Klinik für Strahlentherapie und Radioonkologie

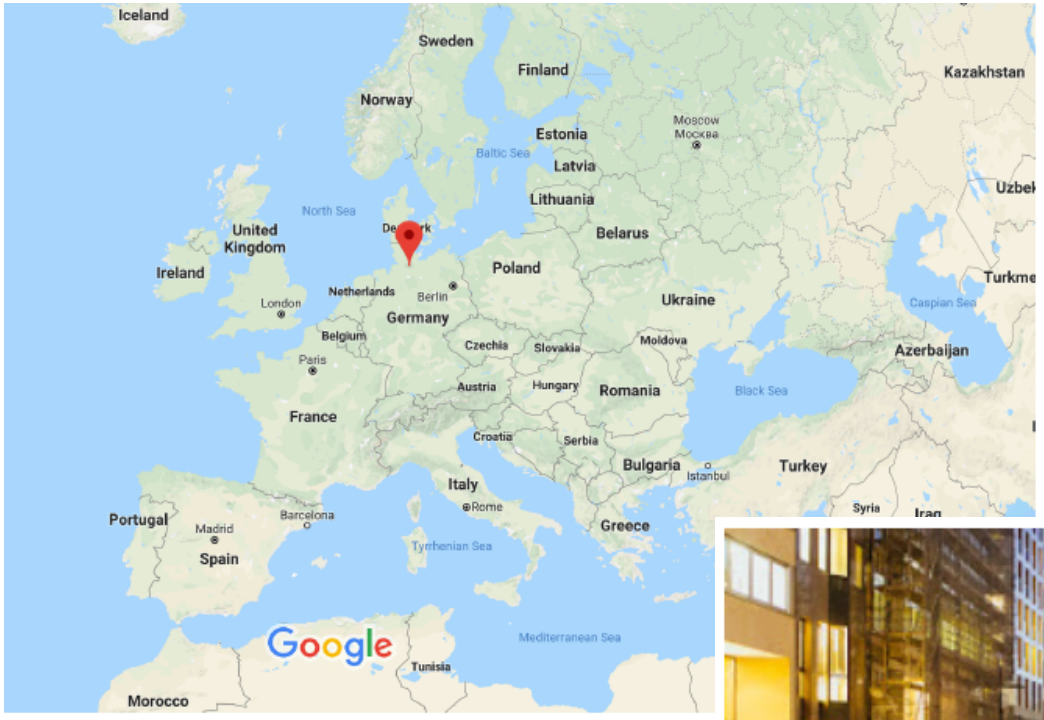
4th Annual LLU Algorithm Workshop

Radiobiological Modelling in Radiation Therapy (of Prostate Cancer)

Elisabetta Gargioni, Alexandra Albanis, Tom Sokolinski, Ilse König, Preena Mehta, Julia Einhausen, Annette Raabe, Rudolf Schwarz

Universitätsklinikum Hamburg-Eppendorf

Hamburg: big international port on the Elbe river



Radiotherapy @UKE

Approx. 2,000 patients/year
Approx 1,700 outpatients/year

1 Brachytherapy unit
3 Varian TrueBeam linacs
1 Siemens 4D-CT
1 Elekta Simulator
1 IntraBeam Intraoperative RT unit
1 TomoTherapy

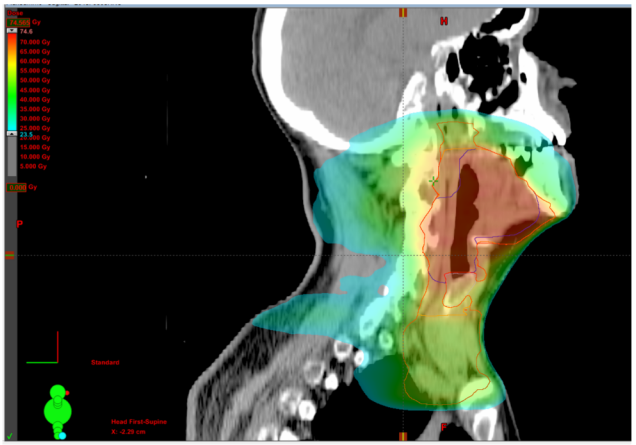
22 doctors (13 specialists)
12 physicists/engineers
30 radiology assistants/medical technicians

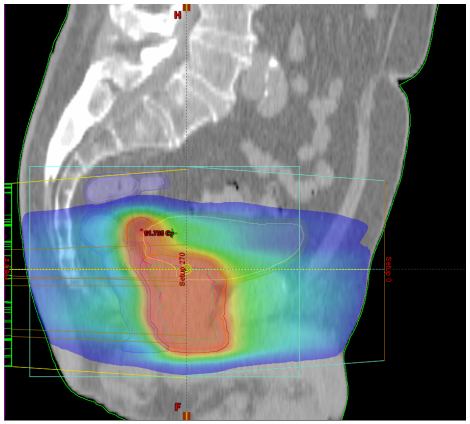
… no protons...

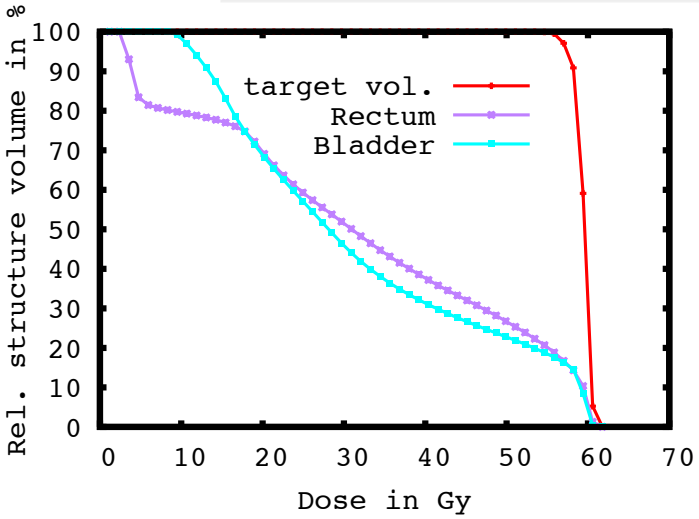
Radiotherapy: balance between cure and toxicity

Conventional treatment plan evaluation

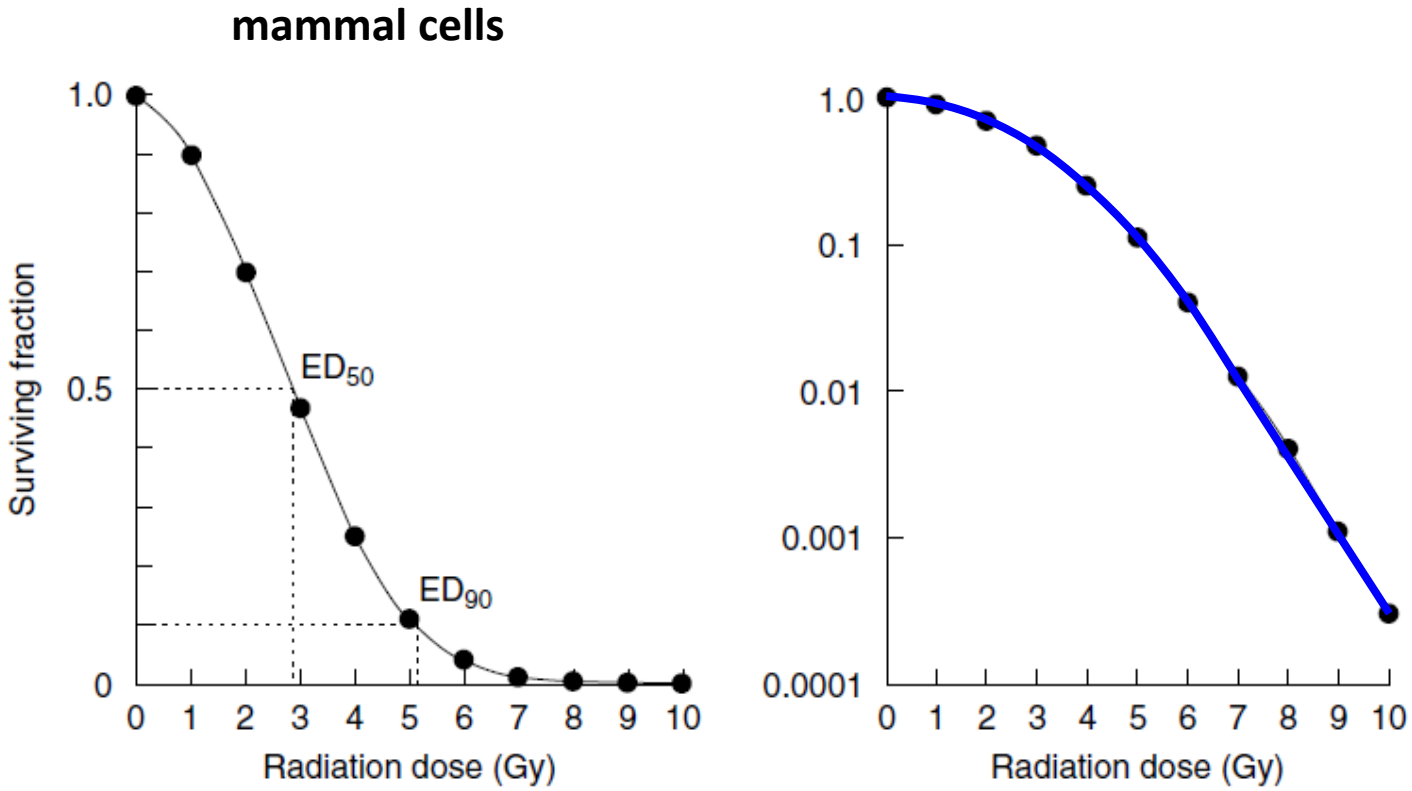
- 3D dose distribution
- Dose-Volume histograms







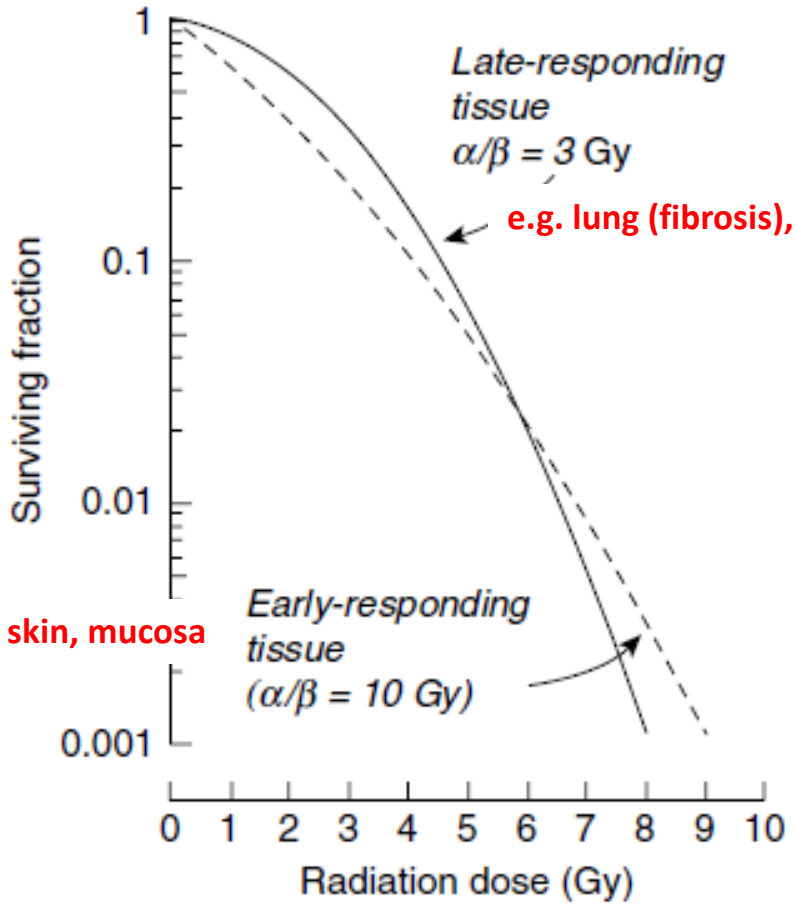
Basis of radiotherapy: Cell survival and LQ model



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

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

α/β for tumor and normal tissue



e.g. lung (fibrosis), eyes, spinal canal (myelopathy)

e.g. skin, mucosa

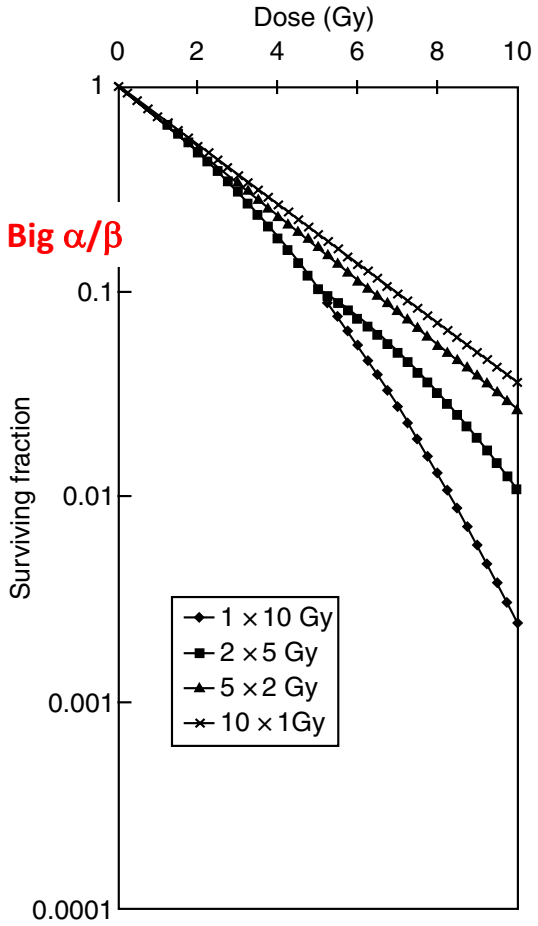
for most tumors:
α/β = 10 Gy

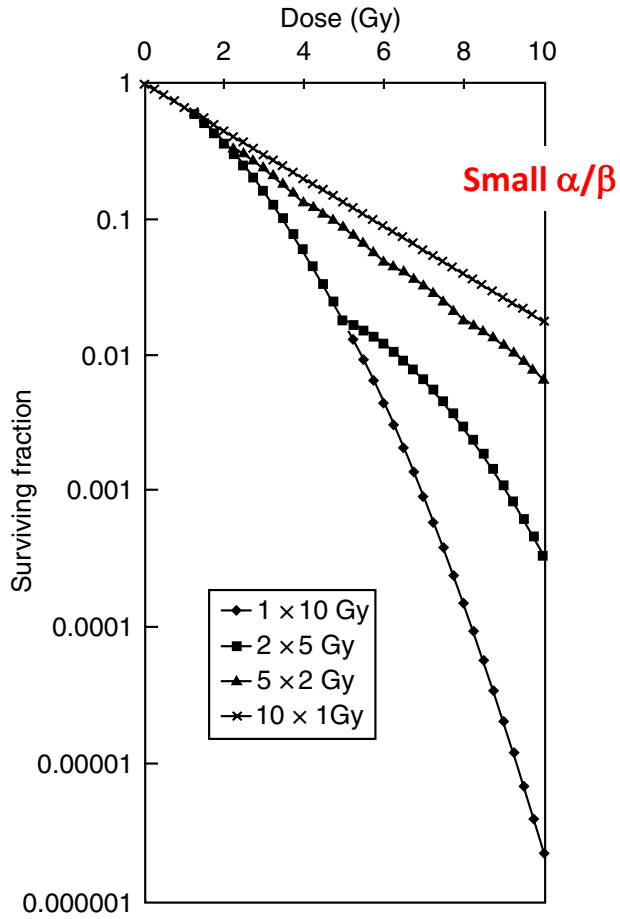
BUT:

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

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

Fractionation and α/β





Source: *Handbook of Radiotherapy Physics*

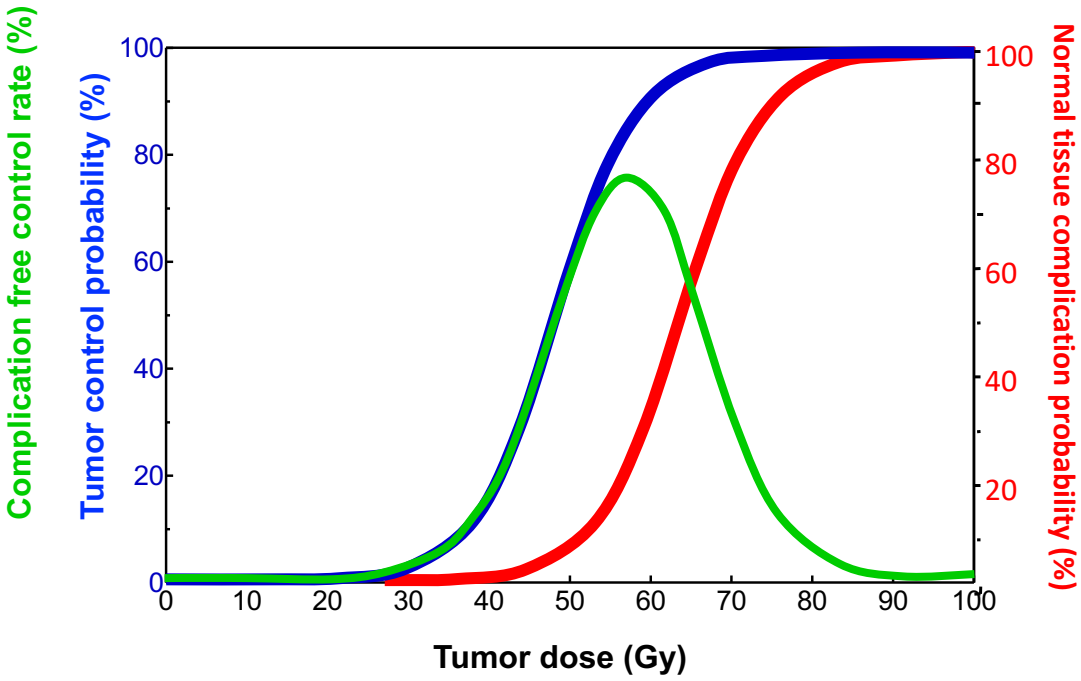
“Emerging” irradiation concepts in prostate cancer

- 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

This project

Using radiobiological models
(e.g. for describing TCP, 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:

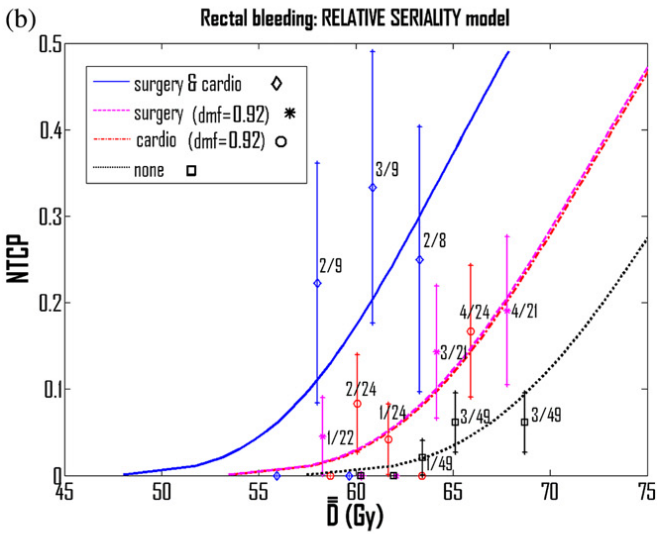
$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{(\mu-\mu_{50})/m\mu_{50}} \exp(-u^2/2)\,du$$

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

Relative Seriality (RS) model:

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

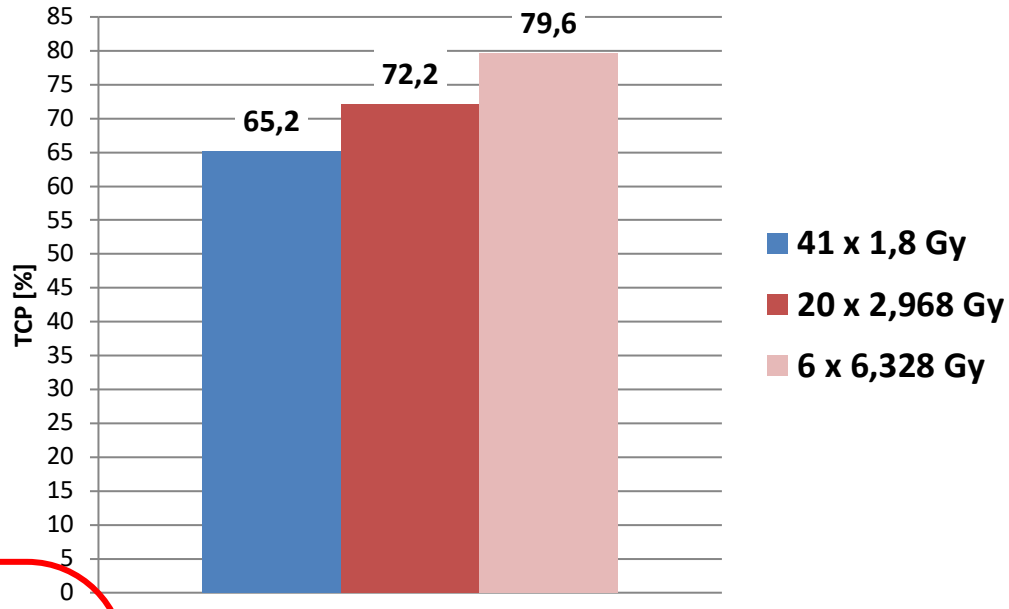
$$P(D_i) = 2^{-e^{e\gamma_s\left(1-\frac{D_i}{D_{50}}\right)}}$$



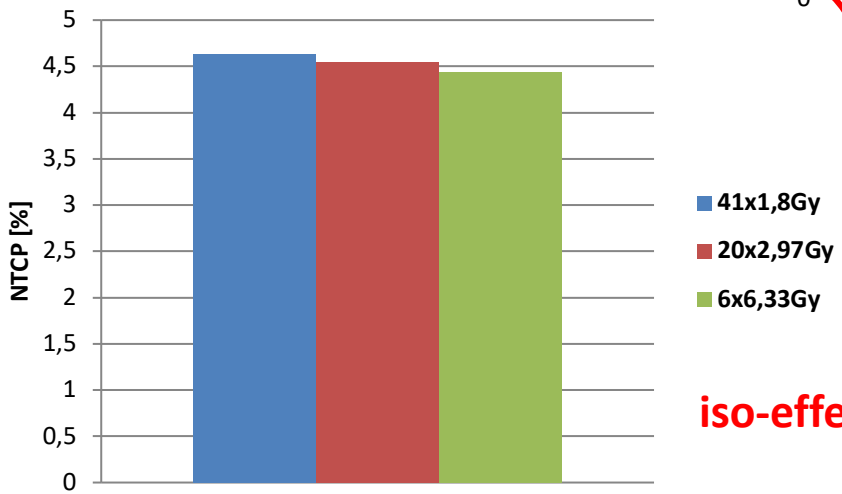
Source: Defraene et al. (2012)

Evaluating alternative fractionation schemes in prostate cancer RT

- Original plan:
  41 x 1.8 Gy
- Alternative plans:
  20 x 3.0 Gy
  6 x 6.3 Gy

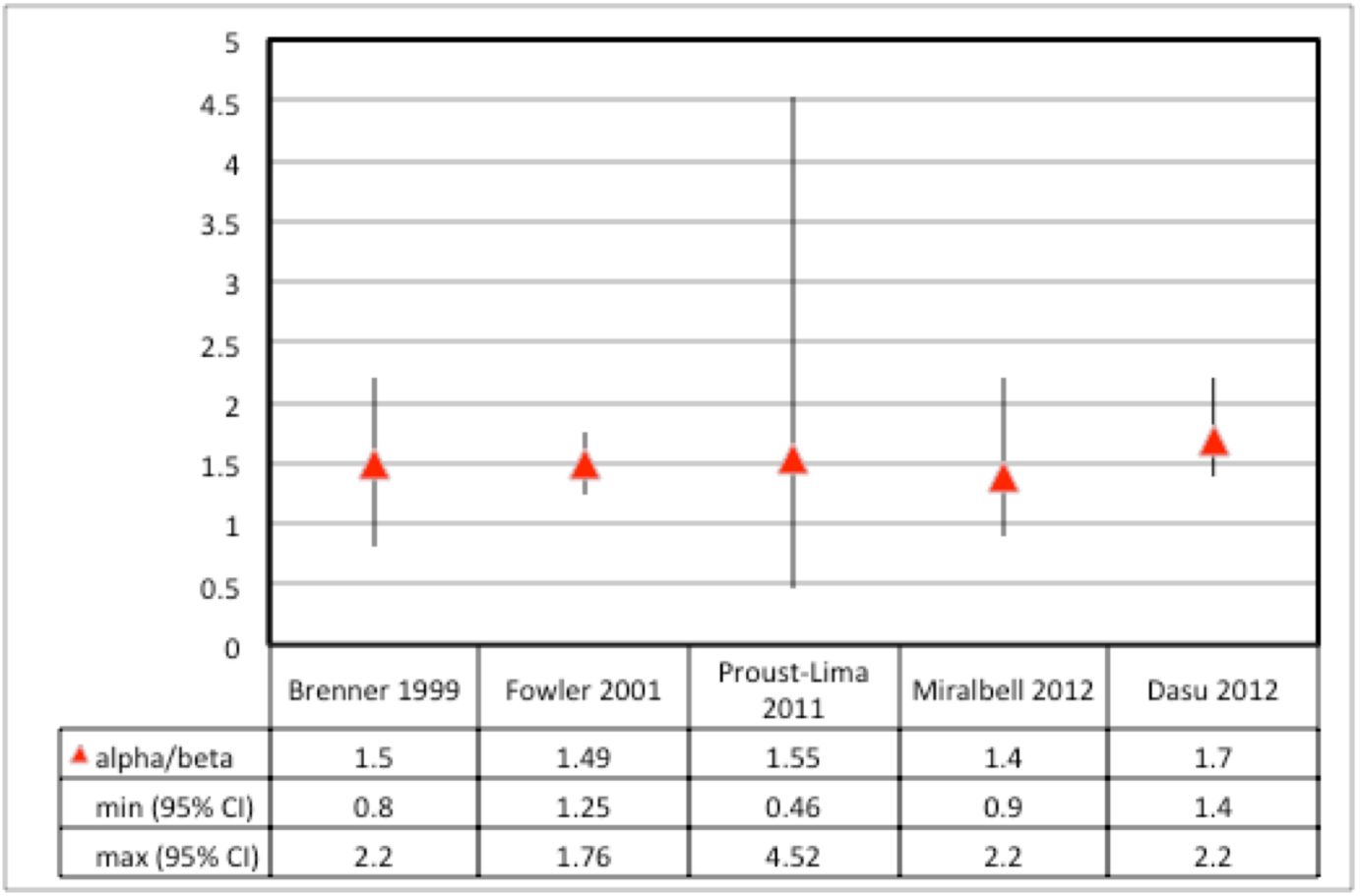


higher TCP if α/β = 1.5 Gy



iso-effective with respect to late rectal bleeding

α/β for prostate cancer: literature



	Brenner 1999	Fowler 2001	Proust-Lima 2011	Miralbell 2012	Dasu 2012
alpha/beta	1.5	1.49	1.55	1.4	1.7
min (95% CI)	0.8	1.25	0.46	0.9	1.4
max (95% CI)	2.2	1.76	4.52	2.2	2.2

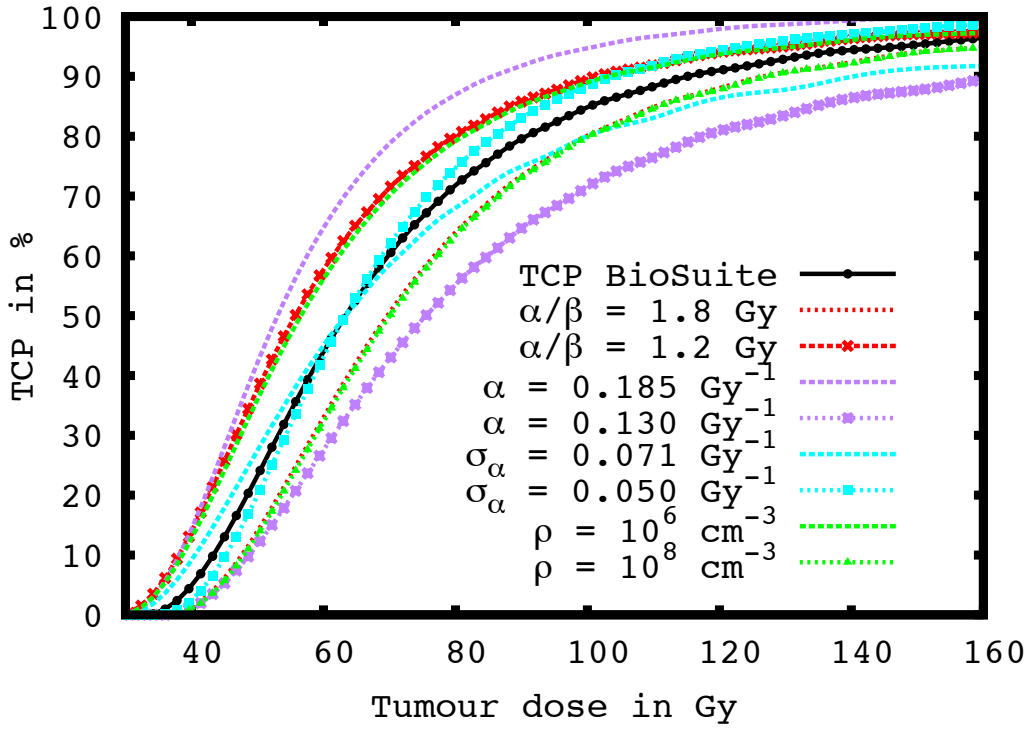
Are these models robust for predicting complications and tumor control rate?

Model parameters available from literature have quite large uncertainties

- We analyzed 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

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



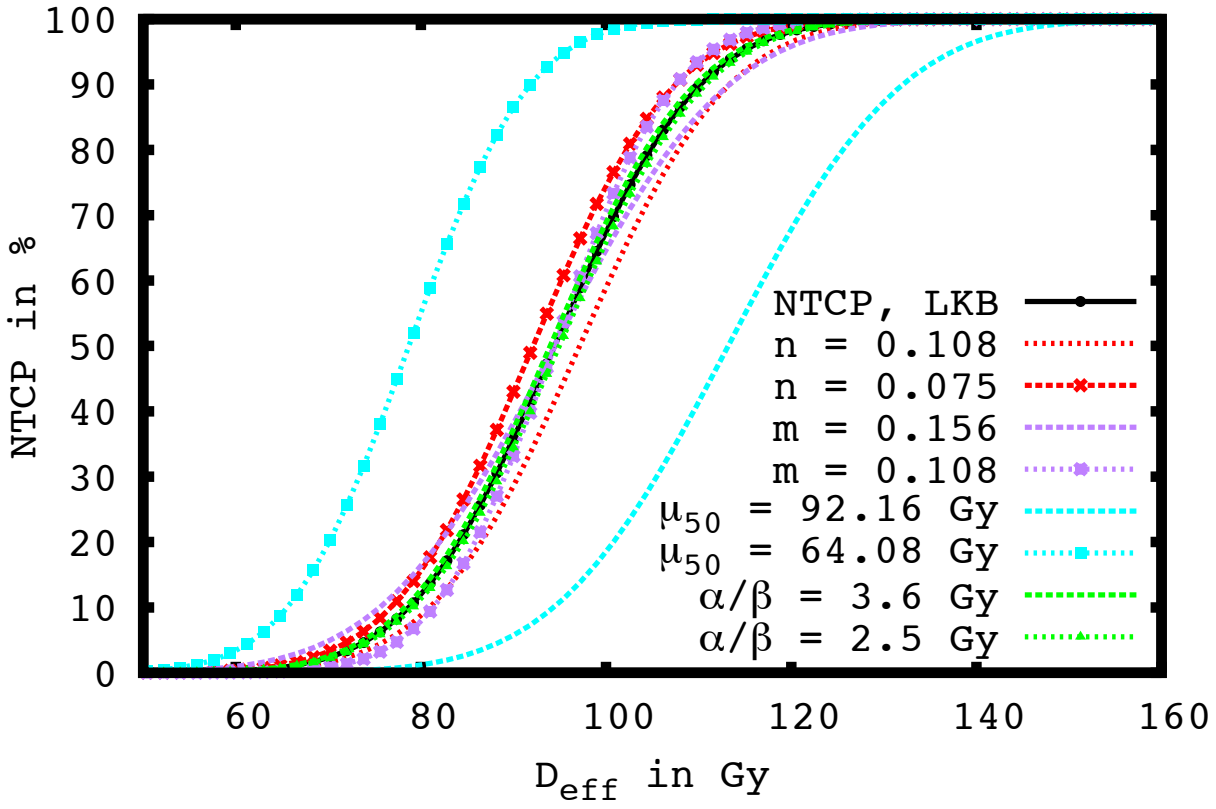
Starting values (BioSuite)*:
α/β = 1.5 Gy, α = 0.155 Gy^{-1}, ρ = 10^7 cm^{-3}

* 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



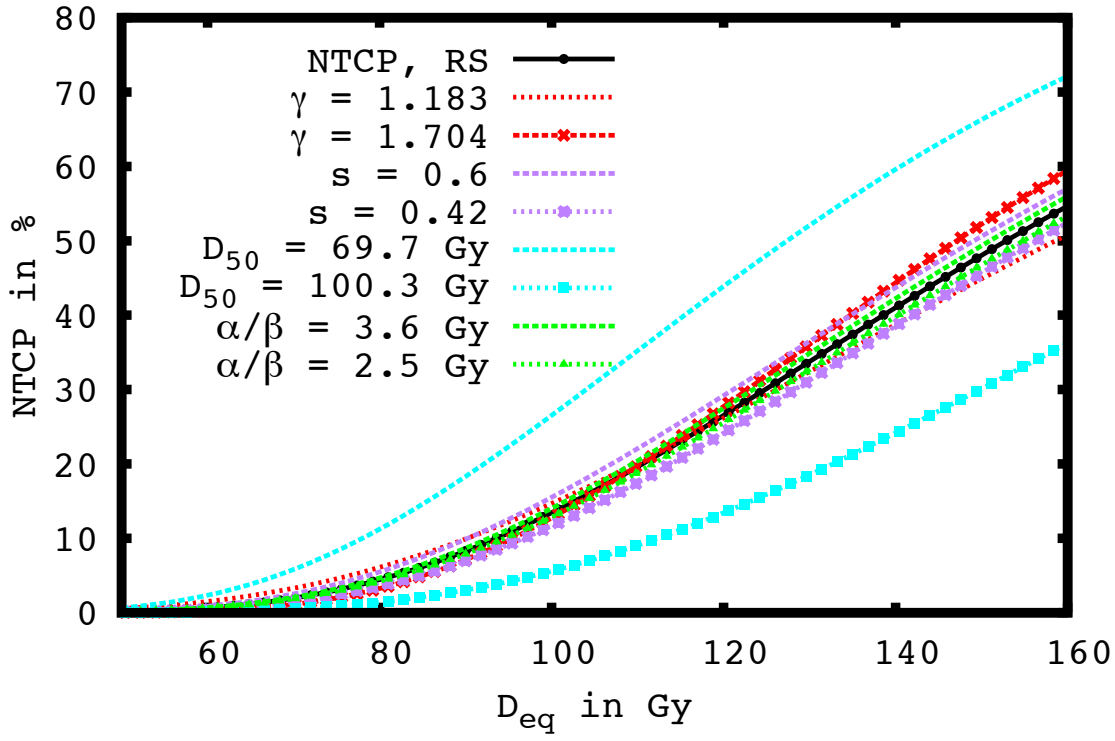
Starting values*:
***n* = 0.09,**
***m* = 0.13,**
μ_{50} = 76.9 Gy,
α/β = 3 Gy

* 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)

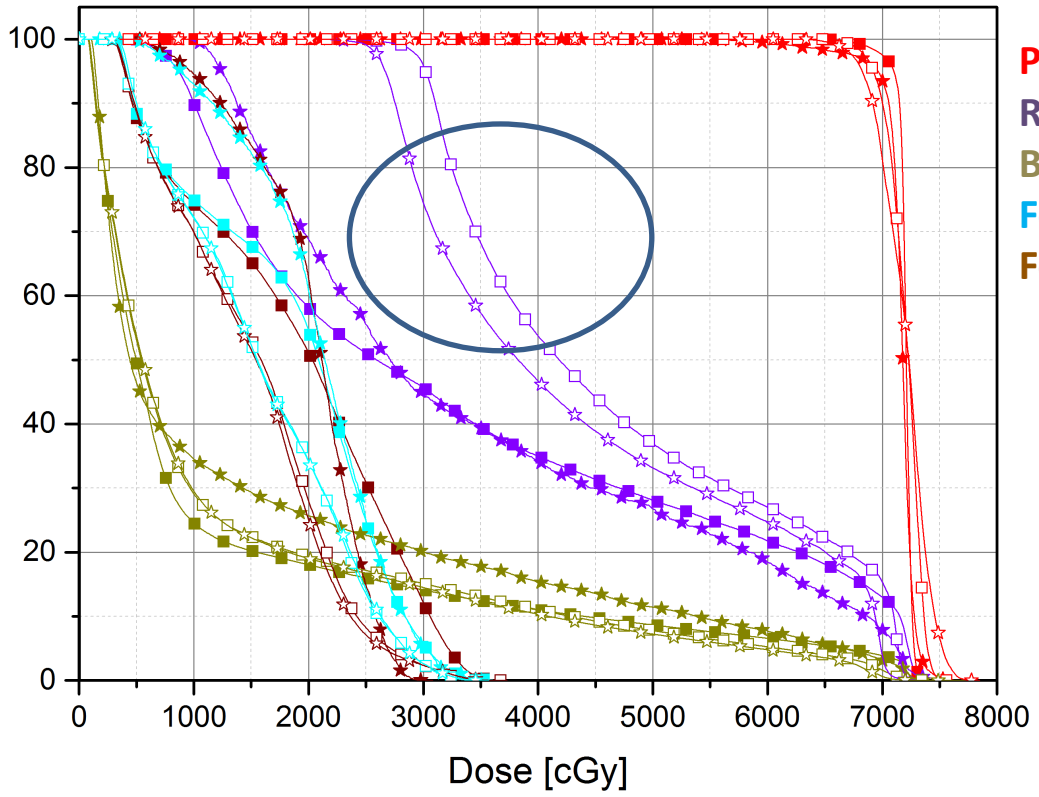
Are these models robust for plan optimization?

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

- We analysed 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?



PTV
Rectum
Bladder
Femoral head left
Femoral head right

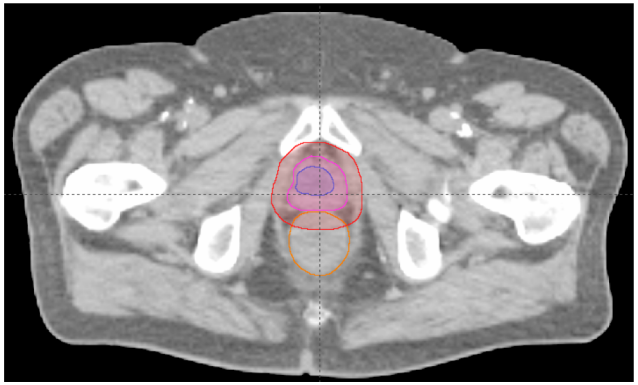
filled symbols:
conventionally optimized VMAT/ TomoTherapy plans

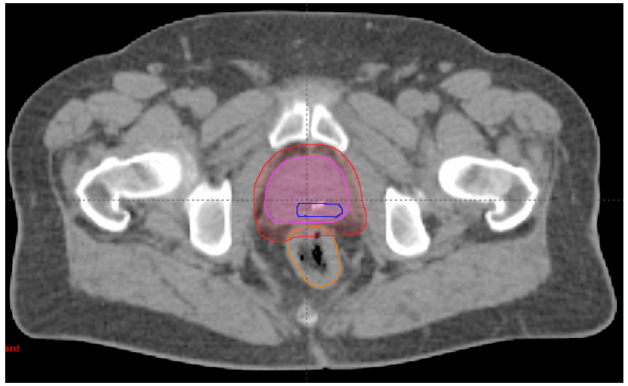
Open symbols:
biologically optimized IMRT plans

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?





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

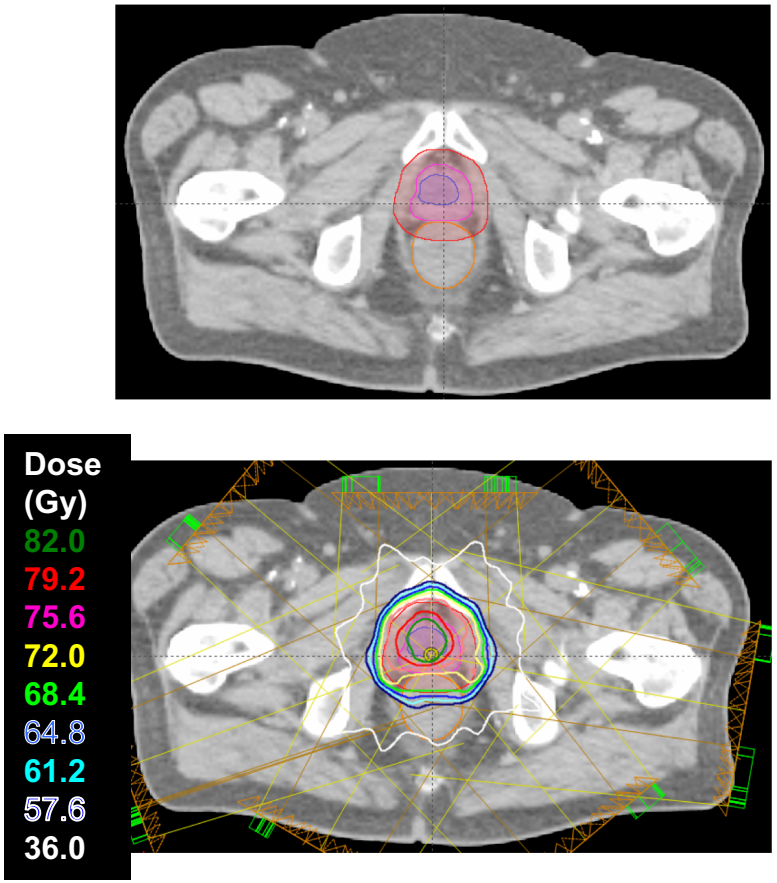
Dose constraint for PTV: 72 Gy in 40 fractions

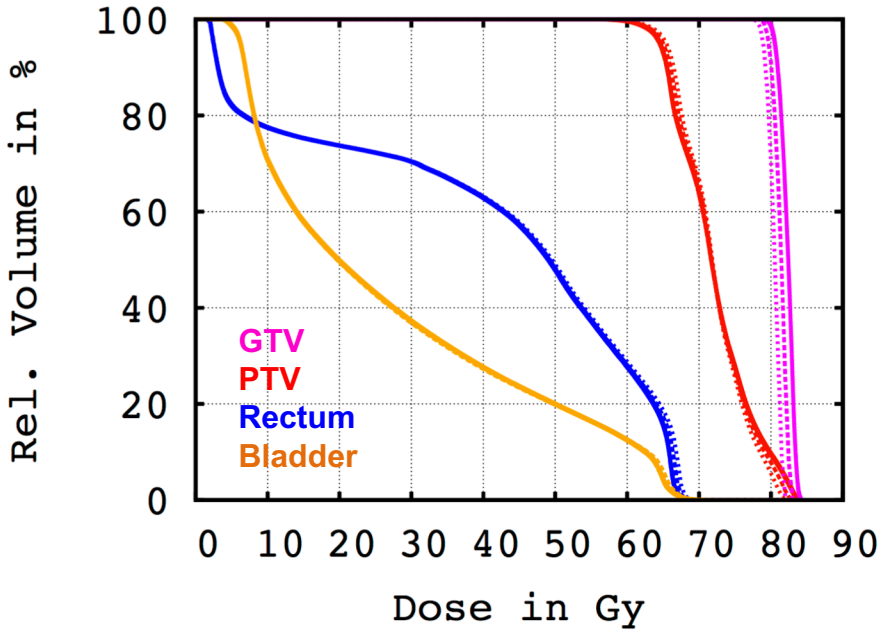
Variation of α/β for prostate cancer:

1.5 Gy
3 Gy
4.5 Gy

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

What about personalized dose escalation?

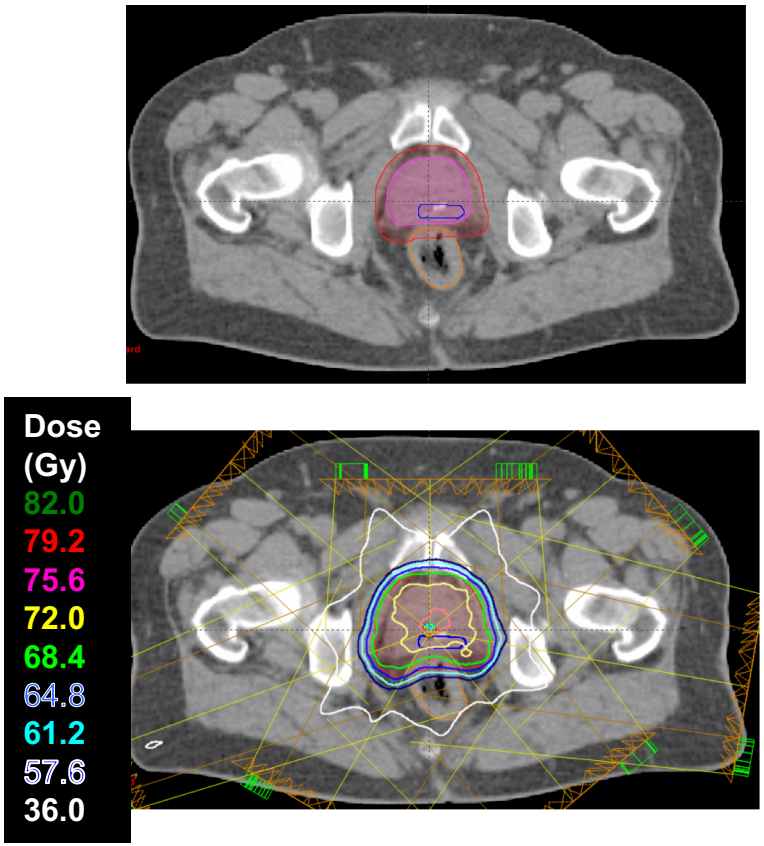


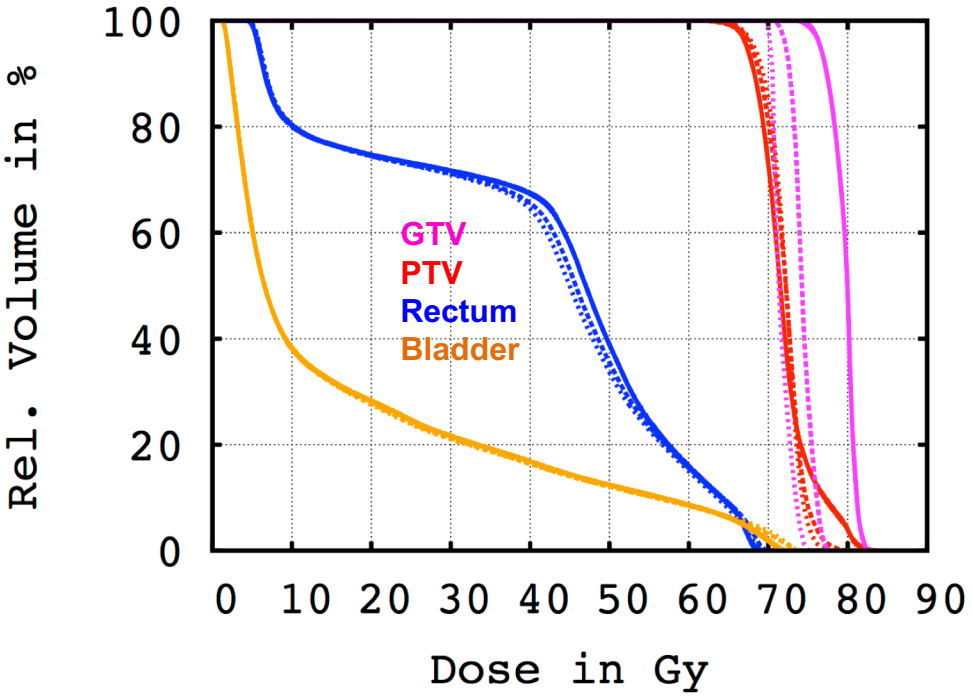


Solid: α/β = 1.5 Gy
Dashed: α/β = 3 Gy
Dotted: α/β = 4.5 Gy

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

What about personalized dose escalation?





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)

ELSEVIER

Seminars in
RADIATION
ONCOLOGY

Finding Value for Protons: The Case of Prostate Cancer?

Eric Ojerholm, MD,[*,†,‡] and Justin E. Bekelman, MD[*,§,‖]

The standard radiotherapy treatment for prostate cancer is intensity-modulated radiotherapy (IMRT). An alternative option is proton beam therapy (PBT). PBT is a safe and effective treatment, but does it add value over IMRT? We explore this controversial question by examining the available dosimetric and clinical evidence.
Semin Radiat Oncol 28:131-137

Photons vs Protons: How to compare?

ELSEVIER

Seminars in RADIATION ONCOLOGY

Clinical Trial Strategies to Compare Protons With Photons

Johannes A. Langendijk, MD, PhD,[*,‖] Liesbeth J. Boersma, MD, PhD,[†,‖] Coen R.N. Rasch, MD, PhD,[†,‖] Marco van Vulpen, MD, PhD,[‡,‖] Johannes B. Reitsma, MD, PhD,[§,‖] Arjen van der Schaaf, PhD,[*,‖] and Ewoud Schuit, PhD[§,‖]

The favorable beam properties of protons can be translated into clinical benefits by target dose escalation to improve local control without enhancing unacceptable radiation toxicity or to spare normal tissues to prevent radiation-induced side effects without jeopardizing local tumor control. For the clinical validation of the added value of protons to improve local control, randomized controlled trials are required. For the clinical validation of the added value of protons to prevent side effects, both model-based validation or randomized controlled trials can be used. Model-based patient selection for proton therapy is crucial, independent of the validation approach. Combining these approaches in rapid learning health care systems is expected to yield the most efficient and scientifically sound way to continuously improve patient selection and the therapeutic window, eventually leading to more cancer survivors with better quality of life.

Semin Radiat Oncol 28:79-87

NTCP-based selection…

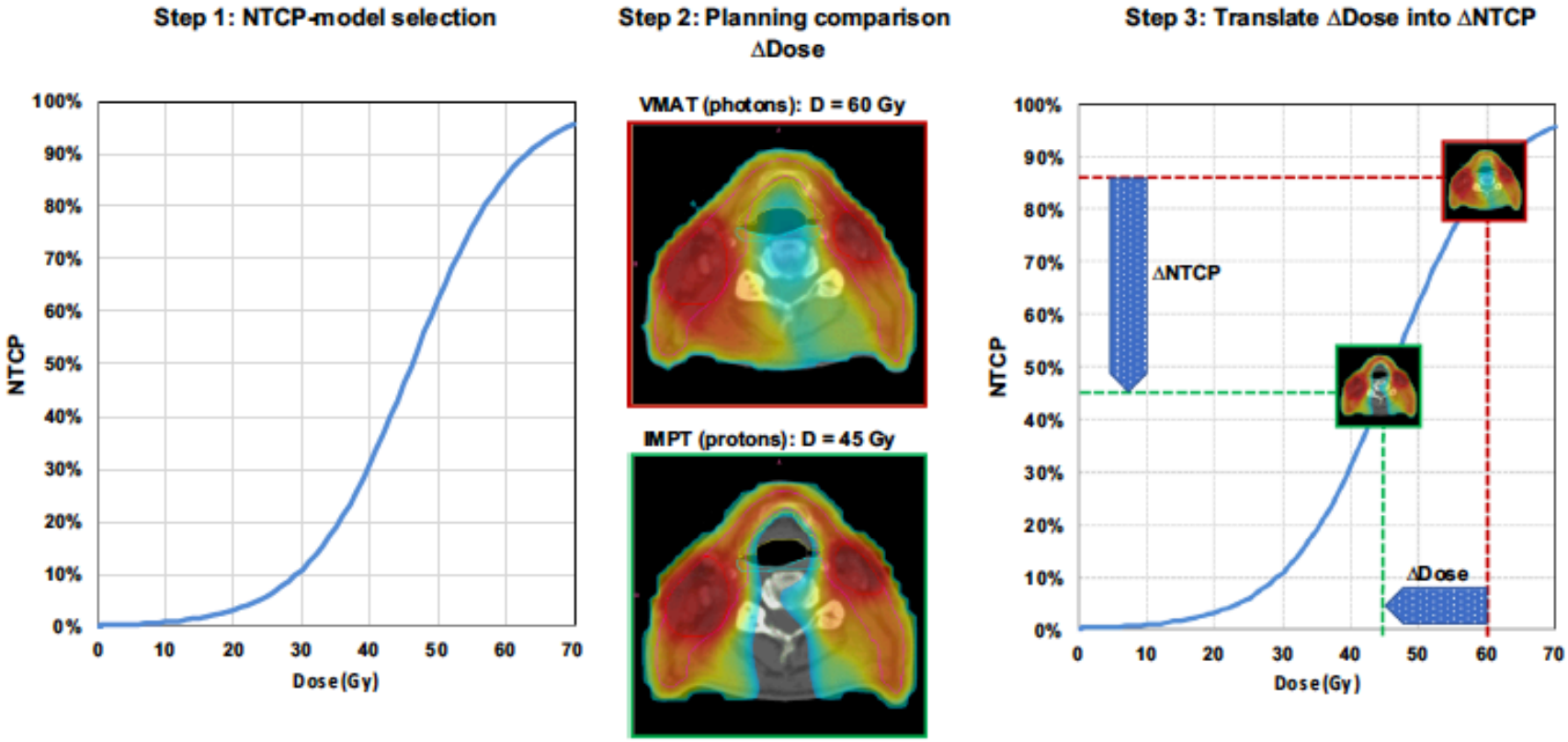


Figure 1 Graphical display of the model-based selection procedure. The first step includes selection of an NTCP-model. Based on the dose-volume parameters included in the selected NTCP-model, the dose distribution is optimized for both techniques (model-based plan optimization) and Δdose is assessed (step 2). Finally, the outcome of step 2 is integrated in the NTCP-model to translate Δdose into ΔNTCP (step 3). (Color version of figure is available online.)