Incorporating clinical and biological factors into (NTCP) models

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AAPM 2018, Nashville, US

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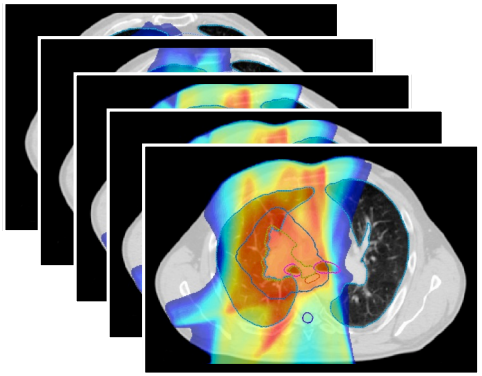
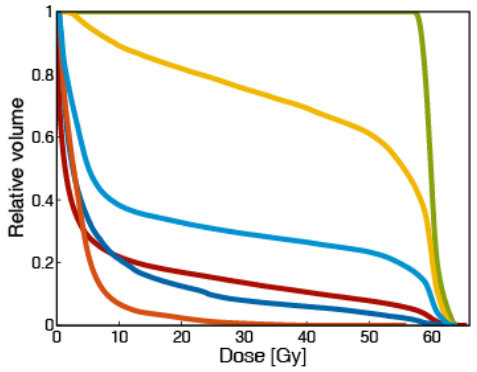
Standard phenomenological modelling methodology

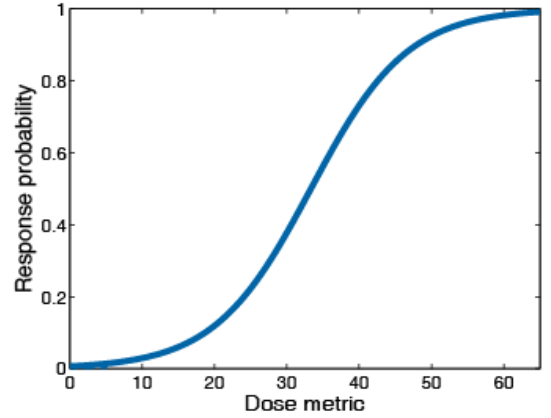


EUD

V_x

D_{mean}





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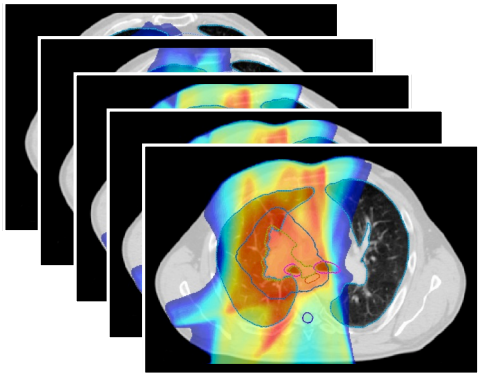
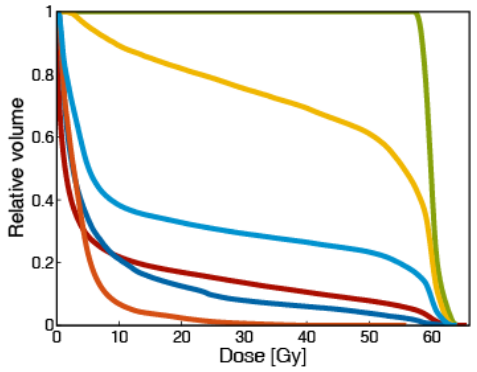
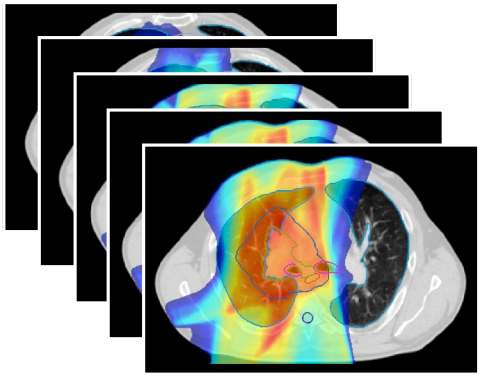


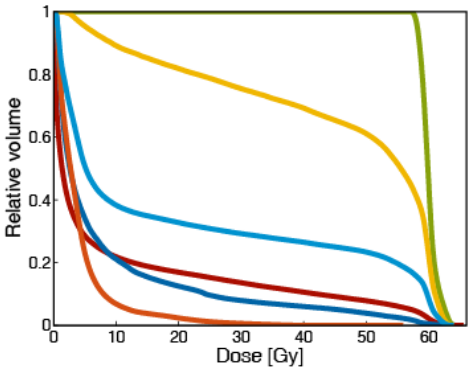


Reduce dose distribution to DVH

- Removes all spatial information
- Assumes equal sensitivity/response of all parts of OAR
- Alternatives:
  - Explicitly model local response on voxel-to-voxel basis
  - Divide into anatomical substructures
  - Dose surface histograms

Standard phenomenological modelling methodology





EUD

V_x

D_{mean}

Reduce DVH to limited number of dose metrics

$$EUD = \left(\sum_k d_k^a \frac{v_k}{V_{tot}} \right)^{1/a}$$

Mean dose: a=1

$$V_x = \sum_k E(d_k) v_k$$

$$E(d_k) = \begin{cases} 0 \ for \ d_k < x \ Gy \\ 1 \ for \ d_k \geq x \ Gy \end{cases}$$

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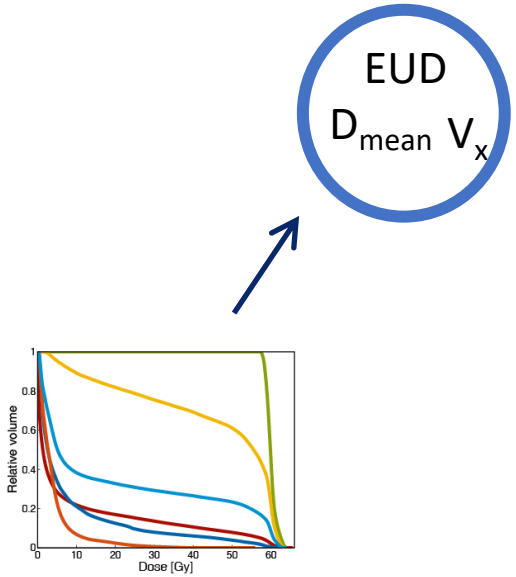
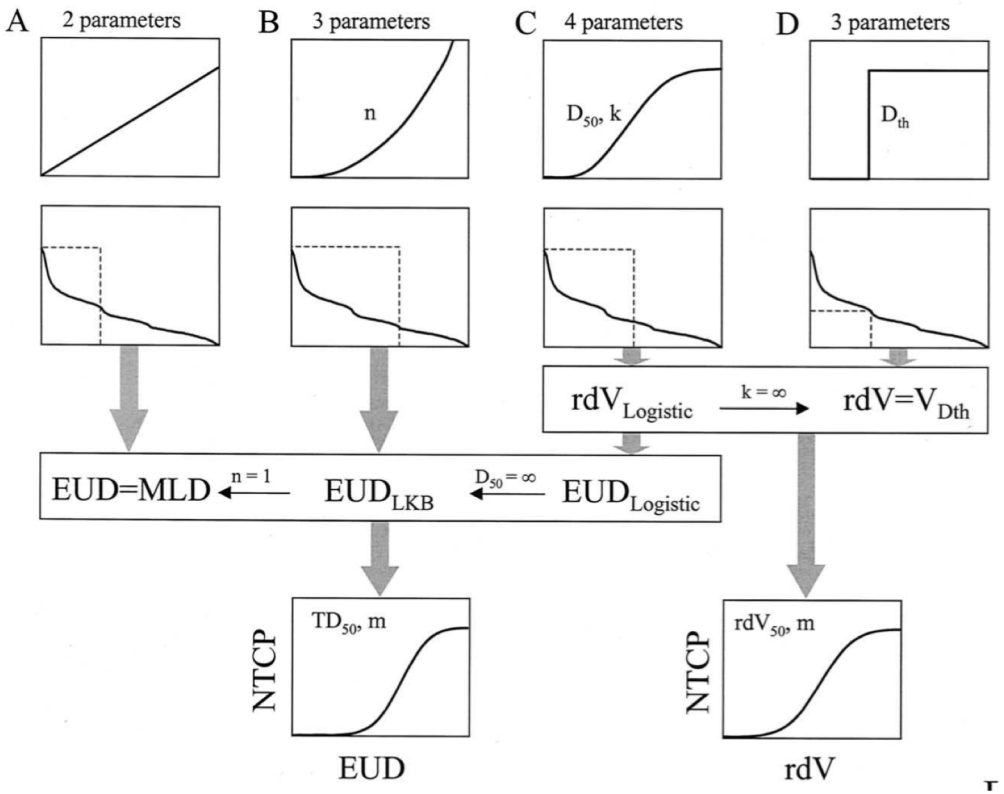
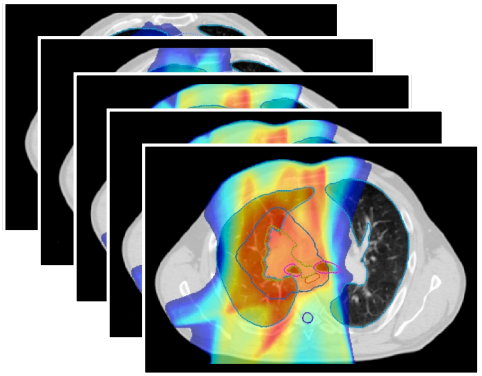


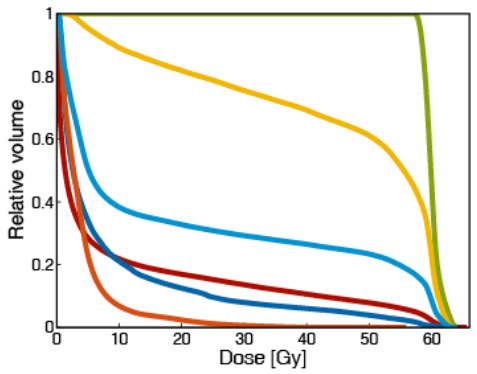
Generalized approach for calculating “equivalent organ dose/volume” from local response



Seppenwoolde et al: Comparing different NTCP models that predict the incidence of radiation pneumonitis. IJROBP 2003, 55(3): 724-35

Standard phenomenological modelling methodology





EUD

V_x

D_{mean}

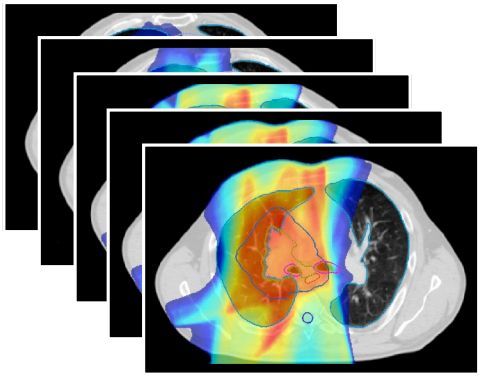
Reduce DVH to limited number of dose metrics

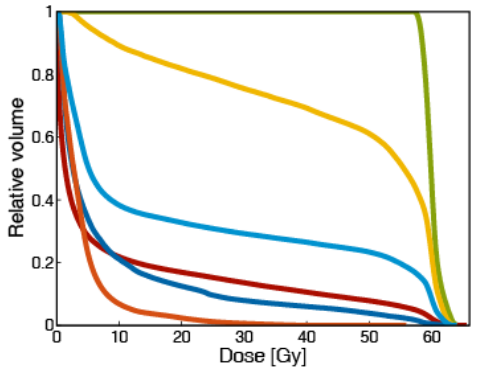
Dose metrics generally highly correlated

Potential solutions:

- Bootstrapping methodologies
- Principal component analysis (PCA)

Standard phenomenological modelling methodology





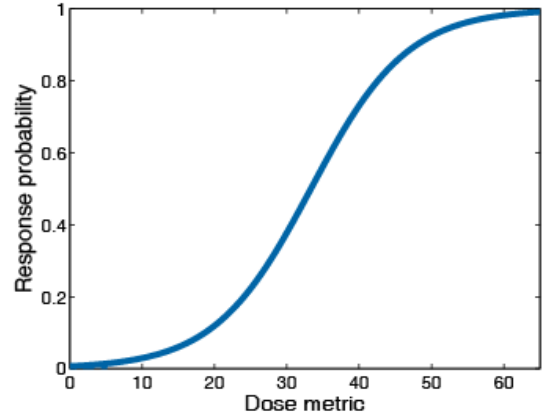
EUD

V_x

D_{mean}

Link funktion:

- Logistic (binary outcome)
- Probit (binary outcome)
- Linear model (continuous outcome)
  - Note underlying model assumptions (data not bounded)
- Ordinal logistic (graded outcome)



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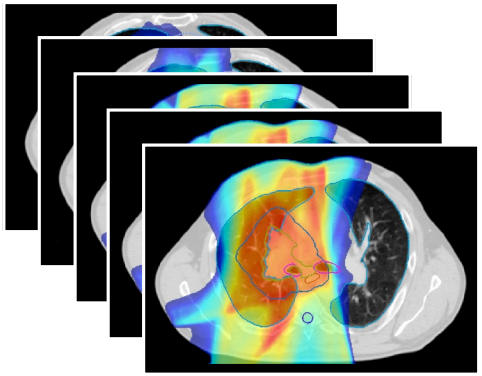
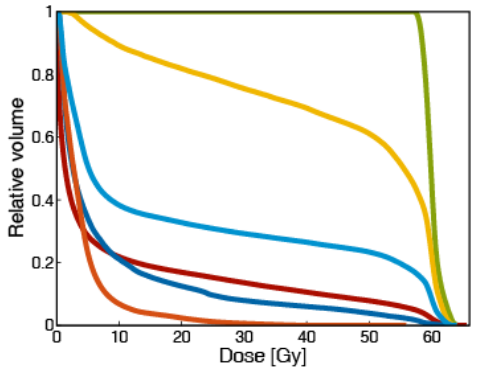




EUD

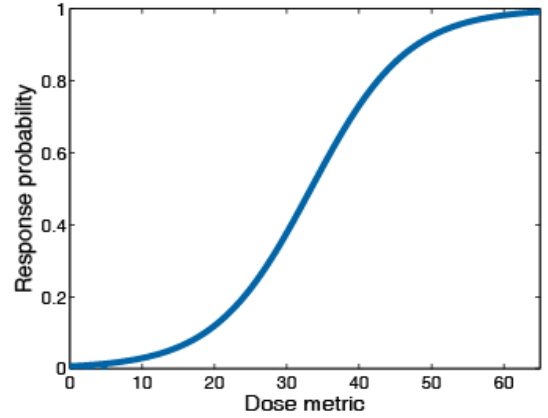
V_x

D_{mean}

Logistic regression

$$\frac{p}{1-p} = \ln(X), \quad X = b_0 + b_1 D$$

$$p(X) = \frac{1}{1+\exp(-X)}$$



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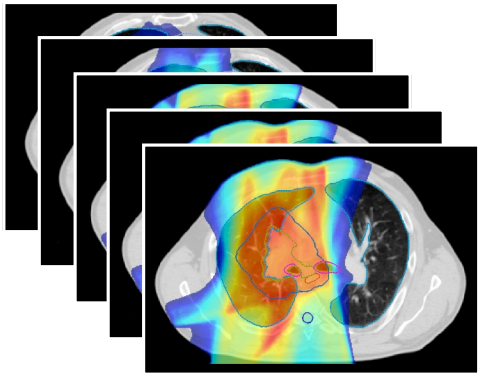
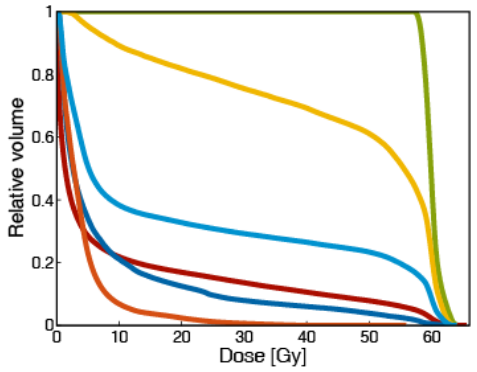


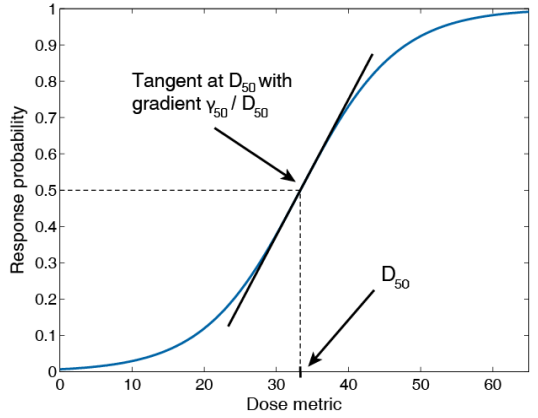
EUD

V_x

D_{mean}

$$D_{50} = D\big|_{p=0.5}, \quad \gamma_{50} = \frac{\partial p}{\partial D} D\Big|_{p=0.5}$$





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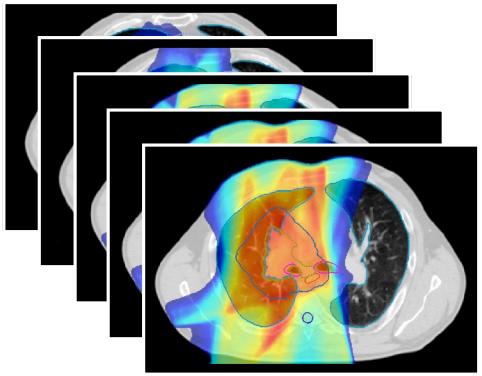
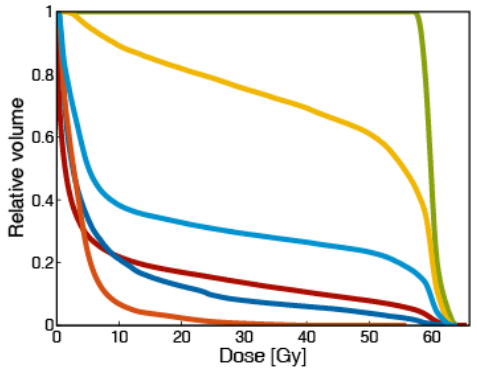




EUD

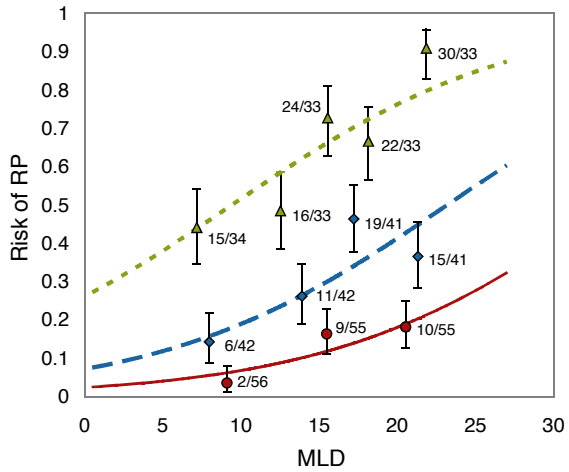
V_x

D_{mean}

Including graded outcome – ordinal logistic regression

$$\frac{p_{\geq i}}{1-p_{\geq i}} = \ln(X), \quad X = b_{0,i} + \bar{b}\,\bar{Y}$$

$$p_{\geq i}(X) = \frac{1}{1+\exp(-X)}$$



Grade 1+

Grade 2+

Grade 3+

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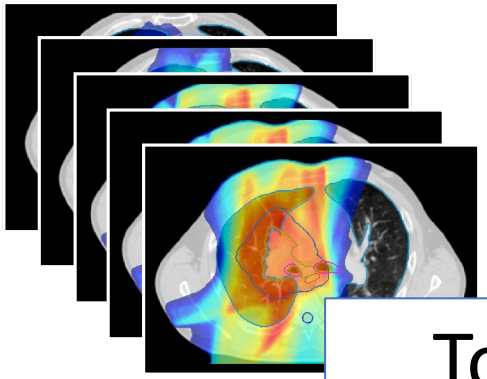
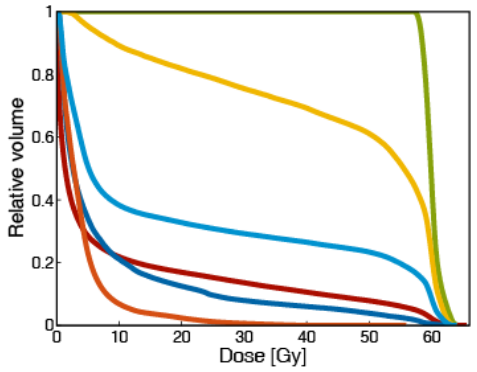


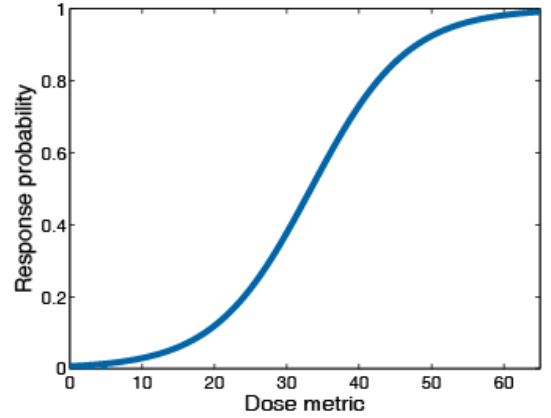
EUD

V_x

D_{mean}

To fit / optimize model: Optimize entire process at once





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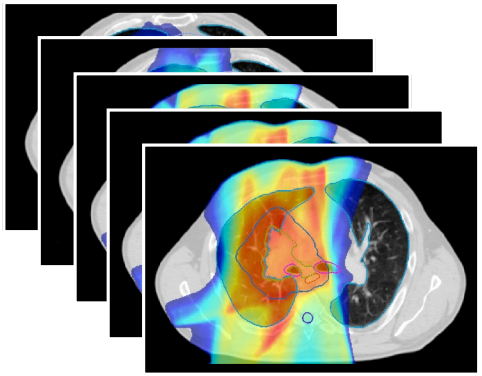
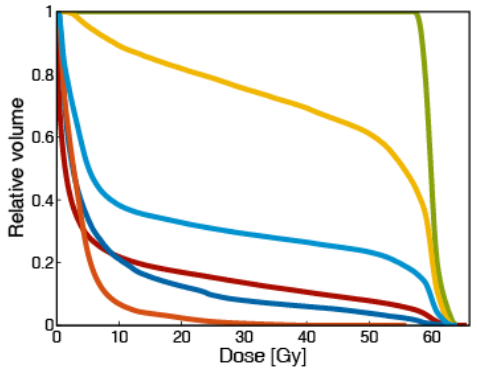
Lyman-Kutcher-Burman (LKB) model





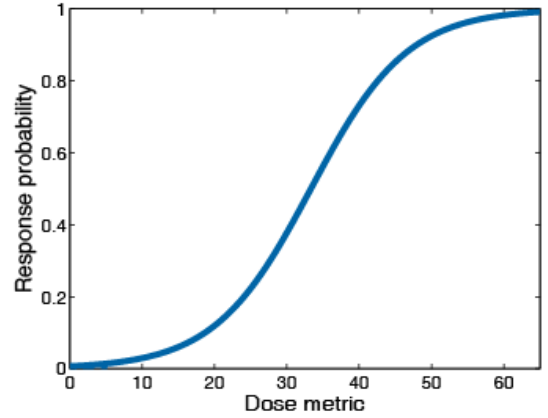
Effective volume

$$V_{eff} = \sum_i \left(\frac{D_i}{D_{eff}}\right)^{\frac{1}{n}}$$

Probit link function

$$NTCP(D_{ref}, v_{eff}) = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-\frac{u^2}{2}\right) du$$

$$t = \frac{D_{ref} - D_{50}(v_{eff})}{m D_{50}(v_{eff})}; \qquad D_{50}(v_{eff}) = D_{50}(1) v_{eff}^{-n}$$



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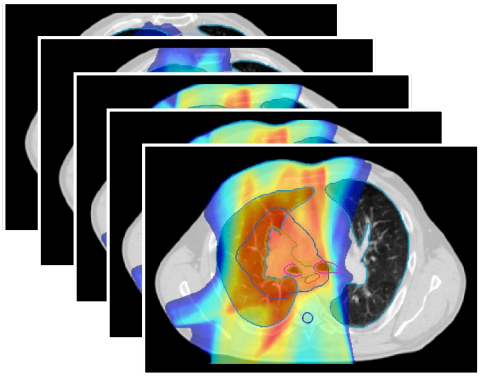
Modelling including clinical factors



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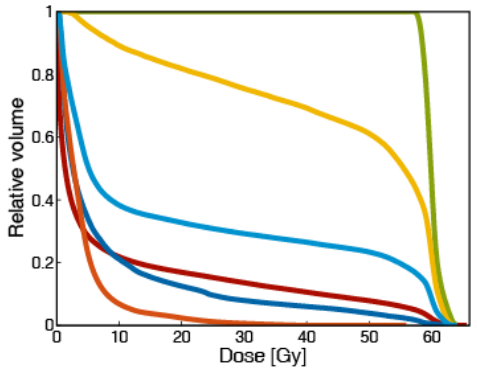

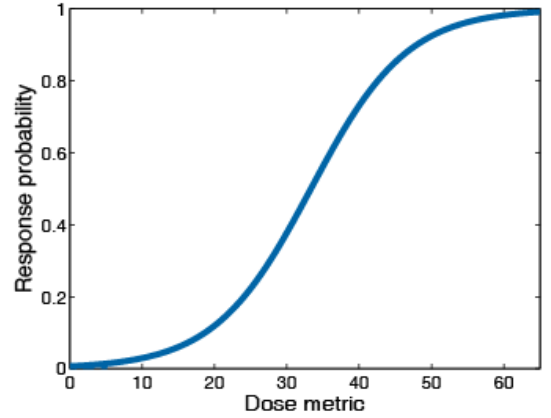

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Modelling including clinical factors

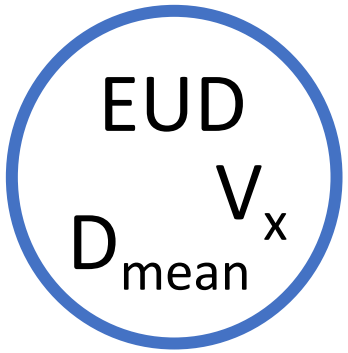
Assume same dose representation for different risk groups

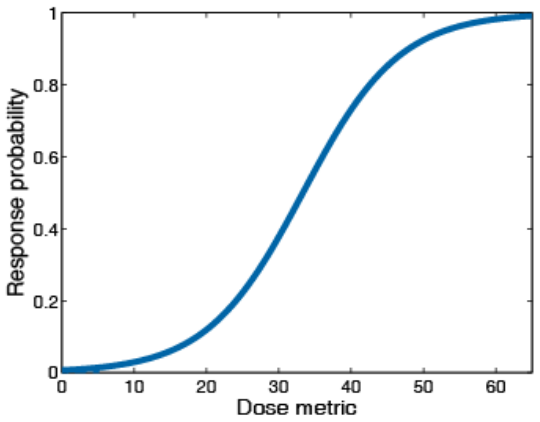
Treat dose metric and clinical factors as standard regression parameters

Generalised linear model (GLM) framework

$$g(p) = X = b_0 + b_1 D + b_i Y_i$$

- First order inclusion: Additive
- Second order: Multiplicative (interaction term)
  - "Dose modification factor





Modelling including clinical factors

Assume same dose representation for different risk groups

Treat dose metric and clinical factors as standard regression parameters

Logistic regression – direct relationship with odds ratios (OR)

$$X = b_0 + b_1 D + b_i Y_i$$

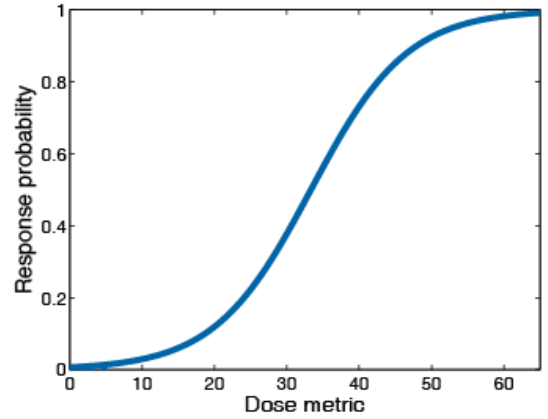
$$p(X) = \frac{1}{1 + \exp(-X)}$$

$$OR_i = e^{b_i Y_i}$$

EUD

V_x

D_{mean}



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EUD

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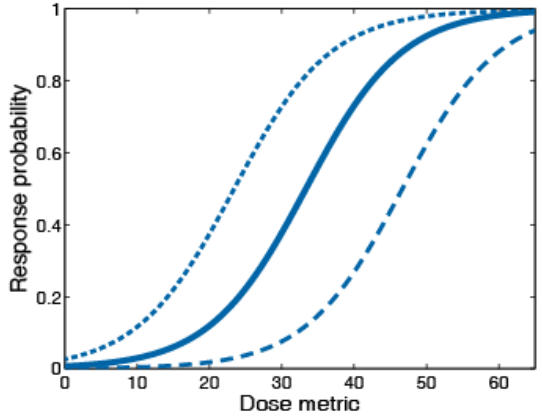
D_{mean}

$$D_{50}^{OR} = D_{50}\left(1 - \frac{1}{4}\frac{\ln(OR)}{\gamma_{50}}\right)$$

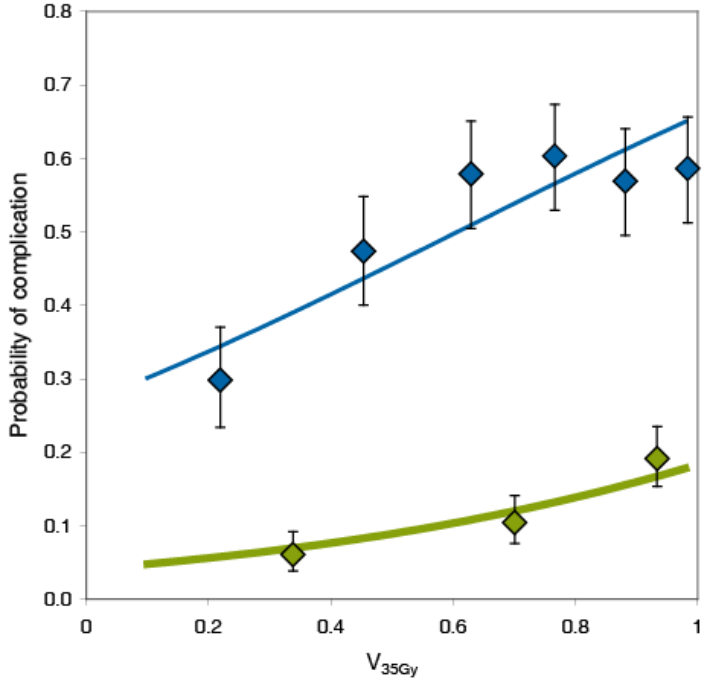
$$\gamma_{50}^{OR} = \gamma_{50} - 0.25\ln(OR)$$



Appelt & Vogelius, Radiother Oncol, 2012

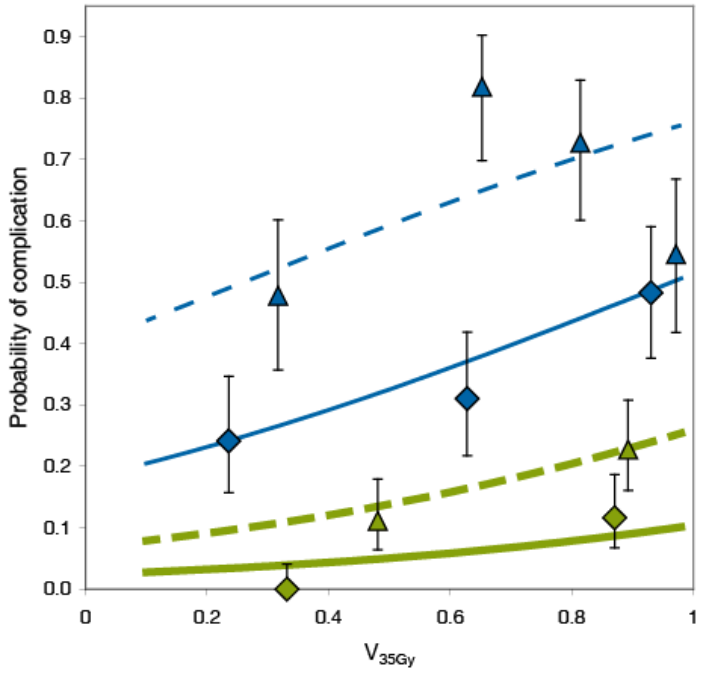
Example: Acute urinary toxicity for rectal cancer radiotherapy

- 345 rectal cancer patients treated with 50-66 Gy / 1.8-2 Gy per fraction, both IMRT and 3D-CRT
- Relationship between acute cystitis (CTCAE v 3.0) and dose to the bladder
- Best predictor: V_{35Gy} to the bladder (relative volume)



Grade 1+

Grade 2+



Grade 1+2:
Men, brachytherapy boost

Grade 1+2:
Women, no brachytherapy

Grade 2:
Men, brachytherapy boost

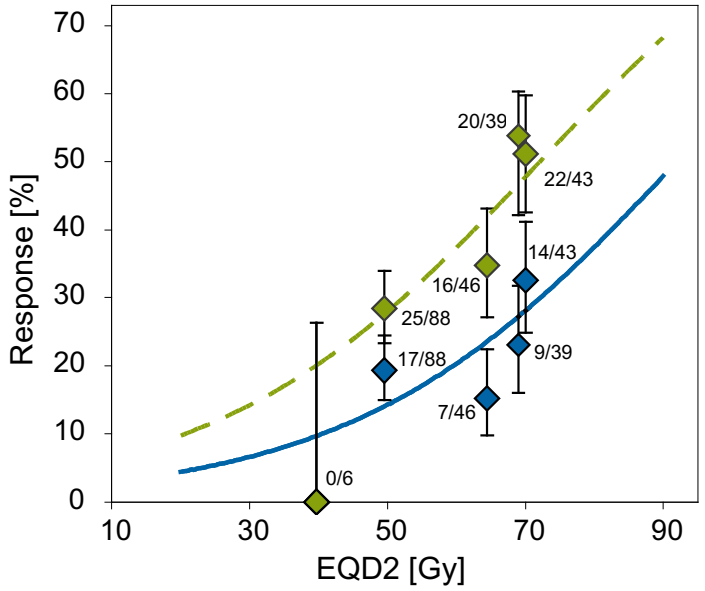
Grade 2:
Women, no brachytherapy

OR_{male} =1.82 (1.17–2.80), Or_{brachy} = 1.36 (1.02–1.80) each 5 Gy

Appelt et al, Acta Oncol, 2015

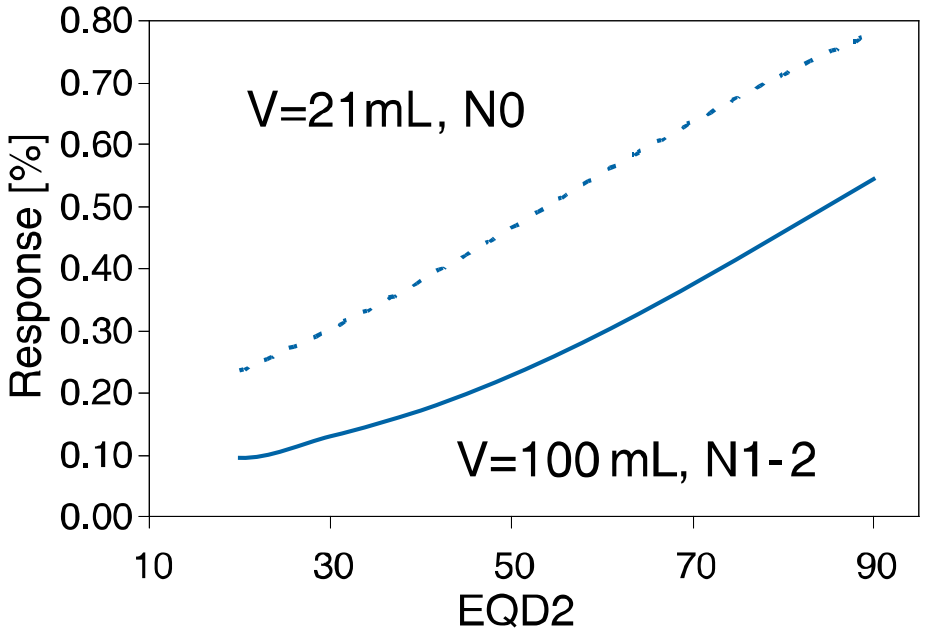
Example: Rectal cancer tumour regression after CRT

- 222 rectal cancer patients treated with 50-66 Gy / 1.8-2 Gy per fraction
- Relationship between EQD2 and tumour regression grade on pathological specimen



Blue, solid: TRG1 (complete response)
Green, dashed: TRG1-2 (major response)

Tumour size and N-stage – TRG 1&2 response



N-stage: OR=2.06 for N0 vs N1-2, p=0.039
Size: OR=0.65 for each 50 mL increase in size, p=0.040

Appelt et al, IJROBP, 2013

Example: Smoking and risk of radiation pneumonitis

Tucker et al. *Analysis of radiation pneumonitis risk using a generalized Lyman model*. IJROBP, 2008

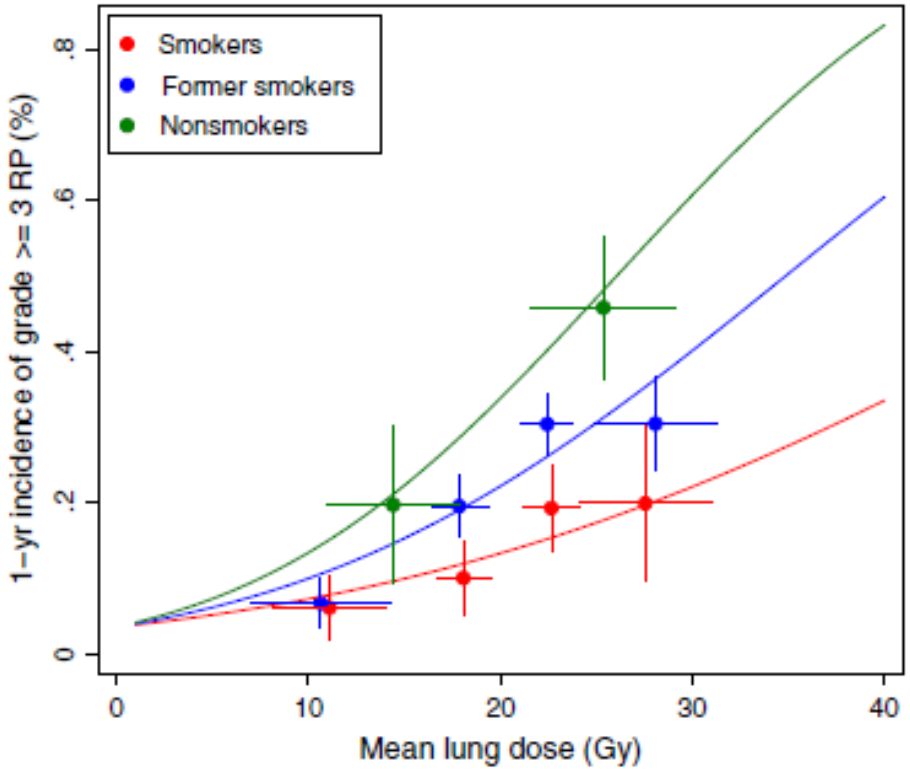
$$\mathrm{NTCP}(D,V) = \frac{1}{\sqrt{2\pi}} \cdot \int_{-\infty}^{t} e^{-u^2/2} du \qquad t = \frac{D - TD_{50}/V^n}{m \cdot TD_{50}/V^n}$$

Introduce dose modifying factor (DMF):

$$t = \frac{D_{\mathrm{eff}} - TD_{50} \cdot \exp(\delta_1 \cdot Y_1) \cdot \ldots \cdot \exp(\delta_k \cdot Y_k)}{m \cdot TD_{50} \cdot \exp(\delta_1 \cdot Y_1) \cdot \ldots \cdot \exp(\delta_k \cdot Y_k)}$$

DMF = $\exp(\delta_i\, Y_i)$

Corresponds to a multiplicative (interaction, second order) effect



Example: SNPs and risk of radiation pneumonitis

Tucker et al. *Incorporating Single-nucleotide Polymorphisms Into the Lyman Model to Improve Prediction of Radiation Pneumonitis*. IJROBP, 2012

$$\mathrm{NTCP}(D,V) = \frac{1}{\sqrt{2\pi}} \cdot \int_{-\infty}^{t} e^{-u^2/2} du \qquad t = \frac{D - TD_{50}/V^n}{m \cdot TD_{50}/V^n}$$

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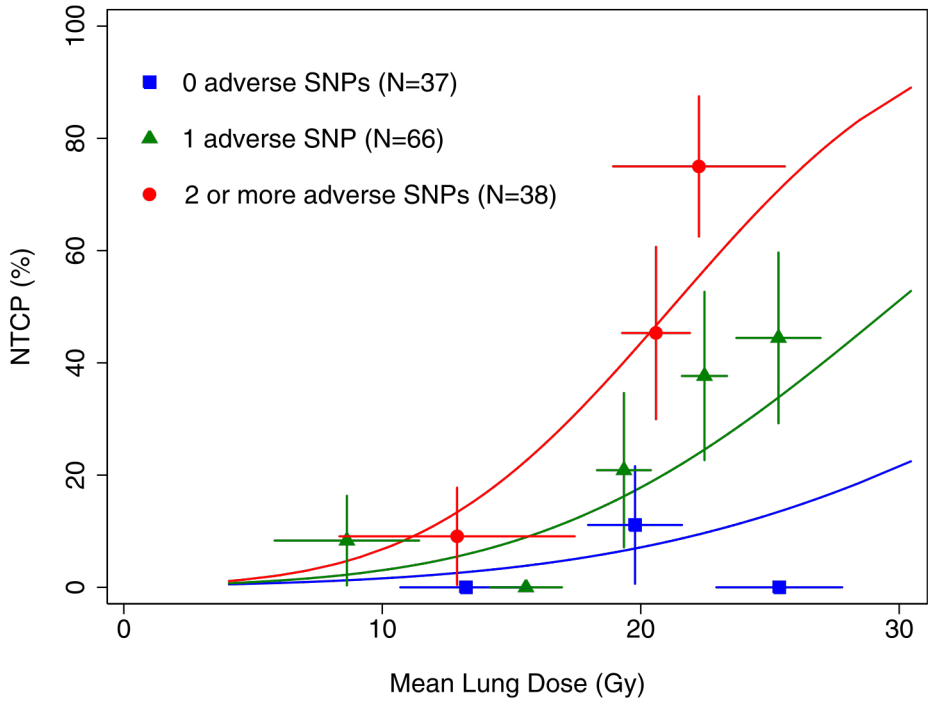
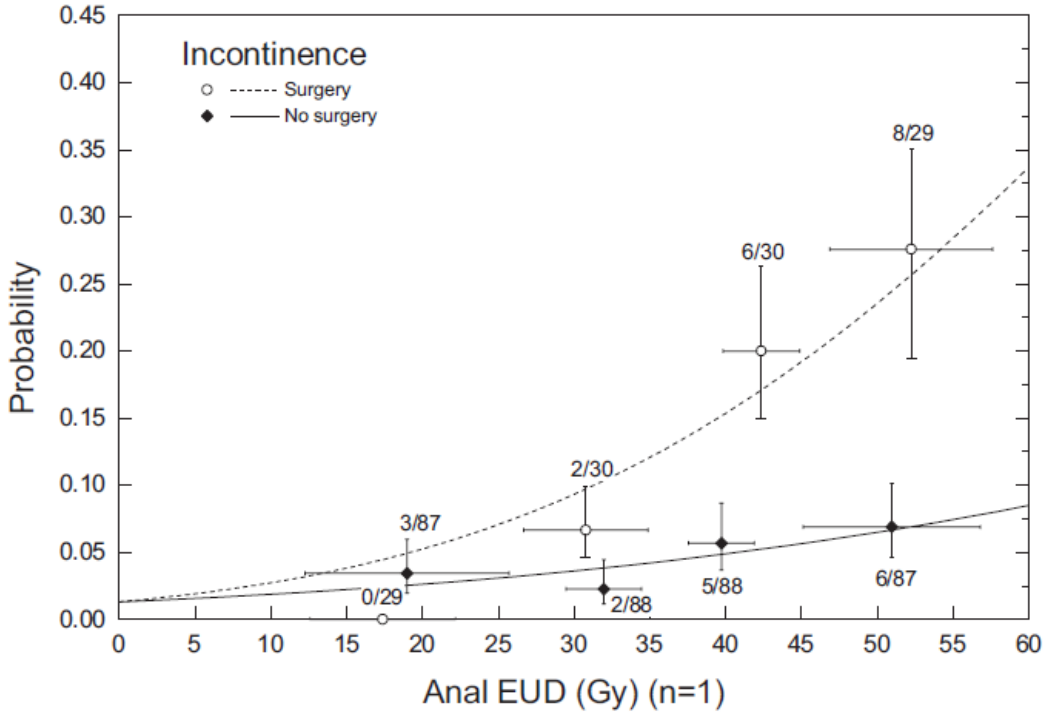
$$\mathrm{DMF} = \exp(\delta_i \, Y_i)$$

Corresponds to a multiplicative (interaction, second order) effect

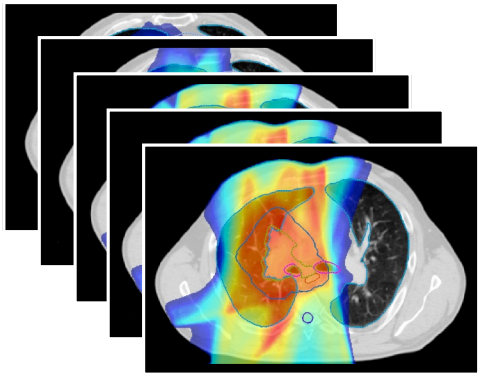


Example: Surgery and risk of incontinence after prostate RT



Peeters et al (IJROBP, 2006)

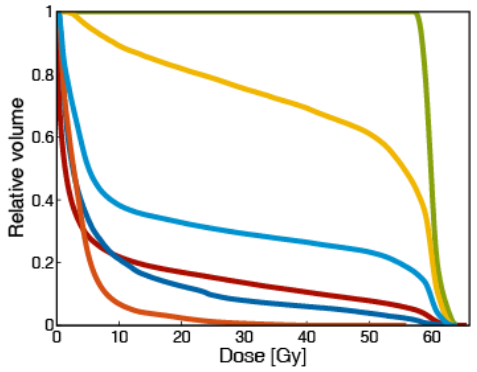
Modelling including clinical factors

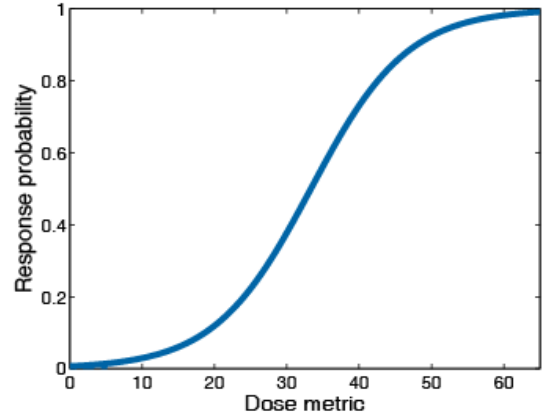


EUD

V_x

D_{mean}





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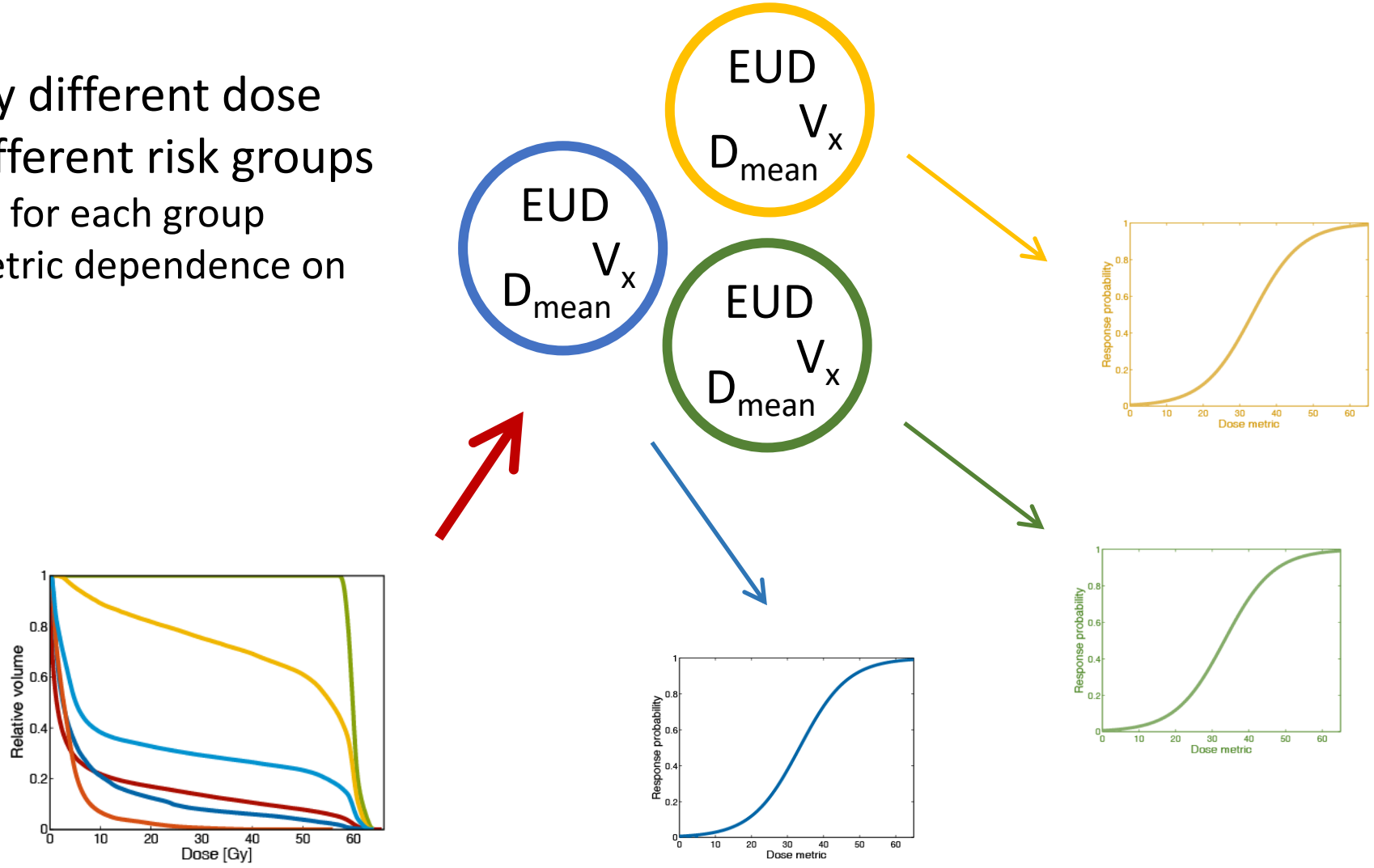
Modelling including clinical factors

Assume completely different dose dependence for different risk groups

- Fit separate models for each group
- Or specify a parametric dependence on clinical factors



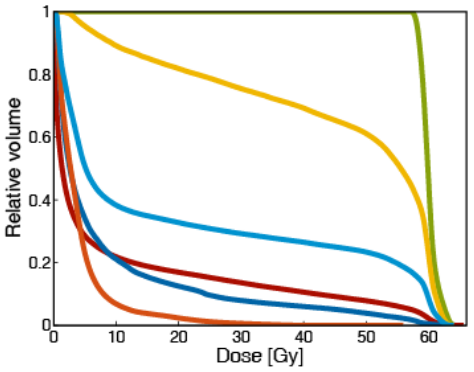
Modelling including clinical factors

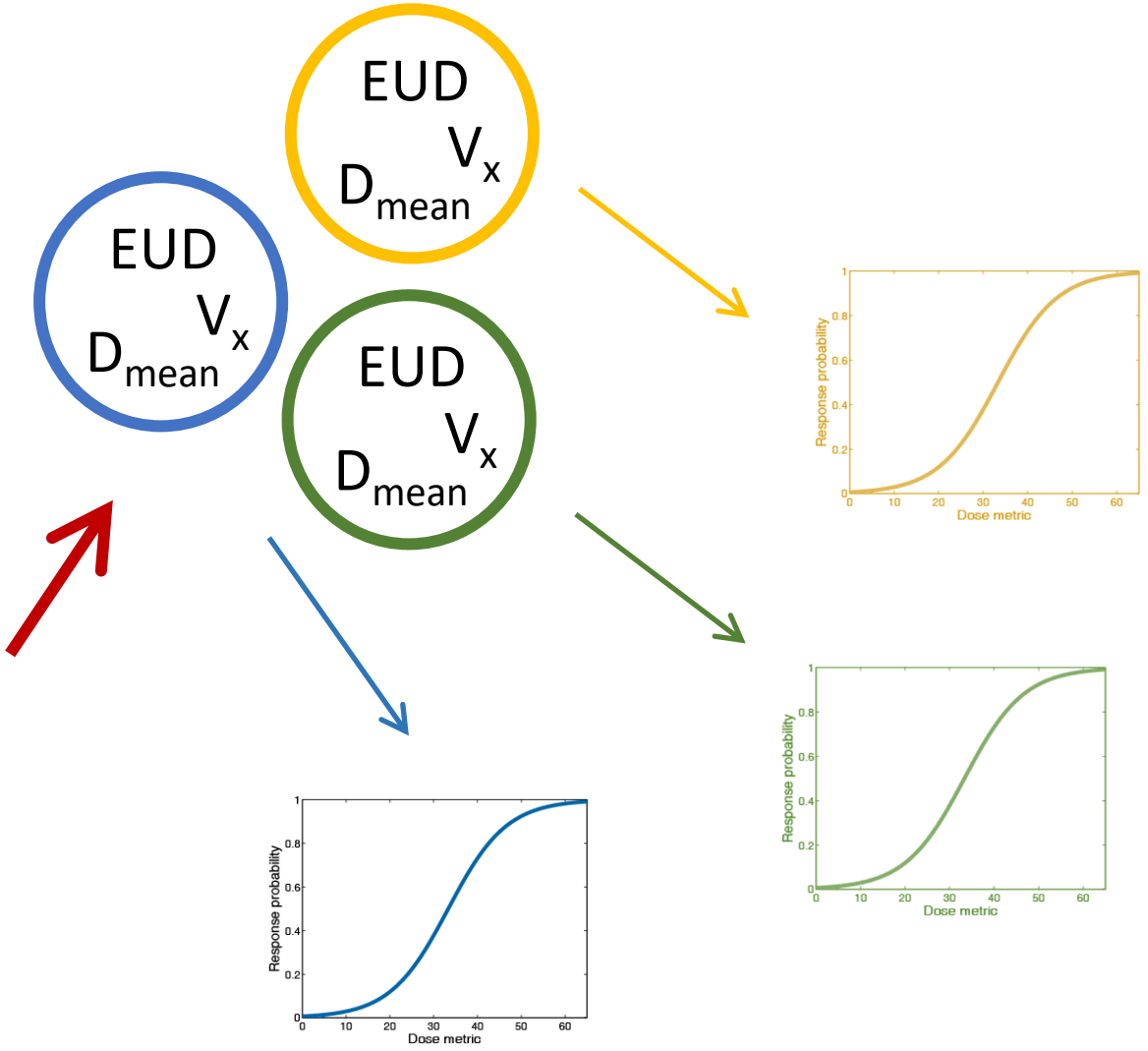
Advantage:

May help to understand underlying differences in pathophysiology

Limitations

- Potential lack of power
- Depends on discrete clinical groups (no continuous factors)





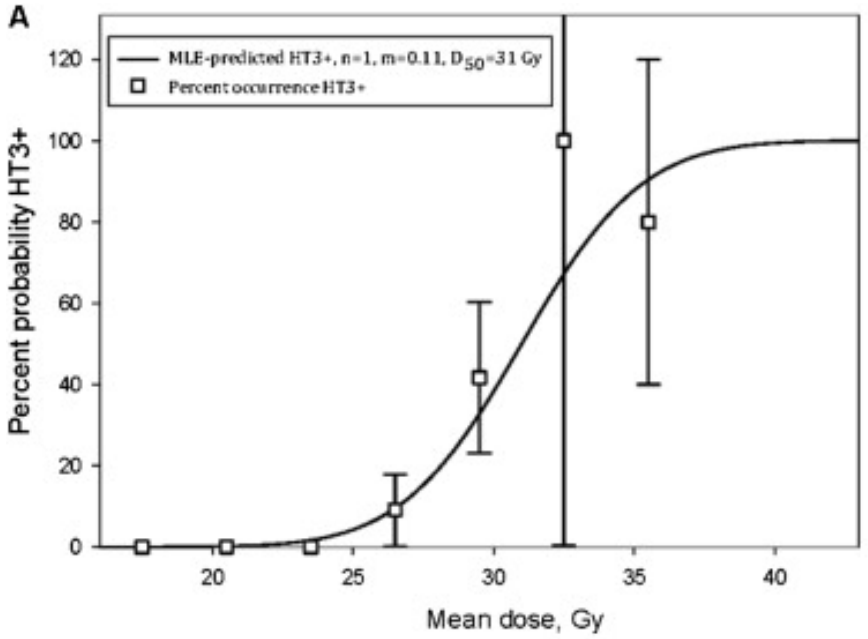
Good robustness check of models

Example: Hematological toxicity during pelvic IMRT

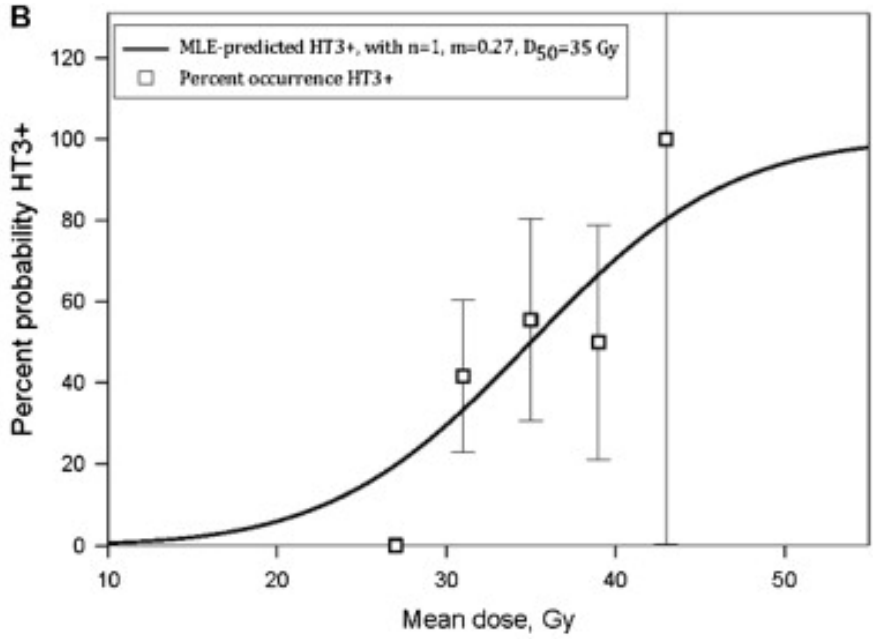
Bazan et al. *Impact of Chemotherapy on Normal Tissue Complication Probability Models of Acute Hematologic Toxicity in Patients Receiving Pelvic Intensity Modulated Radiation Therapy.* IJROBP, 2013

Pelvic bone marrow dose related to acute toxicity using LKB model

Mitomycin + 5FU

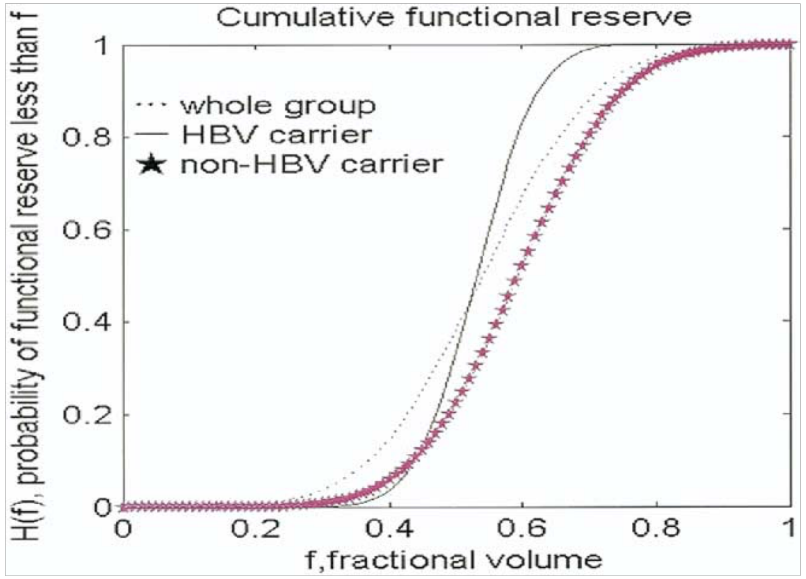


Cisplatin



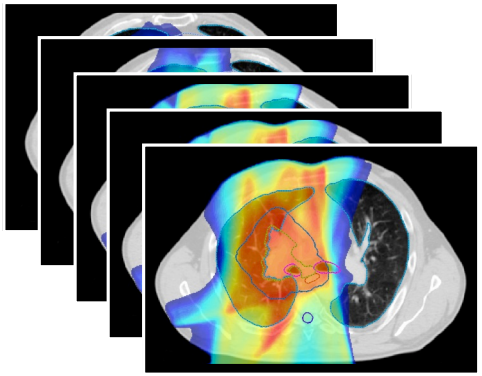
Example: Radiation induced liver disease

Cheng et al. *Inclusion of biological factors in parallel-architecture normal-tissue complication probability model for radiation-induced liver disease.* IJROBP, 2005



Best estimate of parameter (95% confidence interval)	v_{50}	σ	D_{50}	k
Whole group (151 patients)	0.54 (0.51–0.58)	0.14 (0.11–0.16)	50 Gy (24–110)	0.18 (0.11–0.27)
HBV carriers (76 patients)	0.53 (0.51–0.55)	0.073 (0.05–0.15)	50 Gy (0–>100)	4.56×10^{-7} (<0–0.06)
Non-HBV carriers (75 patients)	0.59 (0.52–0.63)	0.12 (0.08–0.13)	25 Gy (21–29)	59.8 (1–>100)

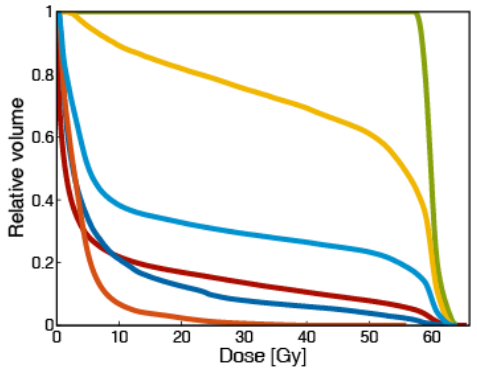
Modelling including clinical factors

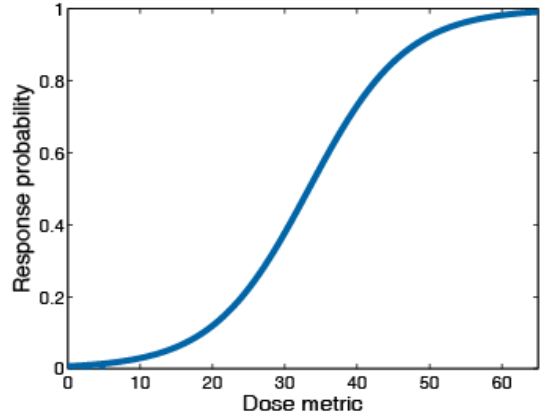


EUD

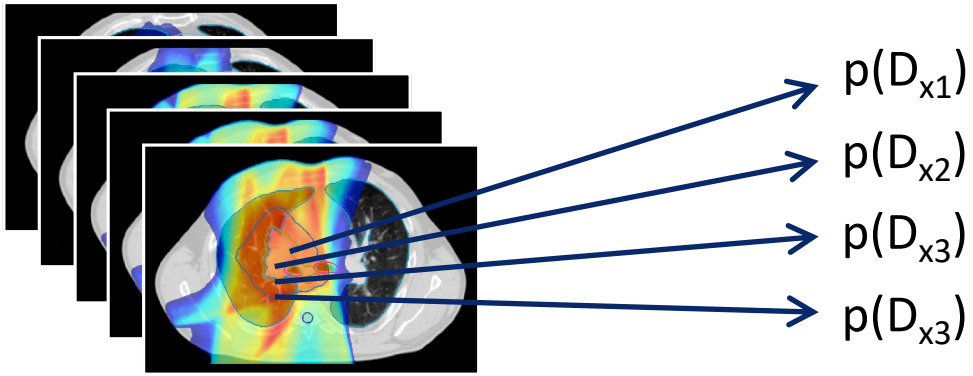
V_x

D_{mean}





Modelling including clinical factors

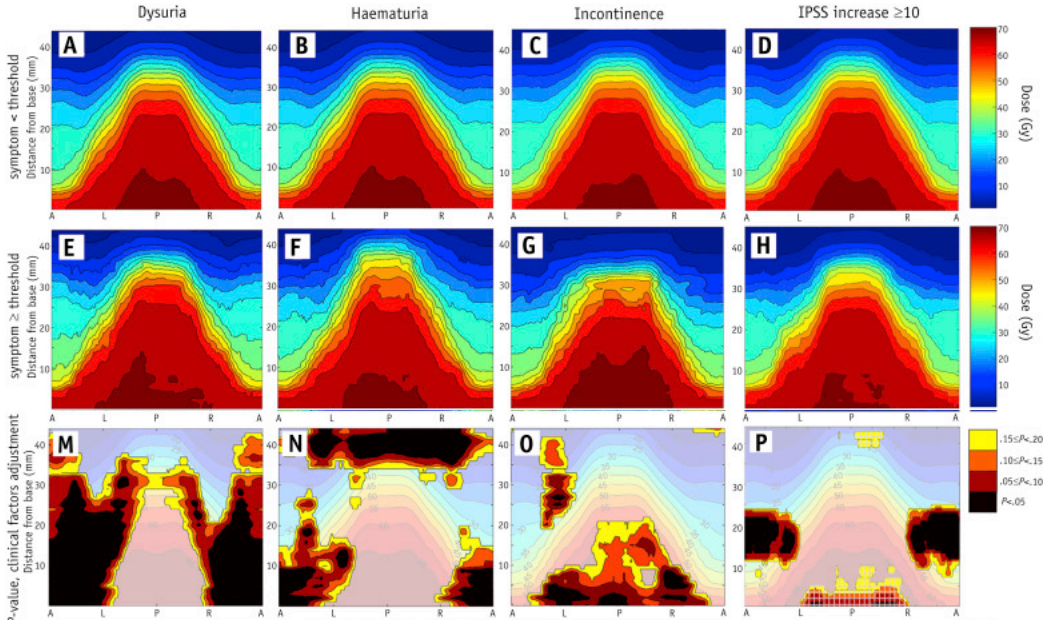


Local dose-response function
=> Determine spatial distribution of dose-dependence

Local
- Dose

Patient-level
- Response / outcome
- Clinical factors

Yahya et al. *Modeling Urinary Dysfunction After External Beam Radiation Therapy of the Prostate Using Bladder Dose-Surface Maps: Evidence of Spatially Variable Response of the Bladder Surface*. IJROBP 2017

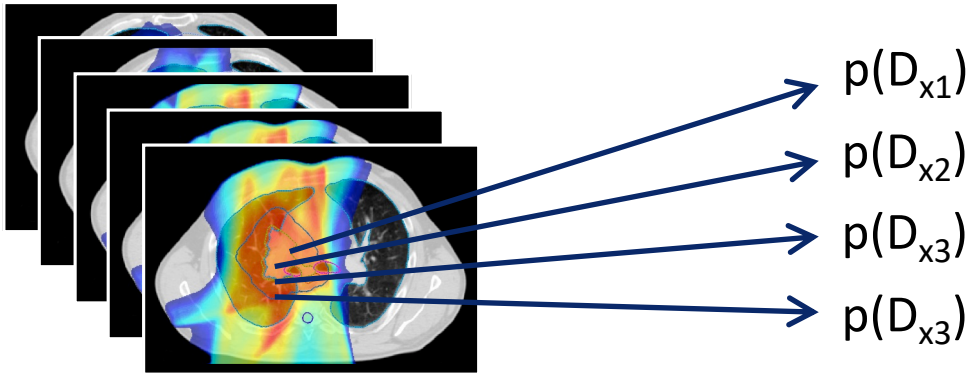


Dose map without symptoms

Dose map with symptoms

Significance map with multivariate modelling

Modelling including clinical factors



Local dose-response function
=> Determine spatial distribution of dose-dependence

Local
- Dose
- Response

Patient-level
- Clinical factors

Radiotherapy and Oncology 109 (2013) 89–94

Contents lists available at ScienceDirect

Radiotherapy and Oncology

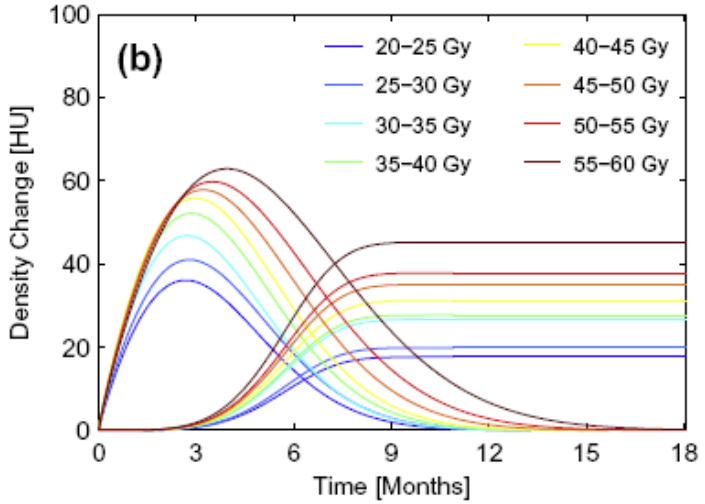
journal homepage: www.thegreenjournal.com

Imaging of late effects in lung cancer

Time evolution of regional CT density changes in normal lung after IMRT for NSCLC

Uffe Bernchou [a,b,*], Tine Schytte [a,c], Anders Bertelsen [b], Søren M. Bentzen [d], Olfred Hansen [a,c], Carsten Brink [a,b]

[a] Institute of Clinical Research, University of Southern Denmark, Odense, Denmark; [b] Laboratory of Radiation Physics; [c] Department of Oncology, Odense University Hospital, Denmark; [d] Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, WI, USA



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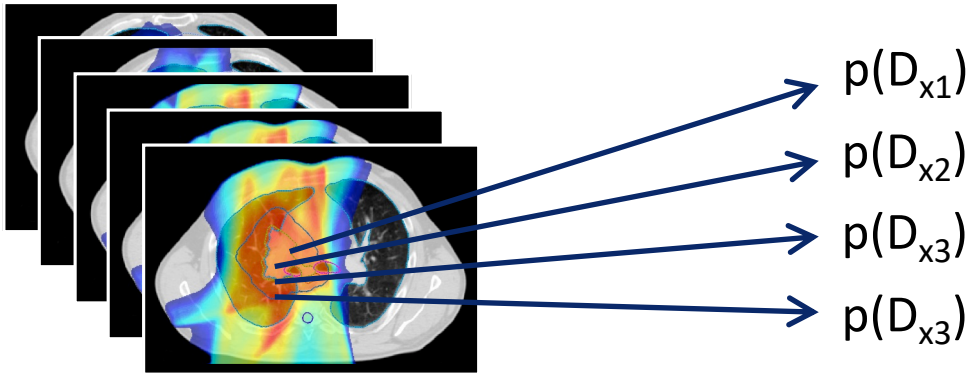
Modelling including clinical factors

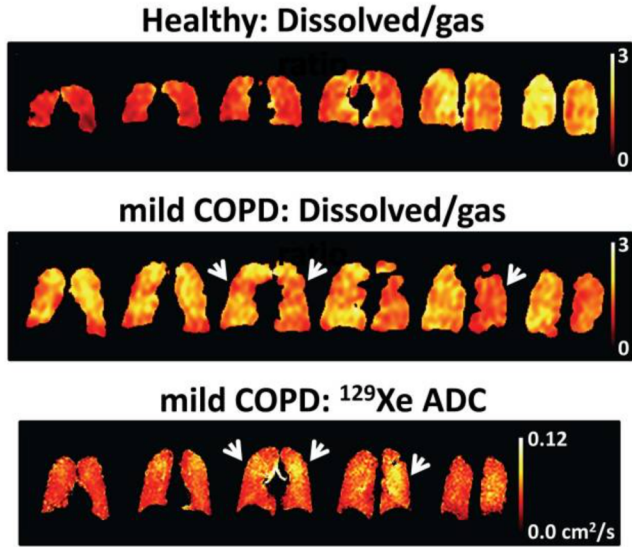


Local dose-response function
=> Determine spatial distribution of dose-dependence

Local
- Dose
- Response
- "Clinical factor"

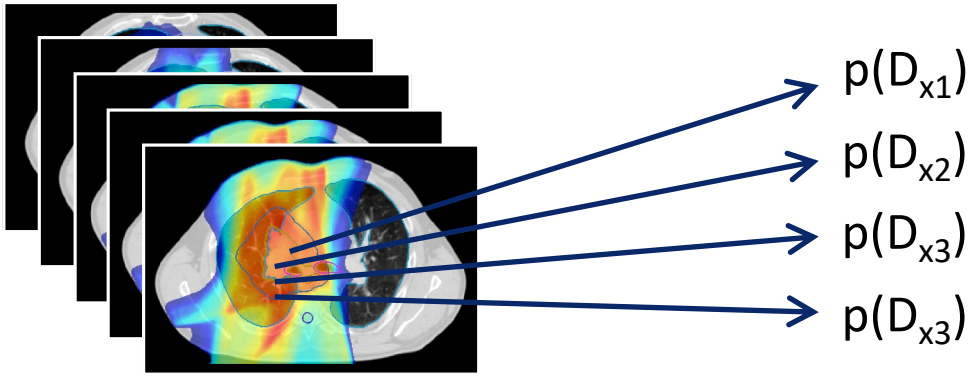
Patient-level
- Clinical factors

Functional imaging



Mugler et al. Hyperpolarized 129Xe MRI of the human lung. J Magn Reson Imaging, 2013

Modelling including clinical factors

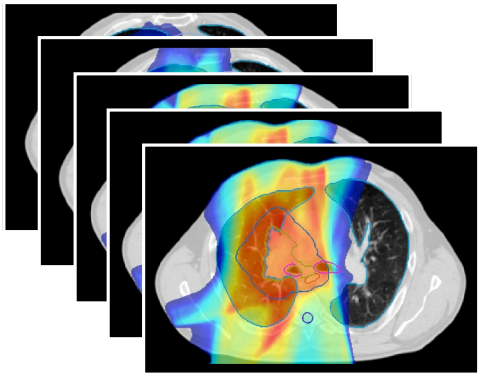


Local dose-response function
=> Determine spatial distribution of dose-dependence

Significant challenges surrounding within- and between patient variation & multiple testing

- Bowen et al. Spatially resolved regression analysis of pre-treatment FDG, FLT and Cu-ATSM PET from post-treatment FDG PET: an exploratory study. Radiother Oncol 2012
- WE-AB-KDBRC-6: Variogram-Weighted Generalized Least Squares Regression to Predict Spatially Variant Tumor Voxel Response On Longitudinal FDG-PET/CT Imaging of FLARE-RT Protocol Patients
- Chen et al. Multiple comparisons permutation test for image based data mining in radiotherapy. Radiat Oncol 2013

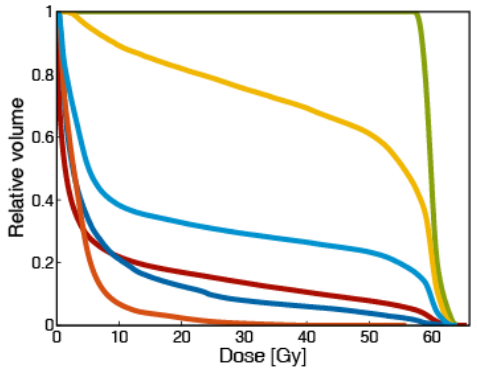
How do we handle larger numbers of risk factors?

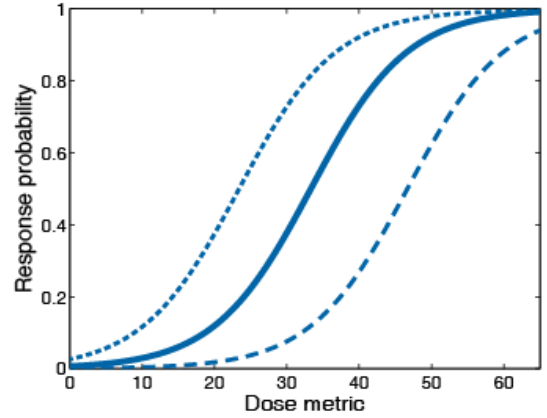


EUD

V_x

D_{mean}





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Estimating the effect of multiple risk factors on dose-response relationships

Example: Radiation pneumonitis

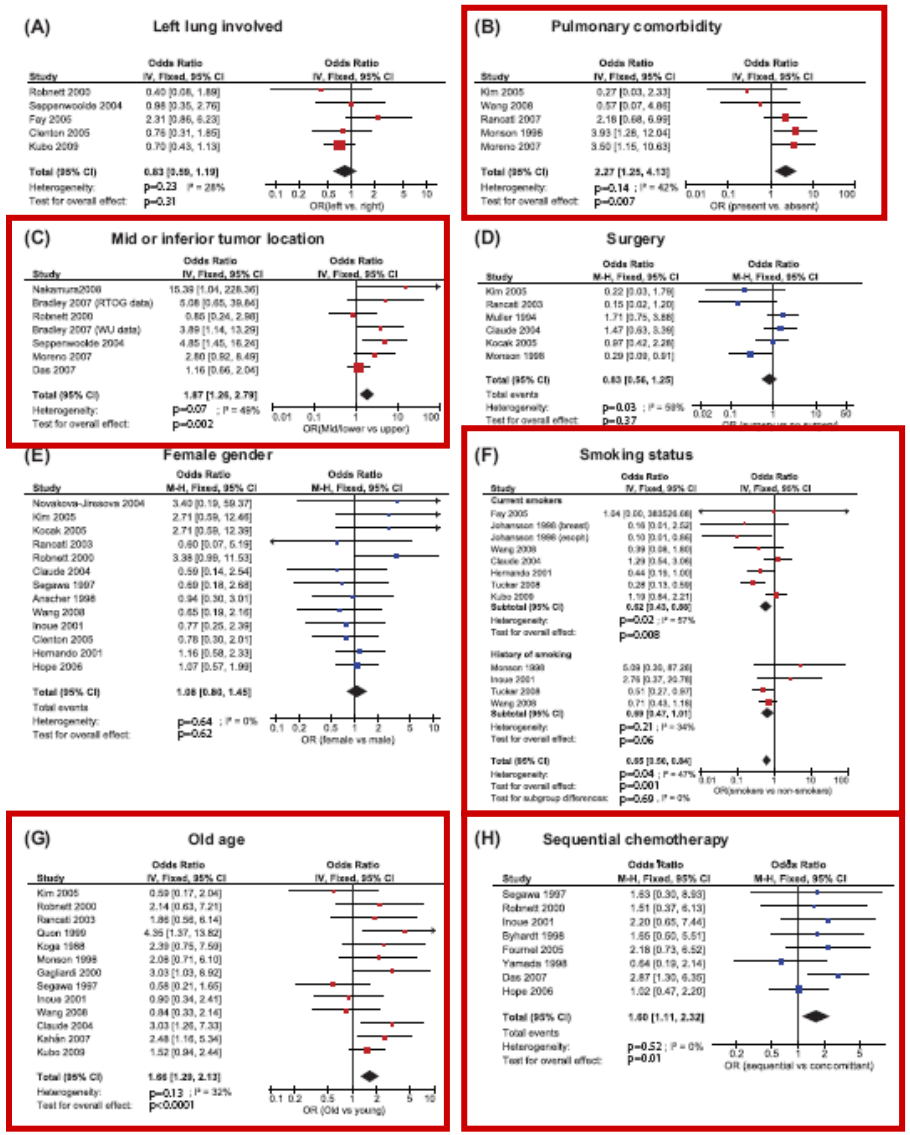
Acta Oncologica, 2012; 51: 975–983

REVIEW ARTICLE

A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis

IVAN R. VOGELIUS[1,2] & SØREN M. BENTZEN[3]

[1]*Department of Radiation Oncology, Rigshospitalet, University of Copenhagen, Denmark,* [2]*Department of Oncology, Vejle Sygehus, Vejle, Denmark, and* [3]*Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA*



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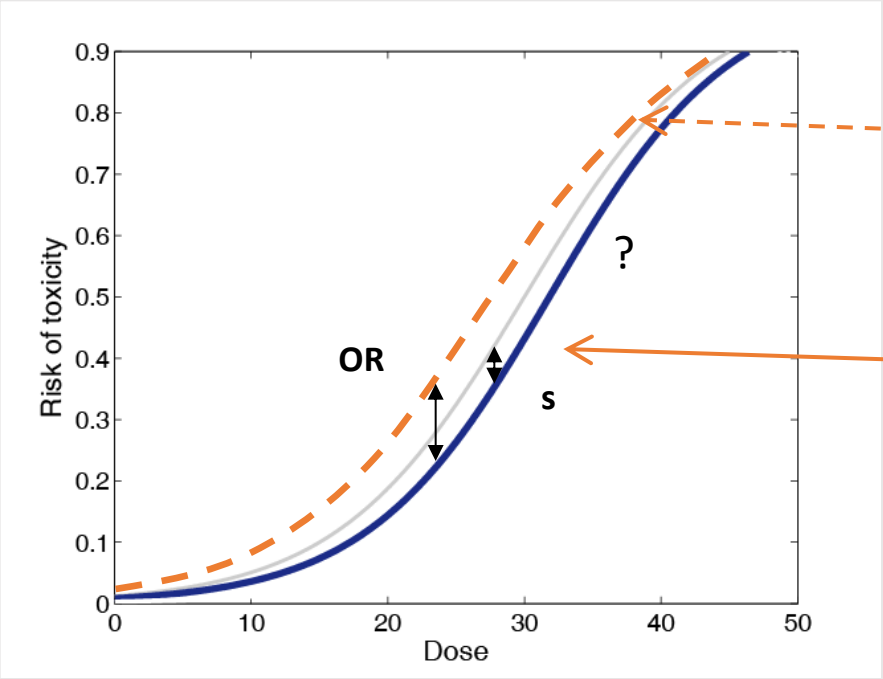
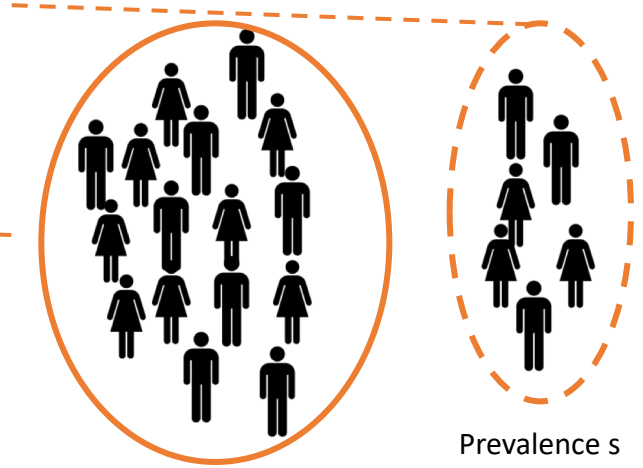
Estimating the effect of multiple risk factors on dose-response relationships

- Multivariate analysis of both dose and risk factors in full patient data sets
  - LARGE number of patients
- Alternative:
  Meta-analysis of already existing studies
  - Combine dose-response relationships with clinical risk factors as found in meta-analysis

Adjusting radiation dose–response relationships for clinical risk factors



Assume a fraction s of the patients had a risk factor with odds ratio OR.

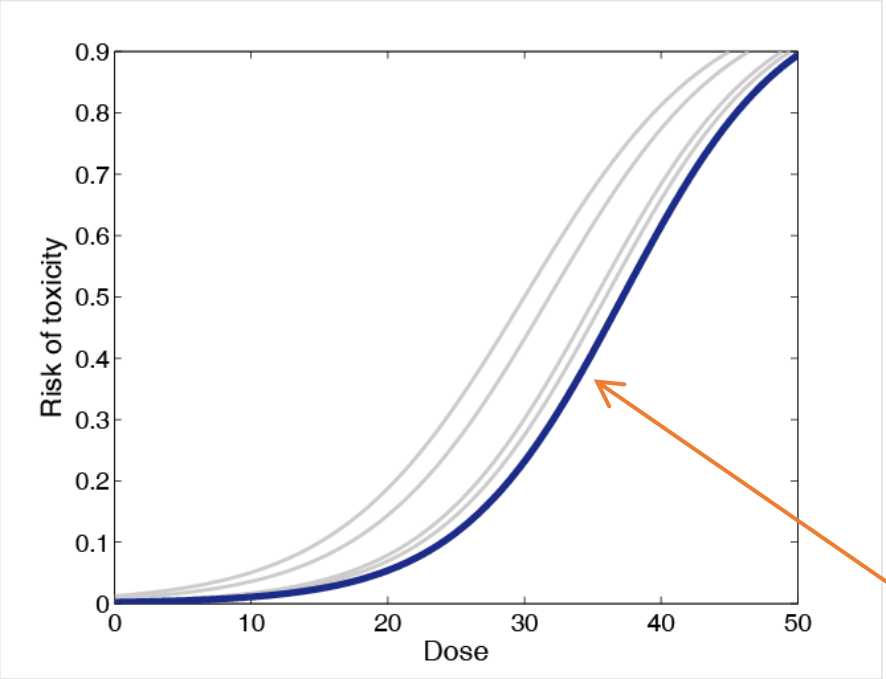


Prevalence s

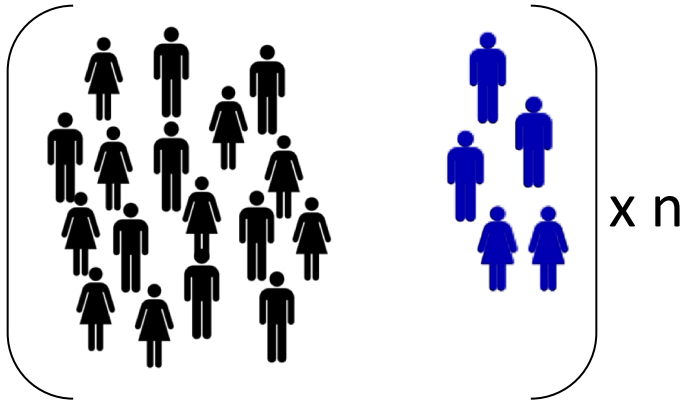
$$NTCP_{adjusted}(D) = \frac{1}{1+\exp\left(4\gamma_{50}^{0}\left(1-\frac{D}{D_{50}^{0}}\right)\right)}$$

Appelt & Vogelius. "A method to adjust radiation dose–response relationships for clinical risk factors", Radiother Oncol 2012;102:352–354

Adjusting radiation dose–response relationships for clinical risk factors



Estimate dose-response for patients without risk factor:



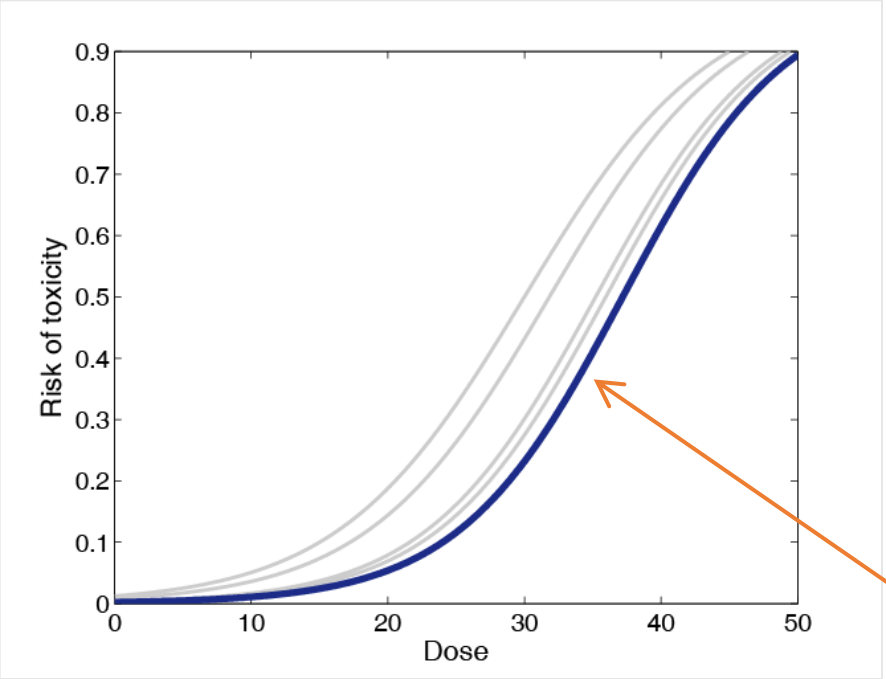
x n

$\Rightarrow$ $OR_{risk\ factor\ 1}$

”Baseline” dose-response relationship,
for patients without any of the risk factors
Assuming:
No correlation between risk factors

Appelt & Vogelius. ”A method to adjust radiation dose–response relationships for clinical risk factors”, Radiother Oncol 2012;102:352–354

Adjusting radiation dose–response relationships for clinical risk factors



Assume a fraction s of the patients had a risk factor with odds ratio OR. Estimate dose-response for patients without risk factor:

$$\left(\begin{array}{c} \mathbf{P} = \frac{1}{2}\left(1 + s\frac{OR-1}{OR+1}\right) \\ D_{50}^{0} = \left(1 + \frac{1}{4}\frac{\ln(\frac{\mathbf{P}}{1-\mathbf{P}})}{\gamma_{50}}\right) D_{50} \\ \gamma_{50}^{0} = \frac{s\mathbf{P}(1-\mathbf{P})}{s-(2\mathbf{P}-1)^2}\left(\ln(\frac{\mathbf{P}}{1-\mathbf{P}}) + 4\gamma_{50}\right) \end{array} \right) \quad \text{x n}$$

$\Rightarrow$

”Baseline” dose-response relationship,

for patients without any of the risk factors

Assuming:

No correlation between risk factors

$$NTCP_{adjusted}(D) = \frac{1}{1+\exp\left(4\gamma_{50}^{0}\left(1-\frac{D}{D_{50}^{0}}\right)\right)}$$

Appelt & Vogelius. ”A method to adjust radiation dose–response relationships for clinical risk factors”, Radiother Oncol 2012;102:352–354

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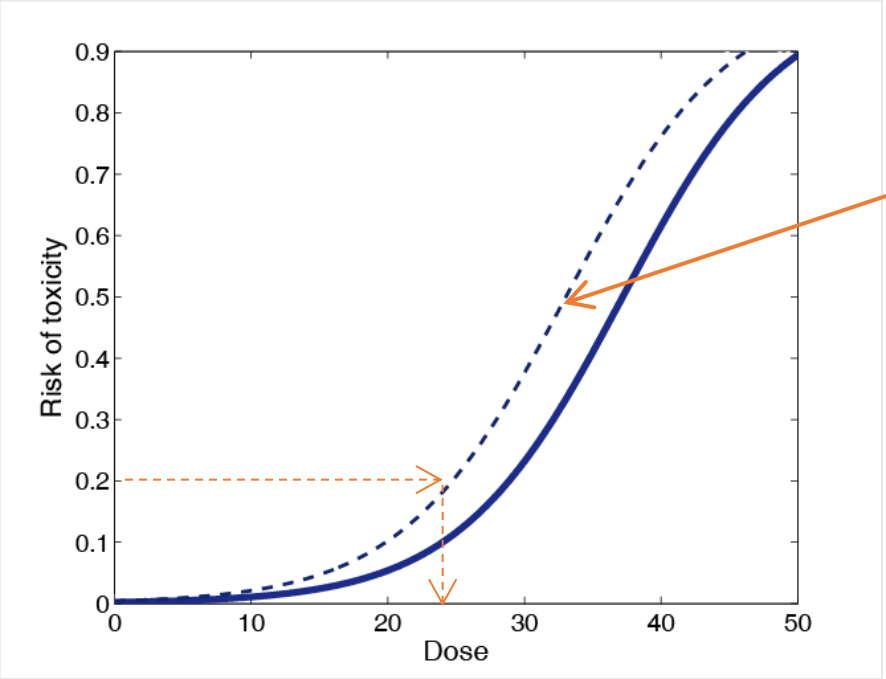
Adjusting radiation dose–response relationships for clinical risk factors



Dose-response for patient with specific set of risk factors

$$D_{50}^{risk} = D_{50}^{0}\left(1-\frac{1}{4\gamma_{50}^{0}}\ln OR_{combined}\right)$$

$$\gamma_{50}^{risk} = \gamma_{50}^{0}-\frac{1}{4}\ln OR_{combined}$$

$OR_{combined} = OR_{risk\ factor\ 1} * OR_{risk\ factor\ 2} * \ldots$

Appelt & Vogelius. ”A method to adjust radiation dose–response relationships for clinical risk factors”, Radiother Oncol 2012;102:352–354

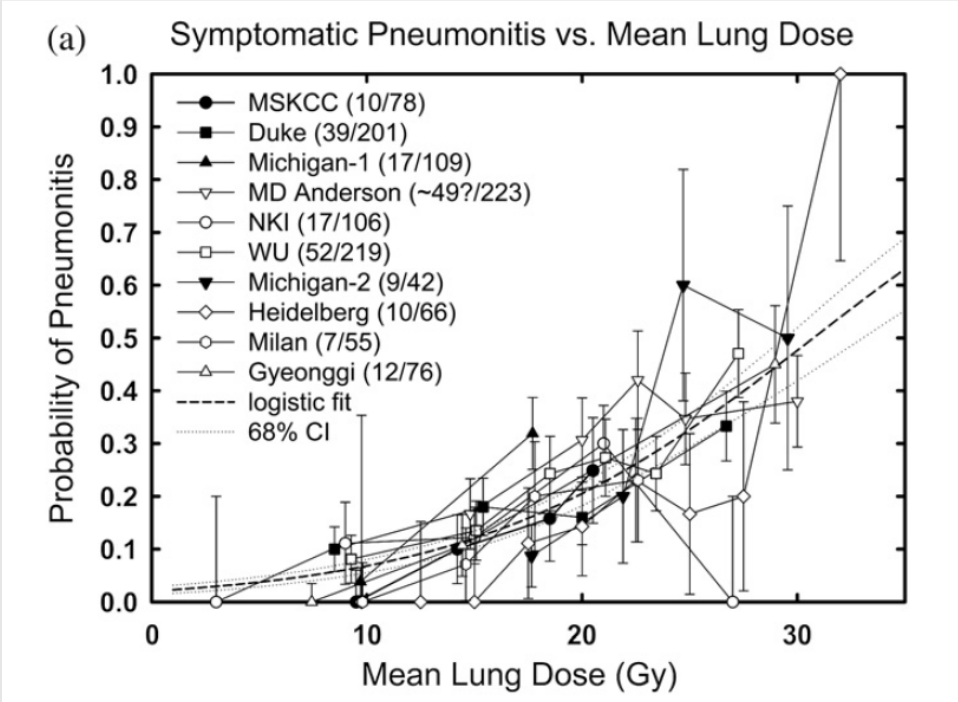
Adjusting radiation dose–response relationships for clinical risk factors

- To use this method, we need
  - A dose-response relationship for an organ at risk
  - A set of risk factors + estimated ORs
  - The prevalence of the risk factors in the patient population that provided the dose-response relationship

Dose-response for radiation pneumonitis

RADIATION DOSE–VOLUME EFFECTS IN THE LUNG

LAWRENCE B. MARKS, M.D.,* SOREN M. BENTZEN, D.SC.,† JOSEPH O. DEASY, PH.D.,‡
FENG-MING (SPRING) KONG, M.D., PH.D.,§ JEFFREY D. BRADLEY, M.D.,‡ IVAN S. VOGELIUS, PH.D.,†
ISSAM EL NAQA, PH.D.,‡ JESSICA L. HUBBS, M.S.,* JOOS V. LEBESQUE, M.D., PH.D.,‖
ROBERT D. TIMMERMAN, M.D.,¶ MARY K. MARTEL, PH.D.,# AND ANDREW JACKSON, PH.D.**



D_{50} = 30.8 Gy (95% CI: 28.7, 33.9)

γ_{50} = 0.97 (95% CI: 0.83, 1.12) .

Risk factors for radiation pneumonitis

REVIEW ARTICLE

A literature-based meta-analysis of clinical risk factors for development of radiation induced pneumonitis

IVAN R. VOGELIUS[1,2] & SØREN M. BENTZEN[3]

[1]*Department of Radiation Oncology, Rigshospitalet, University of Copenhagen, Denmark,* [2]*Department of Oncology, Vejle Sygehus, Vejle, Denmark, and* [3]*Department of Human Oncology, University of Wisconsin School of Medicine and Public Health, Madison, Wisconsin, USA*

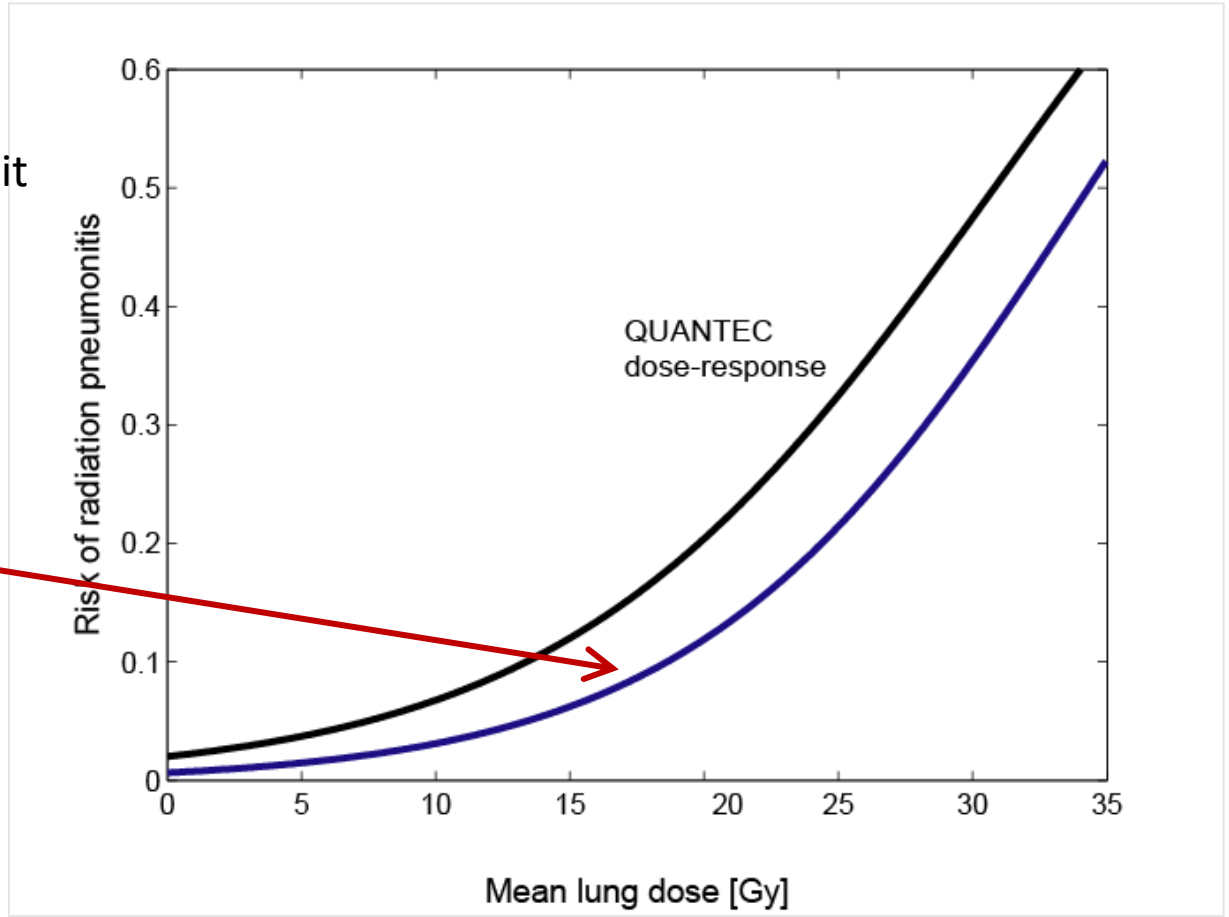
Clinical risk factor		Prevalence in QUANTEC studies
Pre-existing pulmonary co-morbidity	↑	0.258
Mid or inferior tumour location	↑	0.444
Current smoker	↓	0.283
Former smoker	↓	0.663
Old age	↑	0.5
Sequential chemotherapy	↑	0.258

”Baseline” dose-response for radiation pneumonitis

- No pulmonary co-morbidities
- Tumour in the upper lobe
- No history of smoking or current smoking habit
- <63 years old
- Not treated with sequential chemotherapy

D_{50} = 34.4 Gy (95% CI: 30.7, 38.9)

γ_{50} = 1.19 (95% CI: 1.00, 1.43)



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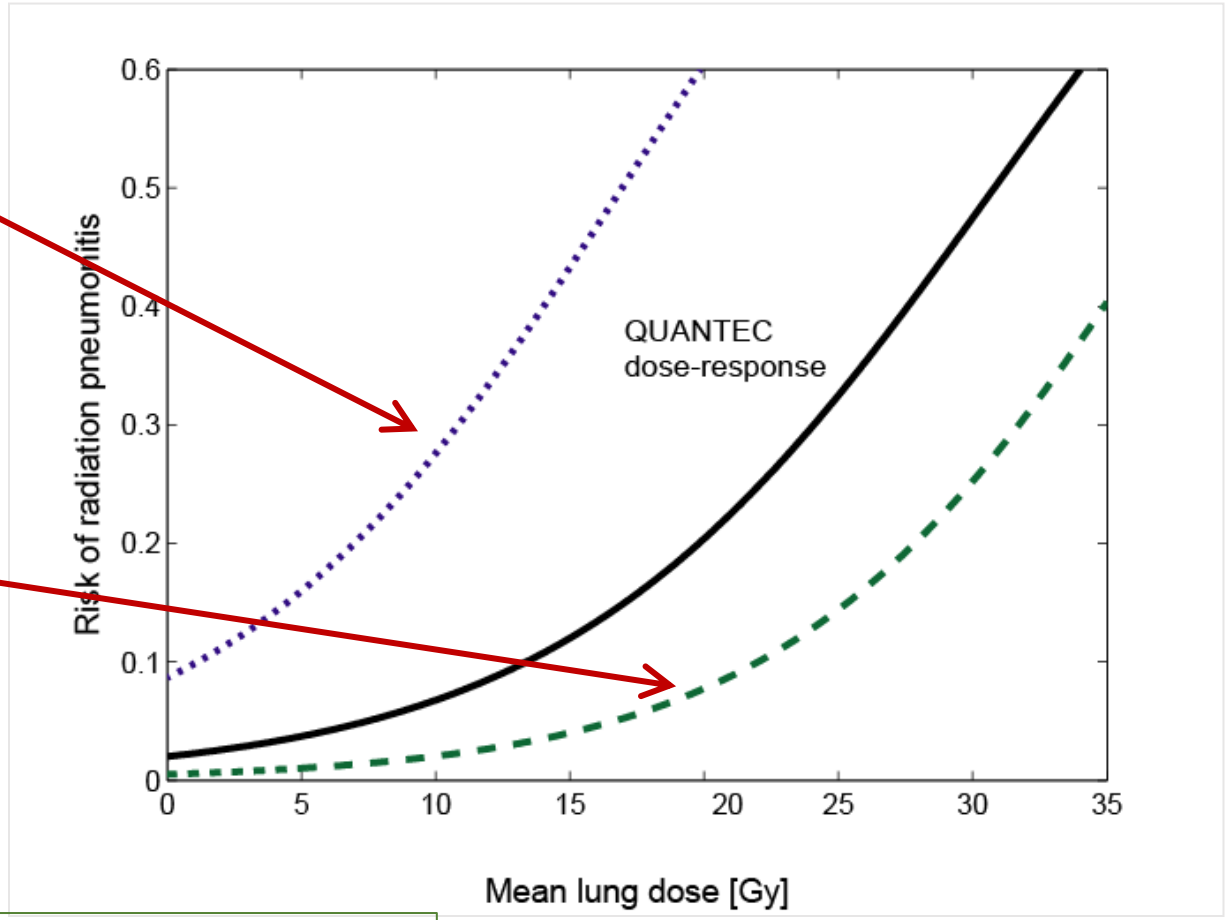
Appelt et al. Acta Oncol 2014

Individualized dose-response for radiation pneumonitis (iQUANTEC)

Smoker, no risk factors

Patient with highest risk:

- Pulmonary co-morbidities
- Tumour in the middle/lower
- No history of smoking or current smoking habit
- >63 years old
- Sequential chemotherapy



Corresponding individualised dose constraints

Appelt et al. Acta Oncol 2014

Using the iQUANTEC model to design clinical proton therapy trials

- Estimate (distribution of) predicted benefit of new technology in representative patient cohort
- Design phase III trial using this estimate - rather than a single effect estimate for all patients
- Use phase III trial to test & validate the NTCP model
  - Misspecified model can be detected
- Feed phase III result into estimate of benefit for future individual patients

- Examplar:
  Randomised phase III trial of proton vs photon treatment for locally advanced NSCLC
  - Simulate output of large number of trials
  - Reduction in sample size of at least 20%
  - Trial result will allow for estimate of individual patient benefit

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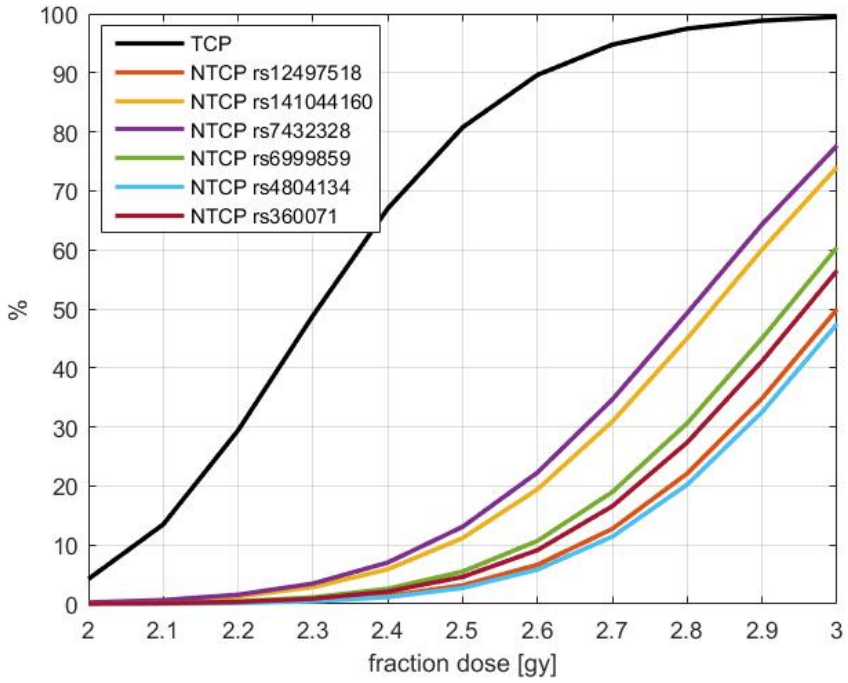
Rydhög, Appelt, et al. Submitted for publication

Individualised NTCP to assess benefit from new technology

- *"Development of an isotoxic decision support system integrating genetic markers of toxicity for the implantation of a rectum spacer"* van Milk et al. Acta Oncol 2018

- Combine
  - QUANTEC model for late rectal toxicity
  - Genetic markers (SNPs) for radiosensitivity identified in meta analysis

- Use image deformation to simulate rectal spacer implantation, and assess individual benefit in treatment planning



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Summary

- Clinical factors can be taken into account on several levels when conducting bioeffect (TCP/NTCP) modelling
- Most common approach: Inclusion alongside dose metrics
  - In this case, standard GLM regression framework can be used
  - Note challenges of estimating CIs / significance levels if also optimising dose metric representation
  - Additive factors (OR in logistic regression):
    First order factors
    Multiplicative factors ("dose modifying factors"):
    Second order factors / interaction effects
- Increasing number of publications examining local dose effects, including clinical factors, but methodology is not standardized
- Consider meta analysis approaches
- Planning prospective studies
  - Consider integrating TCP/NTCP model to be prospectively validated