Models to estimate the risk of normal-tissue complications after radiotherapy

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TETRIS webinar, 22 January 2026

This lecture

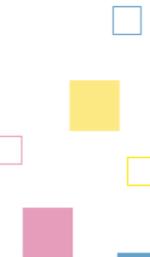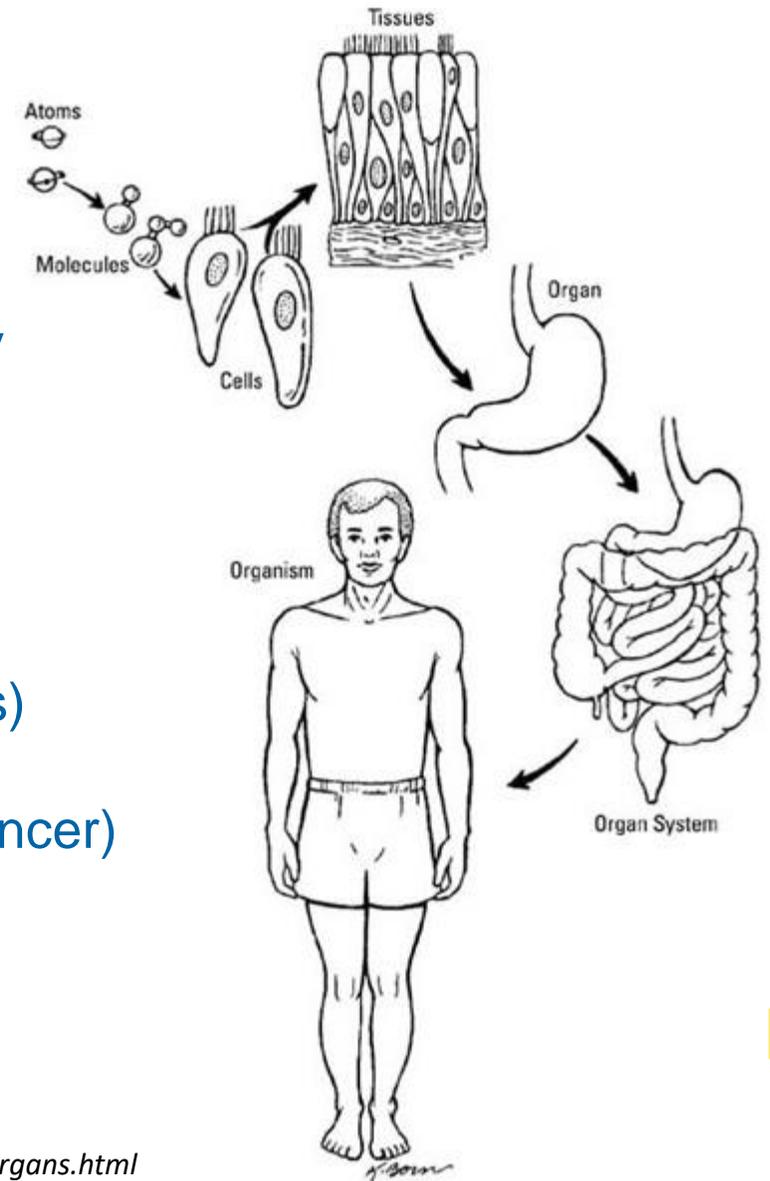- Basics of predictive models in radiotherapy

- The role of predictive models in the TETRIS project
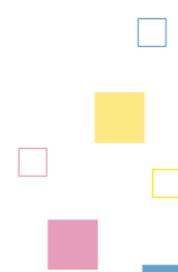
- Model performance metrics

Radiotherapy side effects

- Tumour cell death the primary effect of radiation

- Beams passing through normal tissues/organs, may result in loss of function

- Symptoms are typically on organ level

- Clinician-reported scales of side effects:
  - CTCAE (Common Terminology Criteria for Adverse Events)
  - RTOG (Radiation Therapy Oncology Group) / EORTC (European Organisation of Research and Treatment of Cancer)
  - LENT-SOMA (Late Effects of Normal Tissues: Subjective, Objective, Management, Analytic)

- Patient-reported outcome

http://www.dummies.com/how-to/content/building-the-body-from-atoms-to-organs.html

CARDIAC GENERAL

Adverse Event	Short Name	Grade				
		1	2	3	4	5
NAVIGATION NOTE: Angina is graded as Cardiac ischemia/infarction in the CARDIAC GENERAL CATEGORY.						
Cardiac ischemia/infarction	Cardiac ischemia/infarction	Asymptomatic arterial narrowing without ischemia	Asymptomatic and testing suggesting ischemia; stable angina	Symptomatic and testing consistent with ischemia; unstable angina; intervention indicated	Acute myocardial infarction	Death
Cardiac troponin I (cTnI)	cTnI	—	—	Levels consistent with unstable angina as defined by the manufacturer	Levels consistent with myocardial infarction as defined by the manufacturer	Death
Cardiac troponin T (cTnT)	cTnT	0.03 – <0.05 ng/mL	0.05 – <0.1 ng/mL	0.1 – <0.2 ng/mL	0.2 ng/mL	Death
Cardiopulmonary arrest, cause unknown (non-fatal)	Cardiopulmonary arrest	—	—	—	Life-threatening	—
REMARK: Grade 4 (non-fatal) is the only appropriate grade. CTCAE provides three alternatives for reporting Death: 1. A CTCAE term associated with Grade 5. 2. A CTCAE 'Other (Specify, __)' within any CATEGORY. 3. Death not associated with CTCAE term – *Select* in the DEATH CATEGORY.						
NAVIGATION NOTE: Chest pain (non-cardiac and non-pleuritic) is graded as Pain – *Select* in the PAIN CATEGORY.						
NAVIGATION NOTE: CNS ischemia is graded as CNS cerebrovascular ischemia in the NEUROLOGY CATEGORY.						
Hypertension	Hypertension	Asymptomatic, transient (<24 hrs) increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; intervention not indicated Pediatric: Asymptomatic, transient (<24 hrs) BP increase >ULN; intervention not indicated	Recurrent or persistent (≥24 hrs) or symptomatic increase by >20 mmHg (diastolic) or to >150/100 if previously WNL; monotherapy may be indicated Pediatric: Recurrent or persistent (≥24 hrs) BP >ULN; monotherapy may be indicated	Requiring more than one drug or more intensive therapy than previously Pediatric: Same as adult	Life-threatening consequences (e.g., hypertensive crisis) Pediatric: Same as adult	Death
REMARK: Use age and gender-appropriate normal values >95th percentile ULN for pediatric patients.						

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This project has received funding under Euratom Research and Training Programme (EURATOM) Grant ID 101166699

TETRIS – Risk assessment tools for severe side effects after breast radiotherapy: radiation safety through biological extended models and digital twins
EU Grant Agreement n. 101166699

Side-effect outcome measures

- Scale not continuous – all steps may not be comparable in effect

- Typically binary outcome, e.g. grade ≥2 brachial plexopathy (figure)

- Logistic regression a natural choice for modelling the *normal-tissue complication probability* (NTCP)

- Evaluated at a given time (e.g. 2 years after RT), or highest recorded grade over time
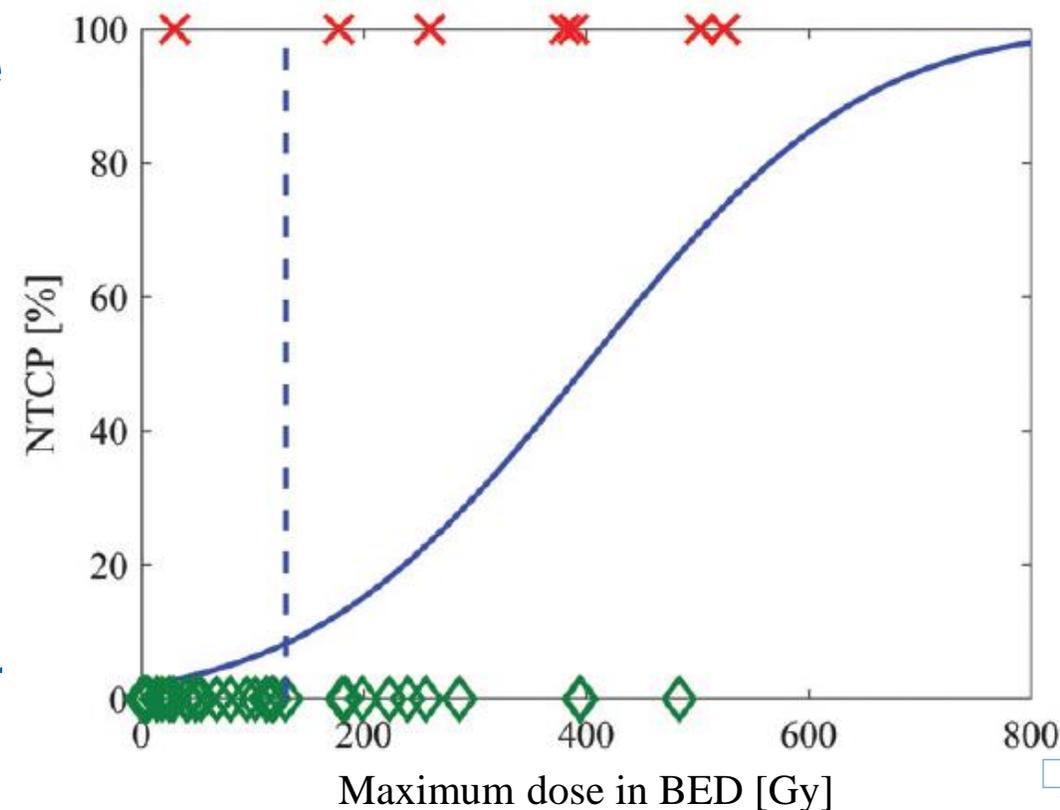
Lindberg et al.. Acta Oncol 2019;58(8):1178-1186

The logistic regression model

- Generalised linear model, combining log odds of all predictors

- Dose is a predictor, but also non-dosimetric variables can be integrated

- Simple computation, common in statistical packages

$$NTCP = \frac{1}{1 + e^{-(\beta_0 + \beta_1 x_1 + \beta_2 x_2 + \cdots)}}$$
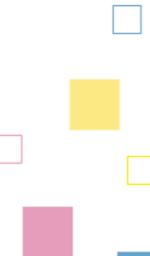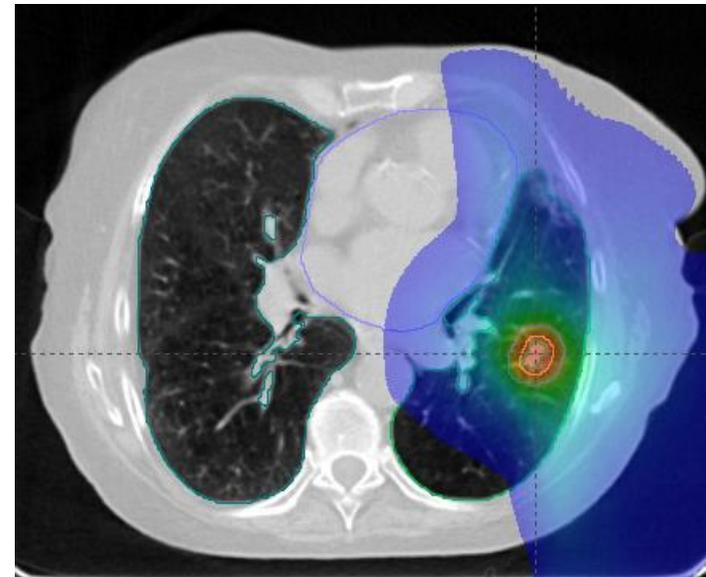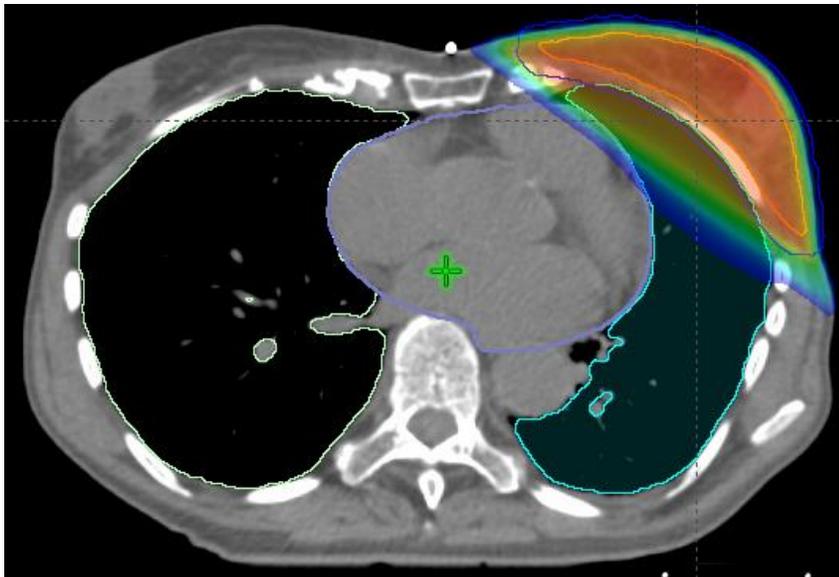
β_0 = intercept

$\beta_{1\text{-}n}$ = coefficients

$x_{1\text{-}n}$ = predictors

Which 'dose' is relevant for normal tissues?

- Modern radiotherapy builds up the target dose through many different beam directions

- Results in a complex 3D dose distribution in the surrounding normal tissue

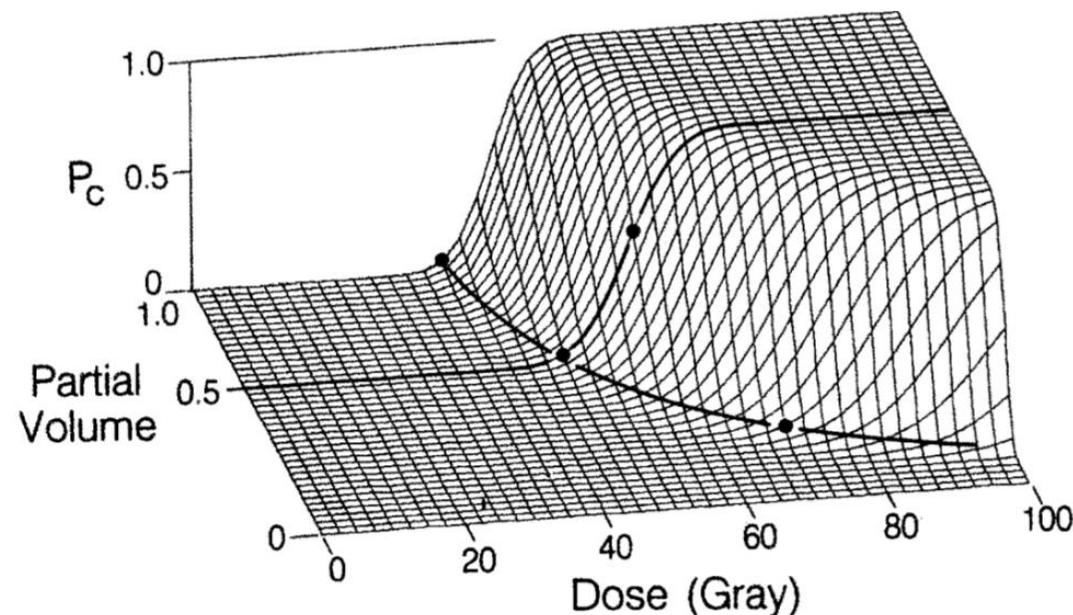- The response depends on the tissue/organ structure and function

Organ response to a 3D dose distribution

Consider partial-organ uniform irradiation:

The organ *volume effect* depends on

- Functional reserve
- Migration of cells
- Stochastic tissue damage
- Inflammatory response

Lyman, J. T. Complication probability as assessed from dose-volume histograms. Radiat Res Suppl, 1985, 8, S13-S19

Dose summary measures

Differential DVHs
— Planning target volume
— Heart

Cumulative DVHs
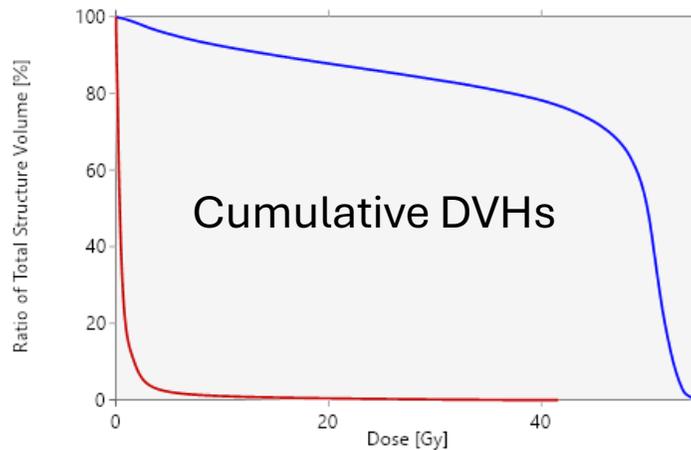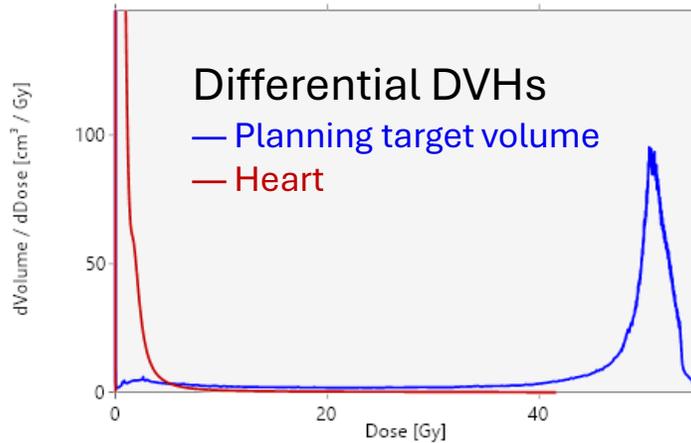
- The 3D dose distribution in an organ can be represented by a dose/volume histogram (DVH)
- The appropriate DVH summary metric depends on the volume effect
- Large volume effect – risk increases with the irradiatied volume
  - Evaluate the mean dose or volume exceeding a threshold dose
- Small volume effect – organ sensitive to high local dose
  - Evaluate the maximum organ dose

Equivalent uniform dose

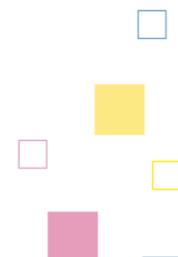The volume effect can be inferred by fitting a summary measure to the data

$$EUD = \sum_i \left(D_i^{\frac{1}{n}} \frac{V_i}{V_{tot}} \right)^n$$

D_i = total dose to bin i
V_i = absolute volume in bin i
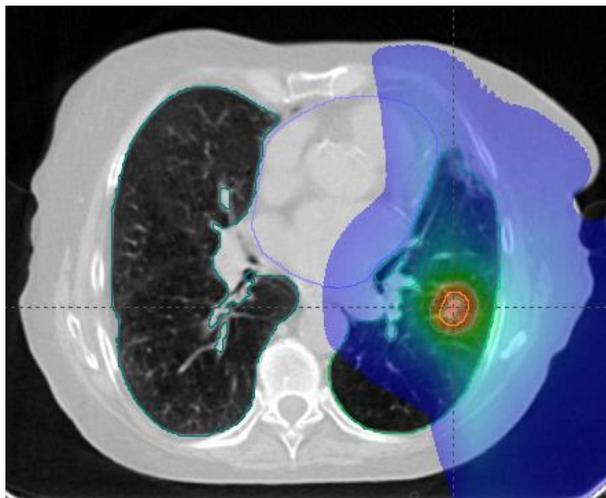V_{tot} = total organ volume
n = volume effect parameter

Parameter 'n' is organ (endpoint) specific

- Low (≈ 0): small volume effect, EUD ≈ max dose

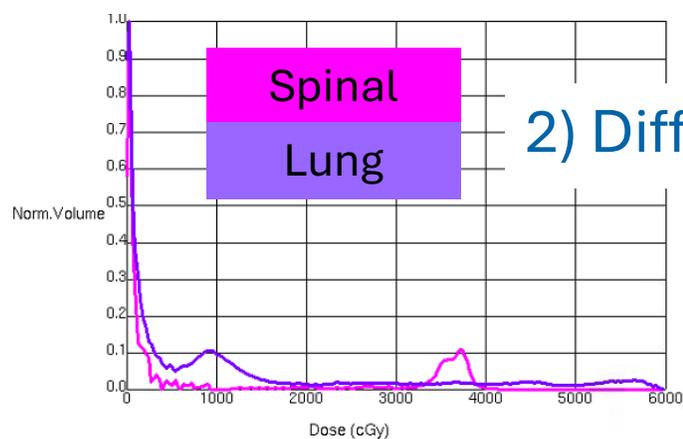- High (= 1): large volume effect, EUD = mean dose

Niemierko 1999 Med. Phys. 26 1100
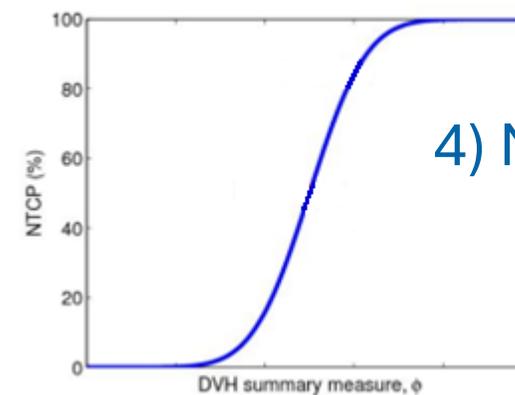
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Summary: from dose to prediction

1) 3D organ dose distribution


2) Differential DVH

3) Summary measure (EUD)

4) NTCP

Fitting an NTCP model to data

ID	Dose (Gy)	Outcome
Patient 1	15	1
Patient 2	21	1
Patient 3	12	0
Patient 4	22	0
Patient 5	25	1
Patient 6	22	1
Patient 7	16	0
Patient 8	28	1
Patient 9	17	0
Patient 10	14	0
Patient 11	8	0
Patient 12	21	0

- Parameter values are fitted to a dataset with the Maximum Likelihood method.

- Maximise the likelihood P of observing **Q** for **NTCP** (calculated for each patient and multiple parameter sets):

$$P = \prod_i NTCP_i^{Q_i}(1 - NTCP_i)^{1-Q_i}$$

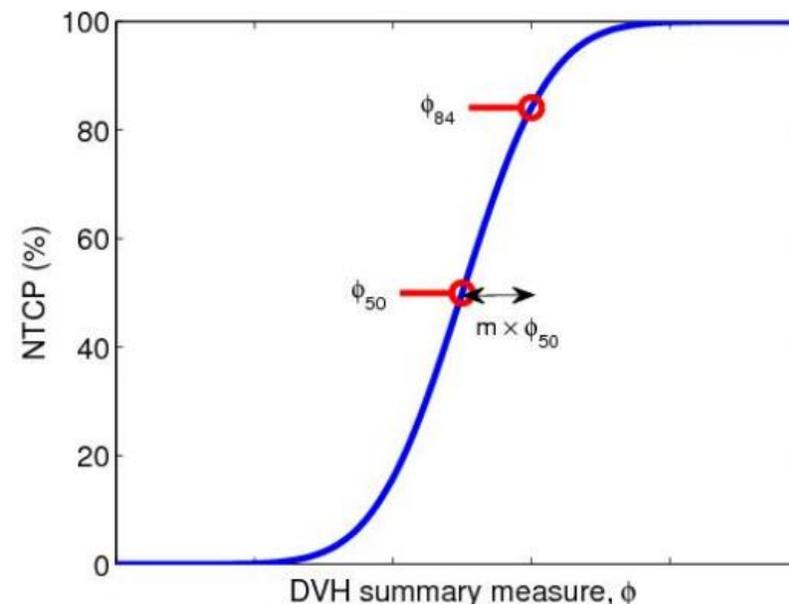Probability, β_0, β_1

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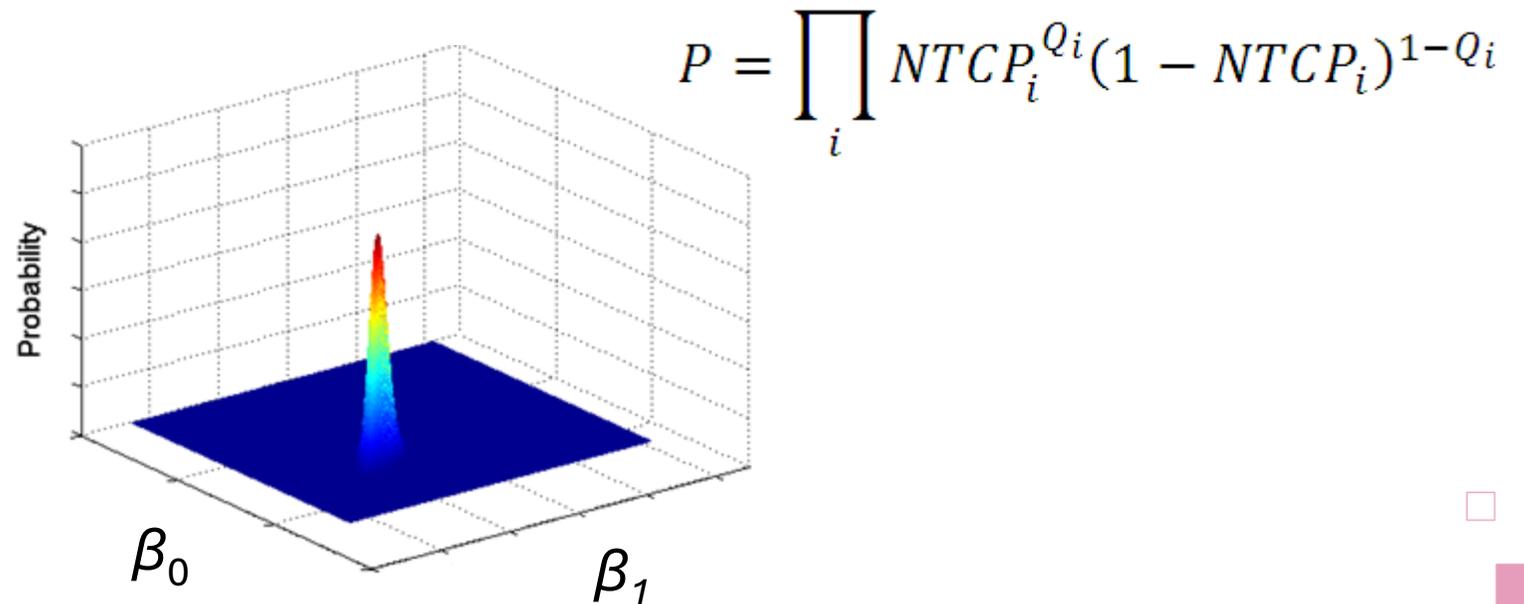
Other model types – the LKB model

Lyman, Kutcher and Burman developed a popular model using a cumulative normal function (probit), i.e. the LKB model.

- Two parameters: φ_{50} (often called TD50) and m

$$\text{NTCP} = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} e^{-x^2/2} dx$$

$$t = \frac{\varphi - \varphi_{50}}{m \cdot \varphi_{50}}$$

Lyman. Radiat Res Suppl, 1985, 8, S13-S19

Kutcher & Burman. Int J Radiat Oncol Biol Phys, 1989, 16, 1623-1630

Other model types - the Relative Seriality model

The Relative Seriality model first calculates a probability of local damage for each dose bin in the DVH:

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

D_i = total dose to bin i
D_{50} = Dose causing 50% probability
γ = slope of the curve

Then NTCP is estimated using the relative seriality parameter 's'.

- Serial organs: $s = 1$, high doses to small volume important

- Parallel organs: $s \approx 0$, large irradiated volume important

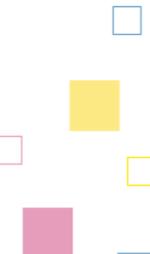$$\text{NTCP} = \left(1 - \prod_i (1 - P(D_i)^s)^{\frac{V_i}{V_{tot}}}\right)^{1/s}$$

V_i = absolute volume in bin i
V_{tot} = total organ volume
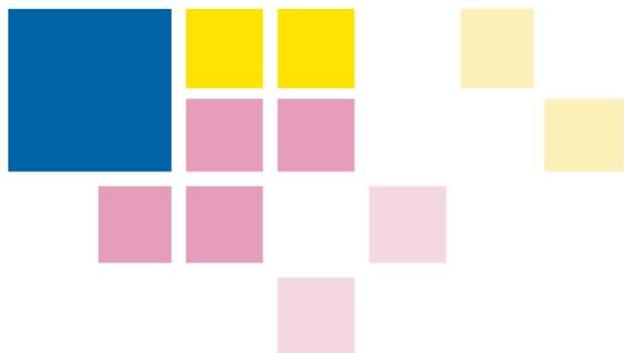s = relative seriality parameter

Källman, Ågren, Brahme. Int J Radiat Biol, 1992, 62, 249-262
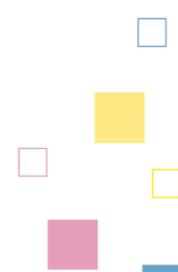
TETRIS work package 2

- TETRIS aims to support personalised follow-up of breast cancer patients

- WP2 will provide predictive models to integrate in a software tool
    - Software developed in WP6 by Aquilab
    - Models to integrate imaging-, genomics- and transcriptomics risk features

- Predictive models for severe late side effects have been collected from the literature:
    - Cardiac effects
    - Pulmonary effects
    - Secondary cancers

- The models will be tested on the retrospective TETRIS cohort:
    - 2000 patients from REQUITE/RADPRECISE projects
    - 3500 patients from real-world cohorts from the TETRIS consortium

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THANK YOU

TETRIS - Risk assessment *Tools* for severe side *Effects* after *breasT Radiotherapy*: radiation safety through biological extended models and *dIgital twinS*

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