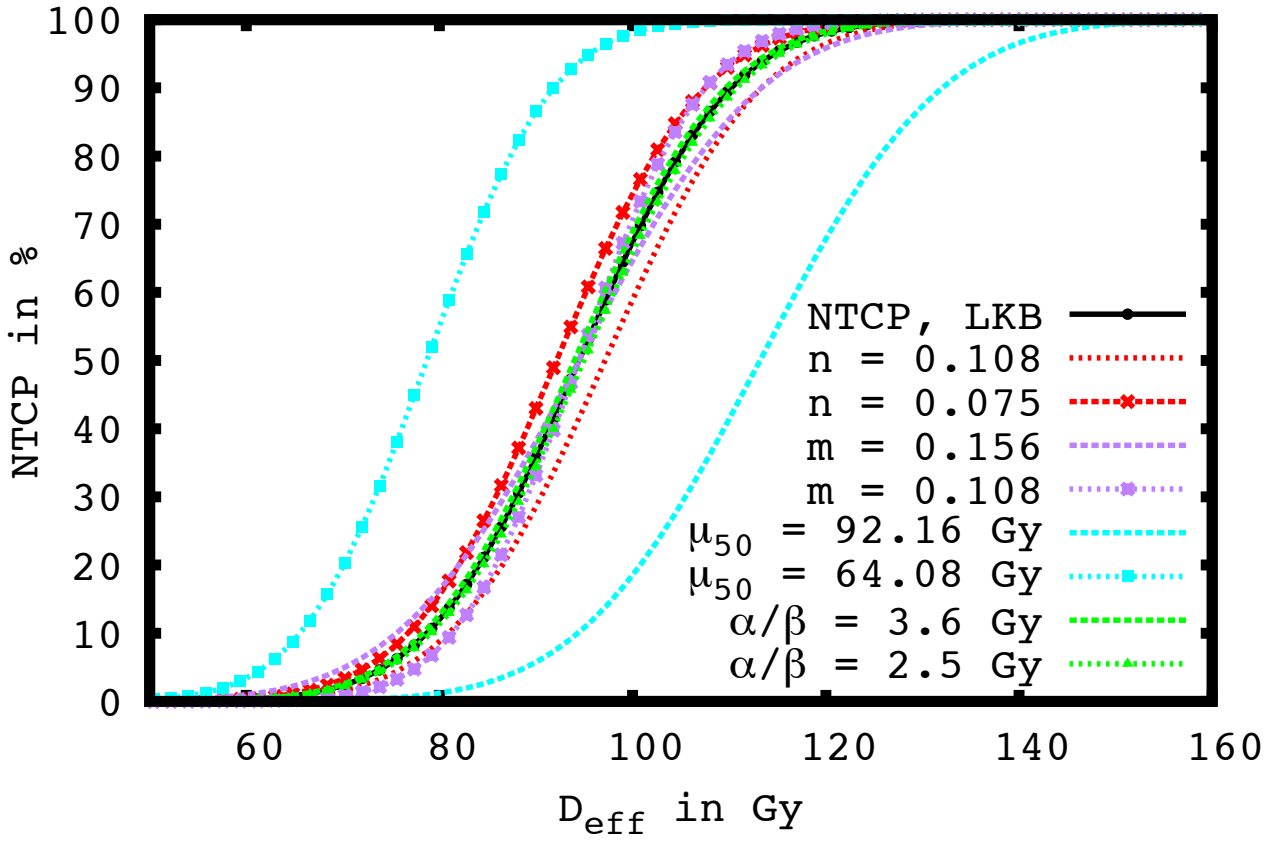
Starting values (BioSuite)*:
α/β = 1.5 Gy, α = 0.155 Gy^{-1}, ρ = 10^7 cm^{-3}

* J Uzan & A E Nahum, Br. J. Radiol (2012) 85: 1279-1286

Results for late rectal complications, LKB model

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{(\mu-\mu_{50})/m\mu_{50}} \exp(-u^2/2)\,du \qquad \mu = D_{eff} = \left(\sum_i v_i D^{1/n}\right)^n$$

Endpoint: rectal bleeding grade ≥ 2



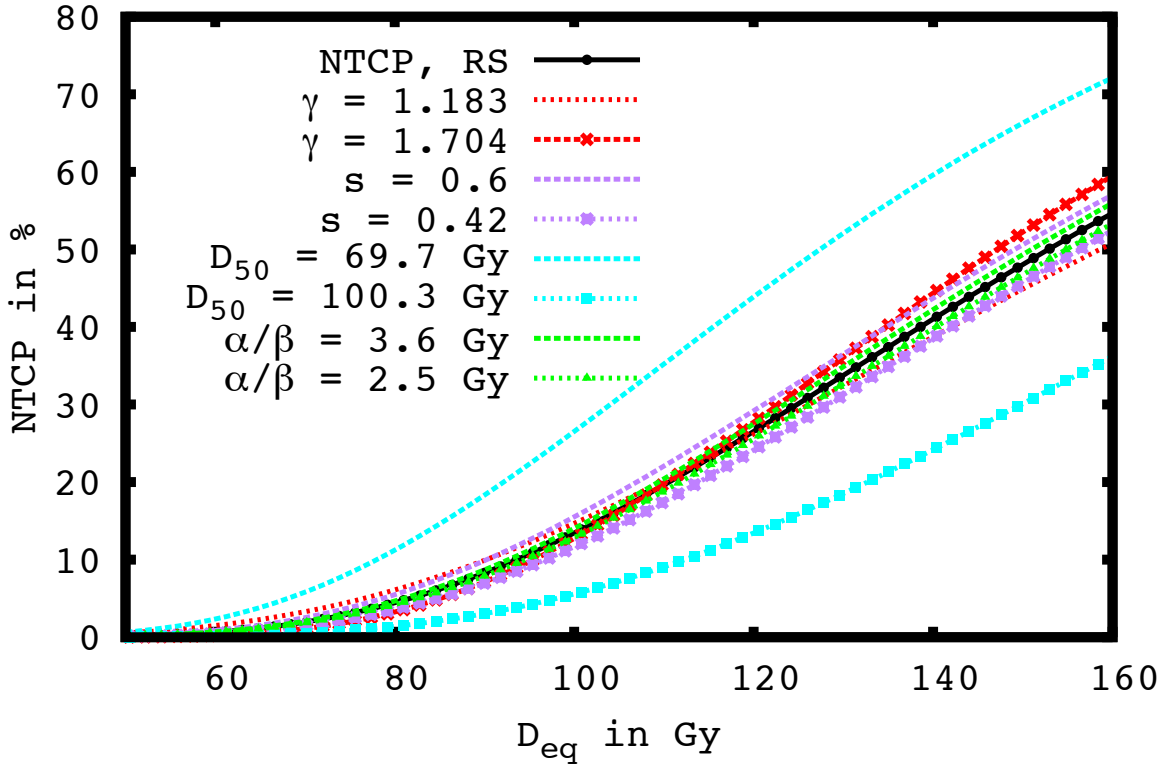
Starting values*:
***n* = 0.09,**
***m* = 0.13,**
μ_{50} = 76.9 Gy,
α/β = 3 Gy

* J.M. Michalski et al. (2010), Int. J. Radiation Oncology Biol. Phys. 76: S123-S129.

Results for late rectal complications, RS model

$$NTCP = \left(1 - \prod_{i=1}^{N} \left[1 - P(D_i)^s\right]^{v_i}\right)^{1/s} \qquad P(D_i) = 2^{-e^{e\gamma_s\left(1-\frac{D_i}{D_{50}}\right)}}$$

Endpoint: rectal bleeding grade ≥ 2



Starting values*:
γ = 1.42, *s* = 0.5,
D_{50} = 83.6 Gy,,
α/β = 3 Gy

* T Rancati et al. (2004). Radiother. Oncology 73: 21-32.

J. Einhausen et al., Strahlentherapie und Onkologie Vol. 190 (2014)

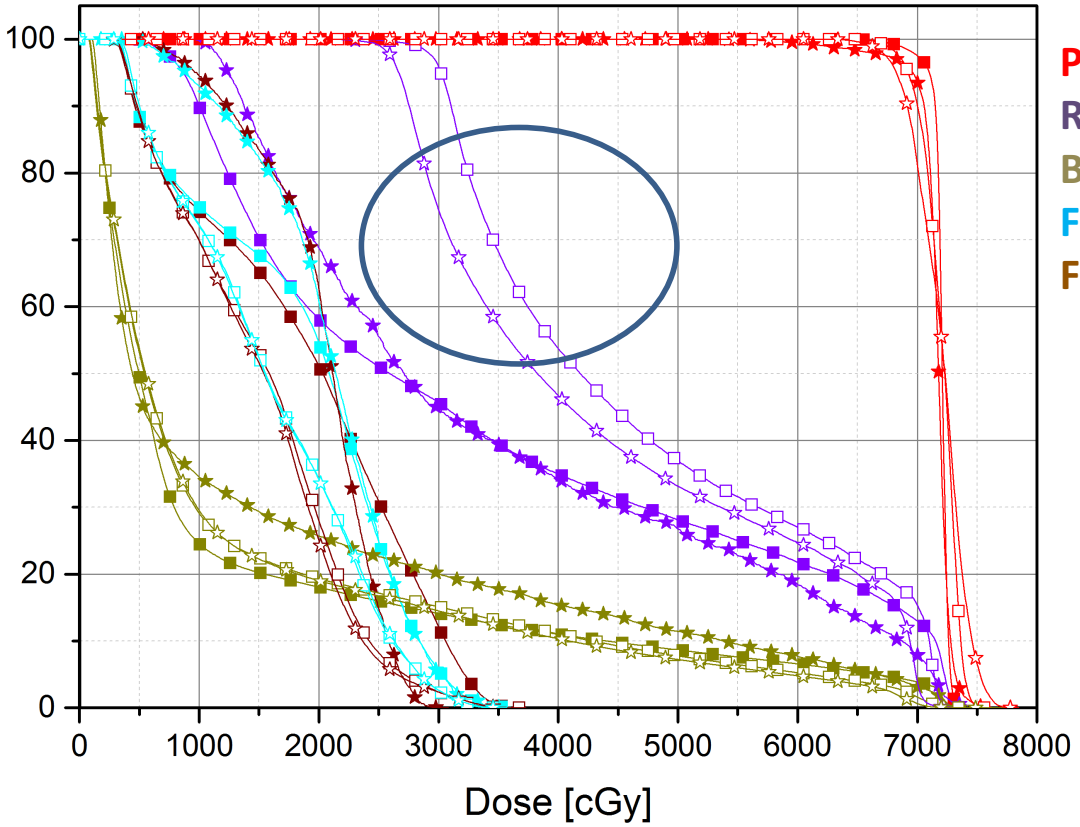
Are these models robust for plan optimization?

Models seem to be robust with respect to the most crucial parameters, still important to know whether the uncertainties could affect their clinical use

- What is the effect of such uncertainties on NTCP-based plan optimization?
- Use of LKB model for NTCP
- Variation of the model parameter values within
  - ± 20% of the reported values, except μ_{50}
  - ± 6% for μ_{50}

- Dosimetric constraint: 72 Gy to PTV, in 40 fractions
- Endpoints for NTCP: late rectal bleeding grade ≥ 2, late bladder toxicity grade ≥ 3

Are these models robust for plan optimization?



PTV
Rectum
Bladder
Femoral head left
Femoral head right

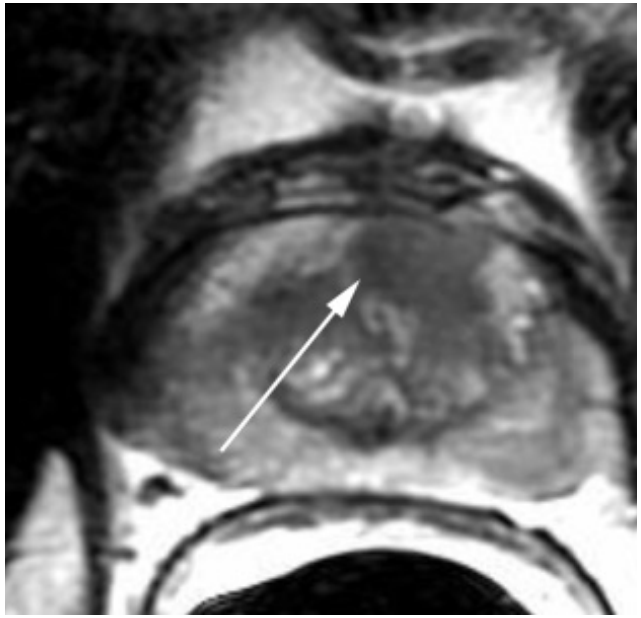
filled symbols:
conventionally optimized VMAT/
TomoTherapy plans

Open symbols:
biologically optimized IMRT plans

Larger deviations among plans for variations of μ_{50}, stronger for low-dose distribution in rectum

E. Gargioni et al., Radiotherapy and Oncology 115:S459 (2015)

What about personalized dose escalation?



multi-parametric MR-images
Dose escalation to MR-lesion

BUT:

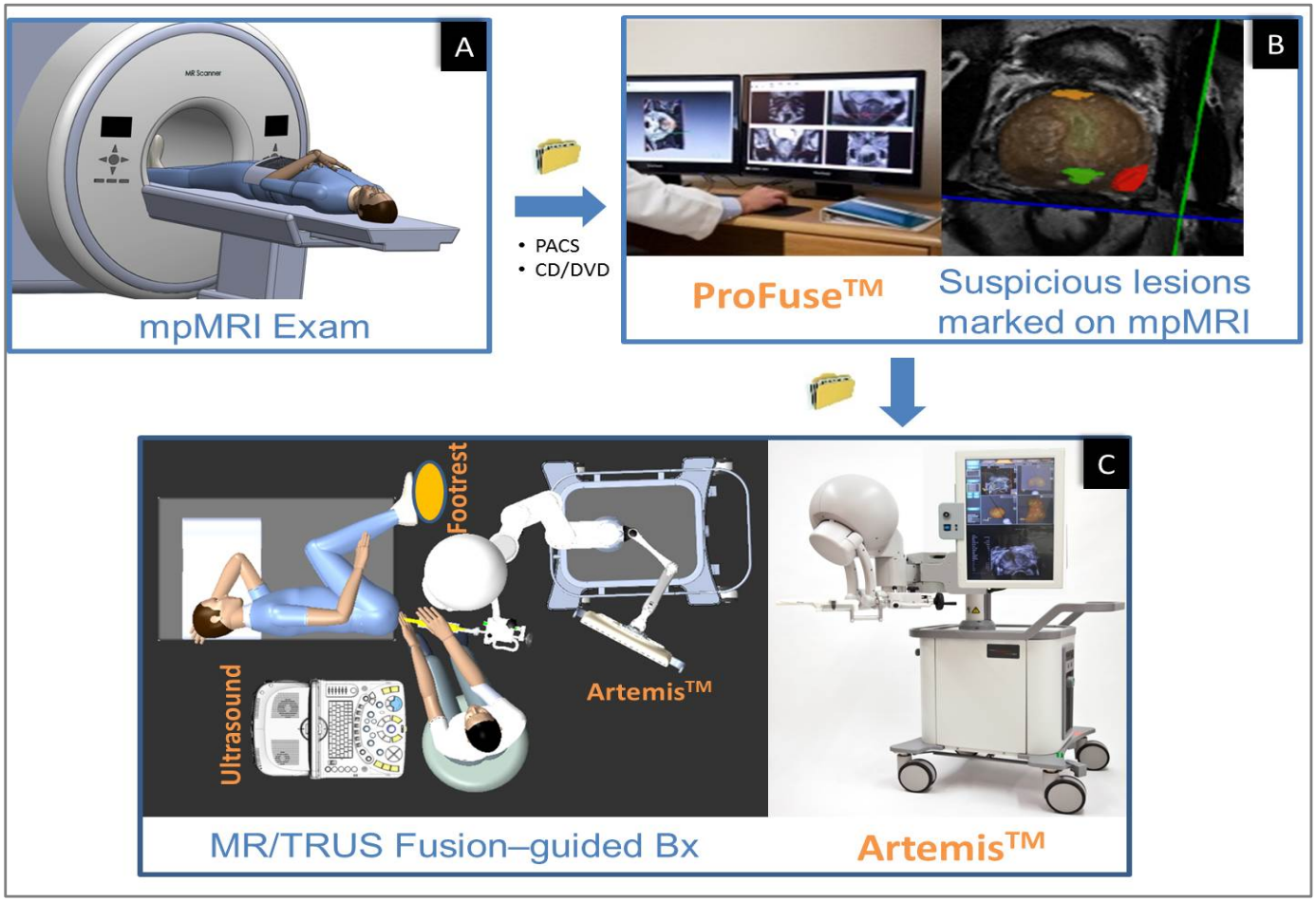
… if the lesion is not detectable with MRI?

… if MRI is not accurate enough?

… how to consider tumor biology?

Personalized dose escalation and biopsy data

Our idea:
Improve contouring by adding information through fusion-guided biopsy



Advantages:

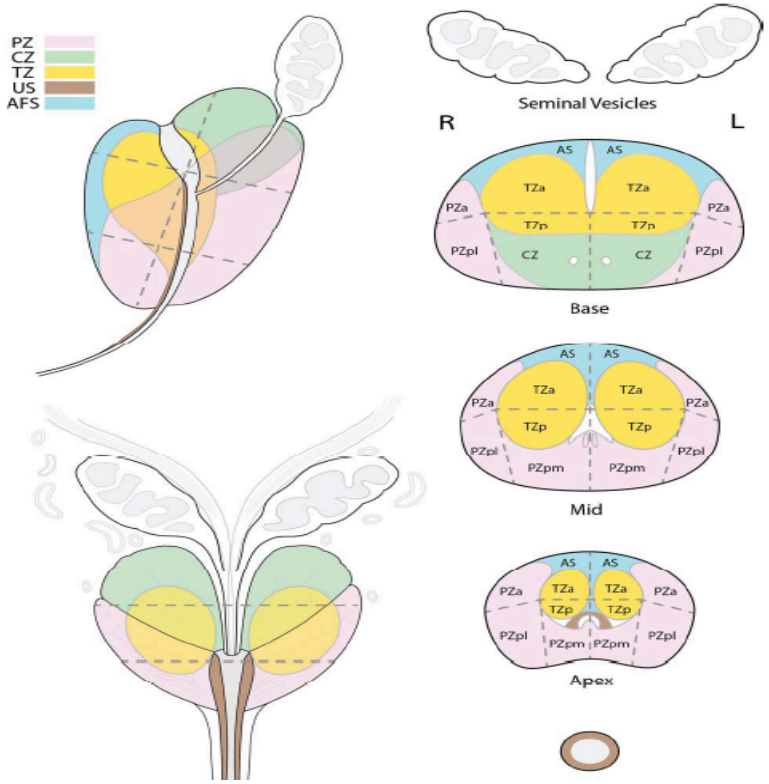
- higher detection of significant cancer (Gleason Score > 6)
- lower detection of non significant cancer
- higher proportion of positive biopsy cores

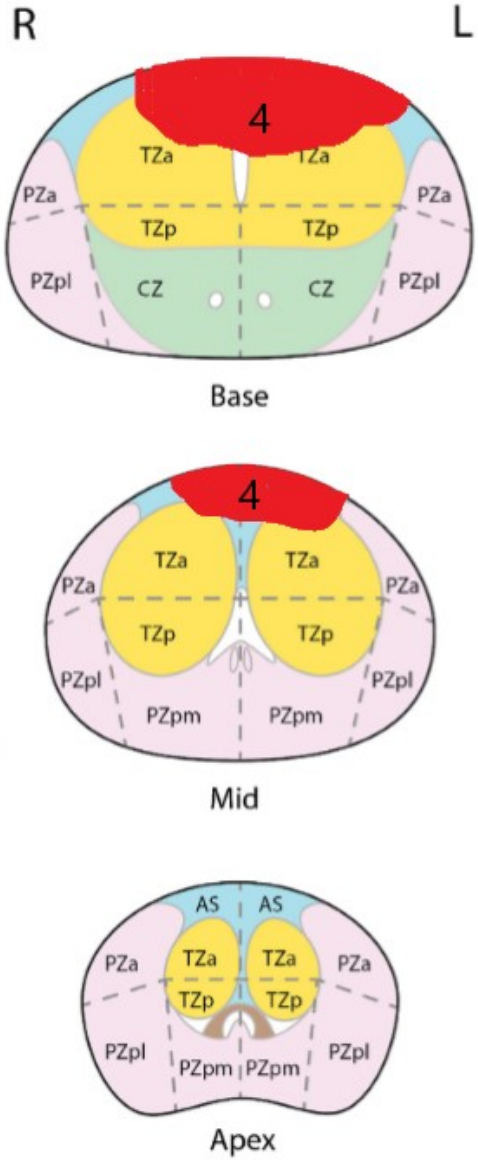
Guidelines of the EAU* for patients receiving biopsy for the first time

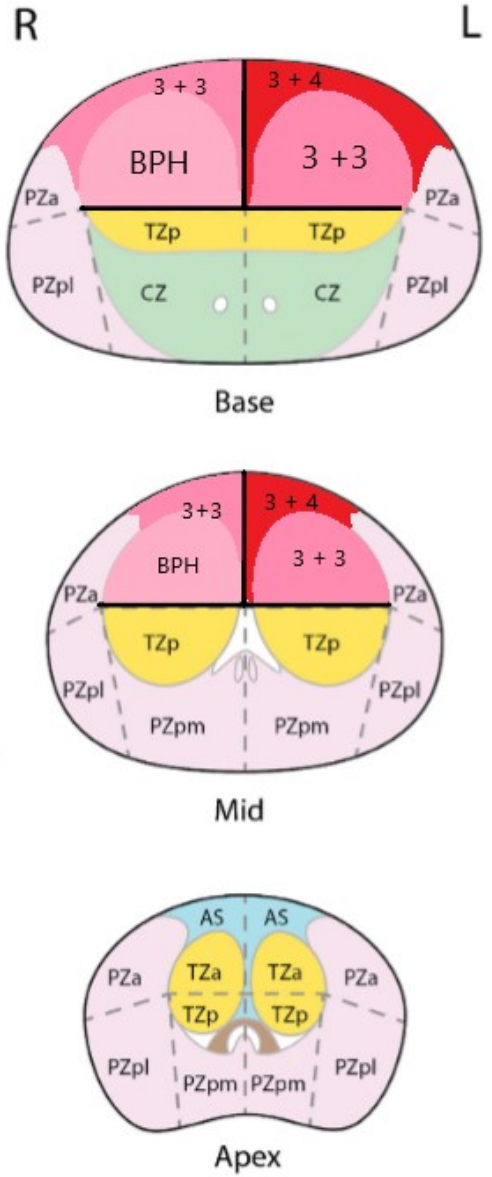
Recommendations in biopsy naïve patients
Perform mpMRI before prostate biopsy.
When mpMRI is positive (i.e. PI-RADS ≥ 3), combine targeted and systematic biopsy.
When mpMRI is negative (i.e. PI-RADS ≤ 2), and clinical suspicion of prostate cancer is low, omit biopsy based on shared decision making with the patient.

*European Association of Urology

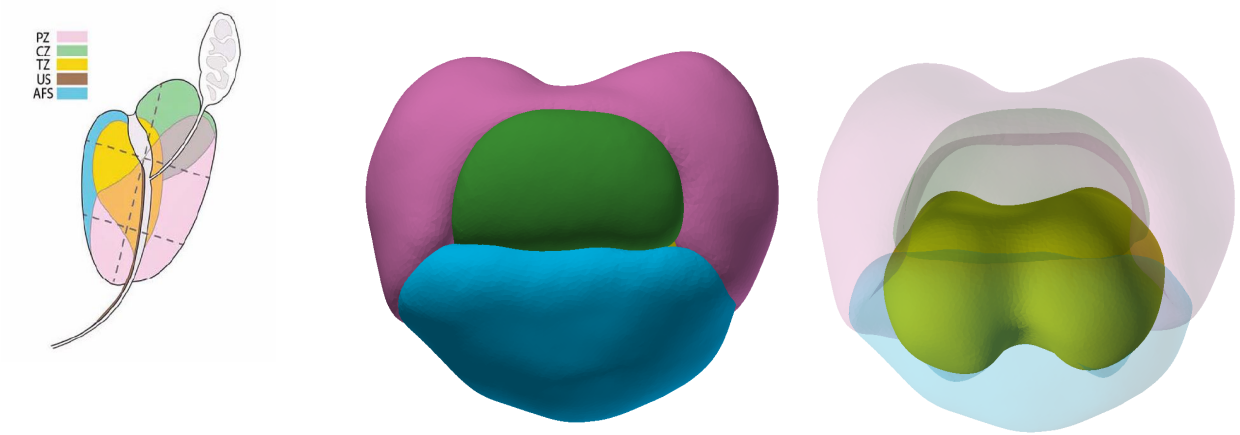
Use of fusion-biopsy data for dose escalation





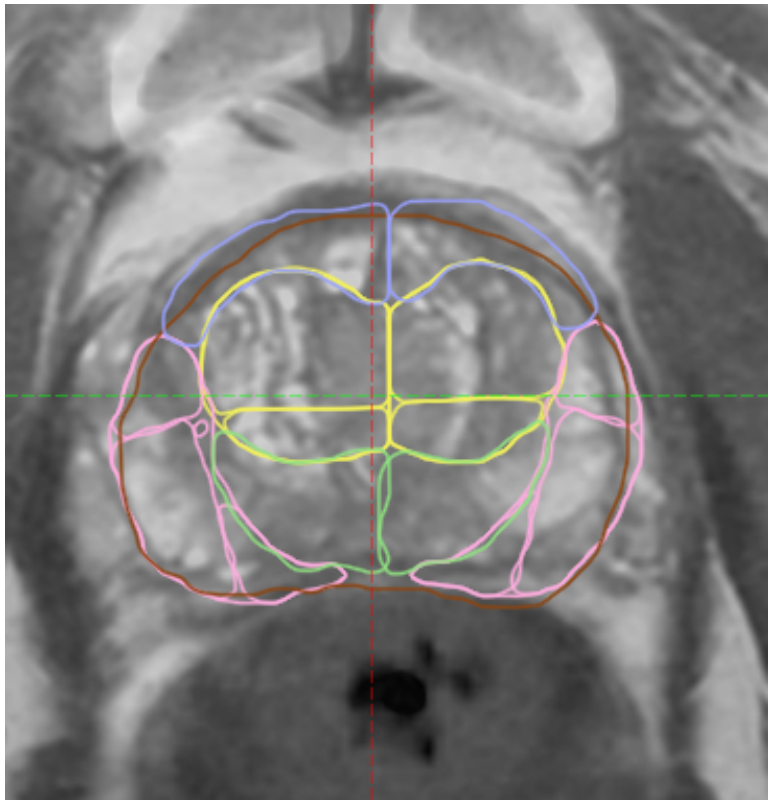


Development of a 39-ROI „standardized“ prostate



Automatic prostate segmentation based on this zone model?

„Automatic“ prostate segmentation

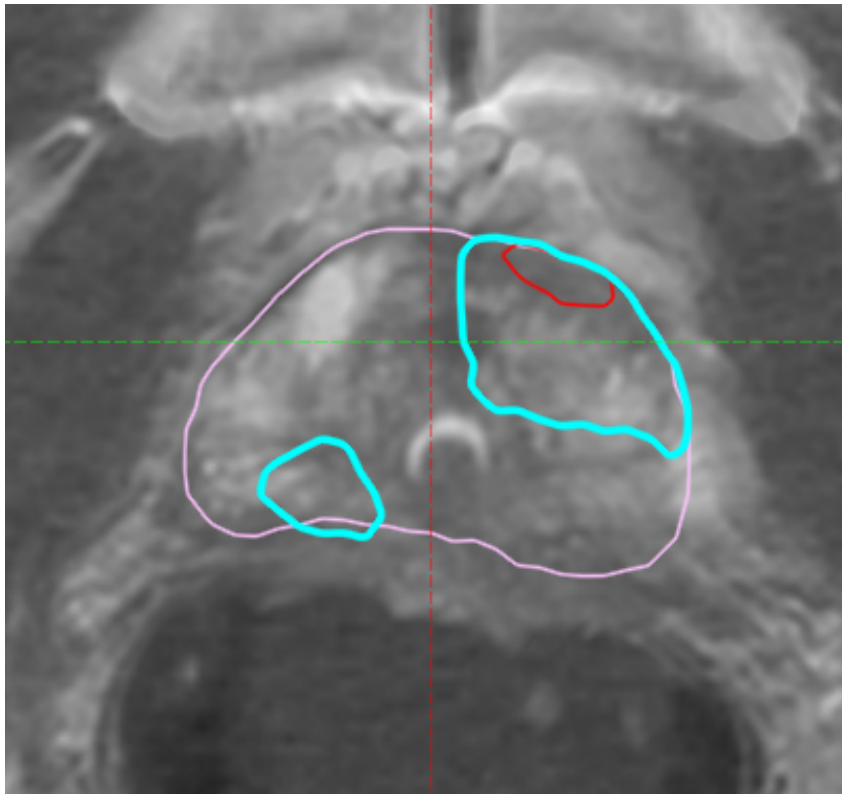


Elastic registration of the segmented prostate with individualized mpMR-images

→ co-localization between mpMR-images and biopsy data for 10 patients

brown: original prostate contour

Example: MRI lesions and biopsy data

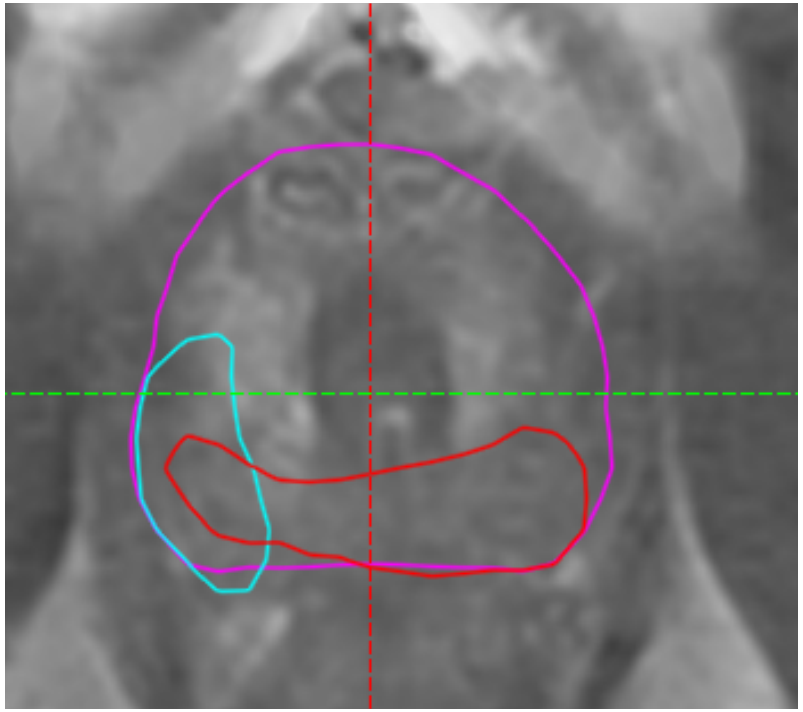


Patient #3

Cyan: biopsy-confirmed lesions (anatomical zone)

Red: mpMRI lesion

Example: MRI lesions and biopsy data

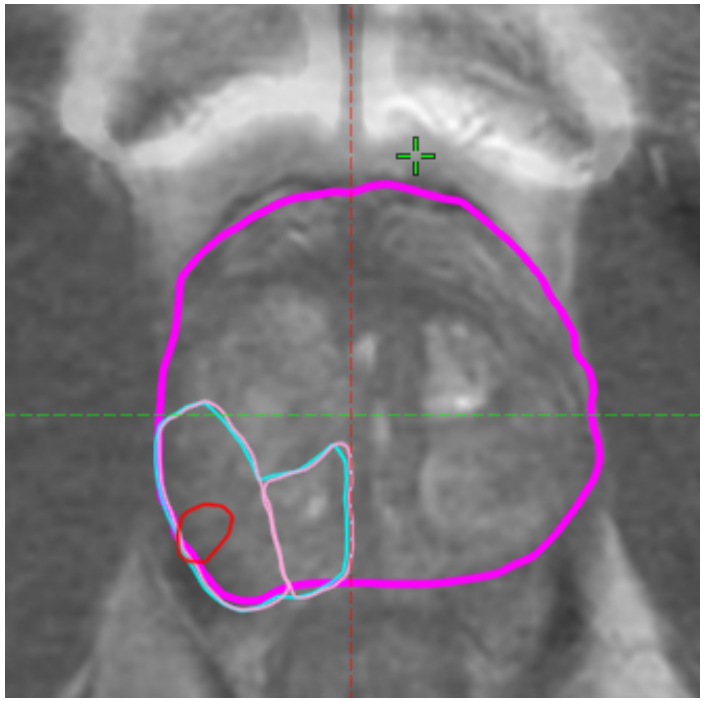


Patient #4

Cyan: biopsy-confirmed lesions (anatomical zone)

Red: mpMRI lesion

Example: MRI lesions and biopsy data

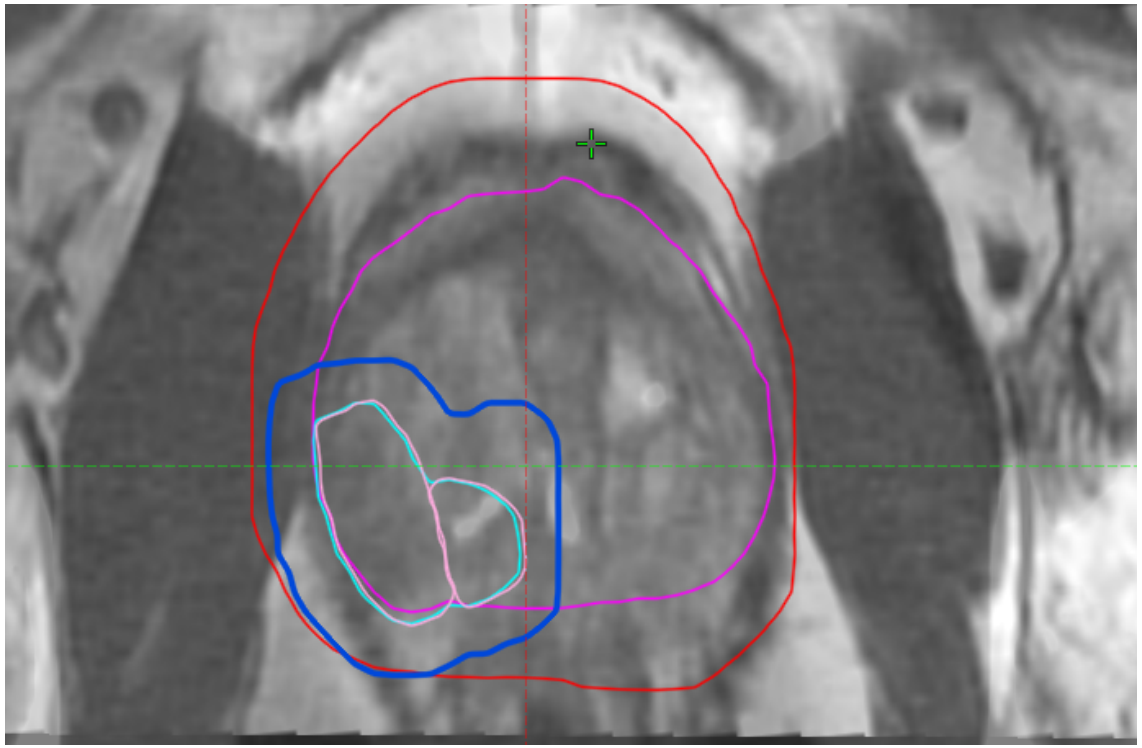


Patient #7

Cyan and pink: biopsy-confirmed lesions (anatomical zone)

Red: mpMRI lesion

Example: PTV definition

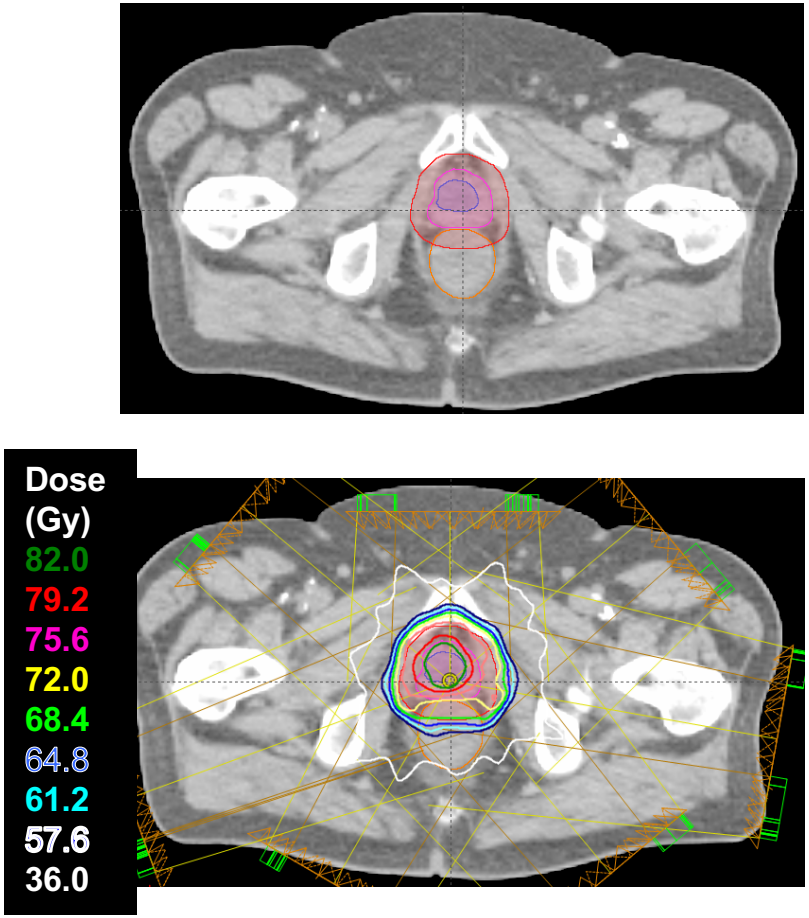


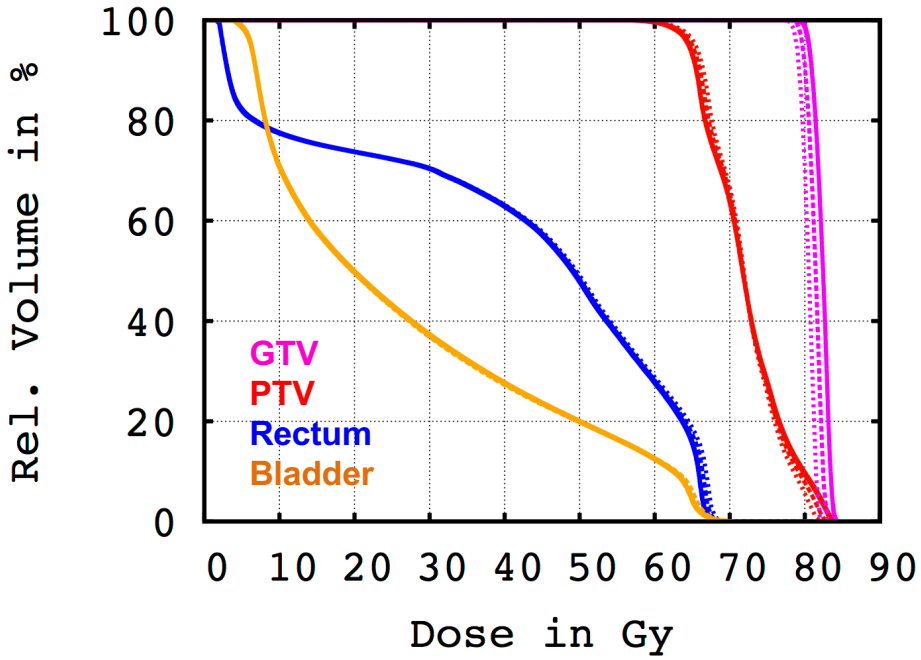
Patient #7

Red: PTV whole prostate

Blue: PTV ”lesion(s)”

Role of uncertainties for α/β?

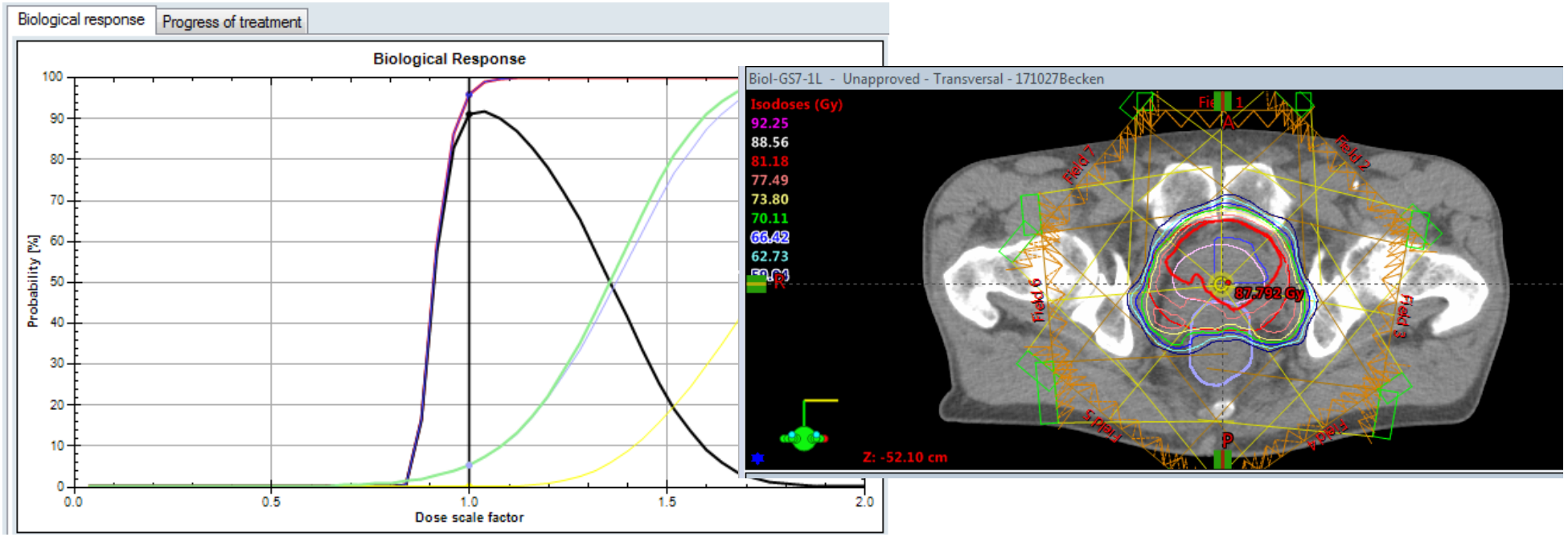




Solid: α/β = 1.5 Gy
Dashed: α/β = 3 Gy
Dotted: α/β = 4.5 Gy

P. Mehta et al., Radiotherapy and Oncology 119:S808-S809 (2016)

Personalized dose escalation using TCP maximisation



MRI-contoured tumor (GTV)
Biological optimization → maximizing TCP for lesion(s)
& minimizing NTCP as before

Dose constraint for whole prostate: 74 Gy in 40 fractions

Work in progress

How to better consider tumor biology into TCP model?

- Gleason score: related to radiosensitivity (α)?

How accurate the segmentation?

GTV-to-PTV margins & movement?