Impostazione biologica e clinico-terapeutica

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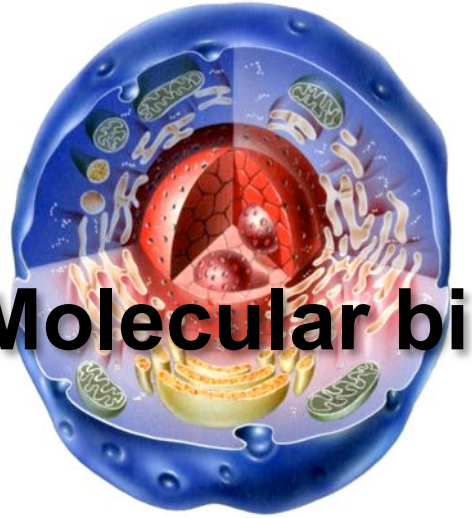
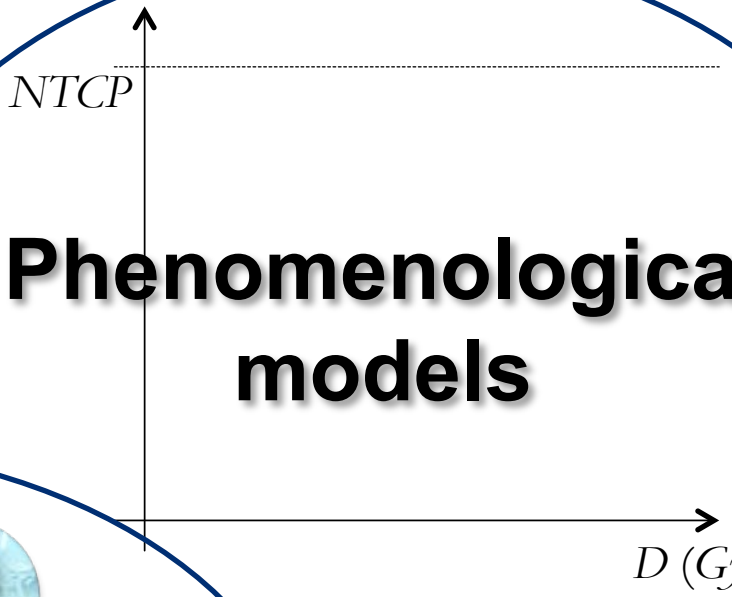
Associazione Italiana Radioterapia Oncologica

UNIVERSITÀ CATTOLICA del Sacro Cuore

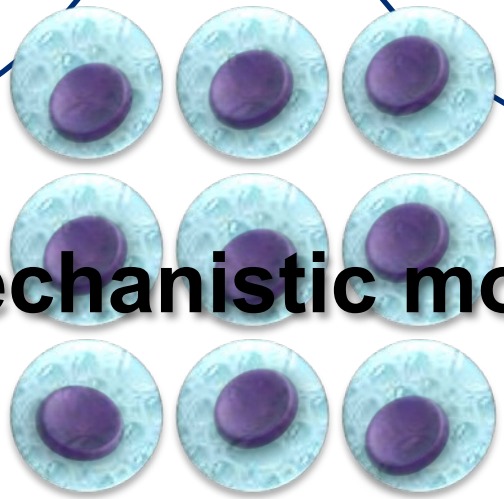
From molecular biology to modeling



Molecular biology

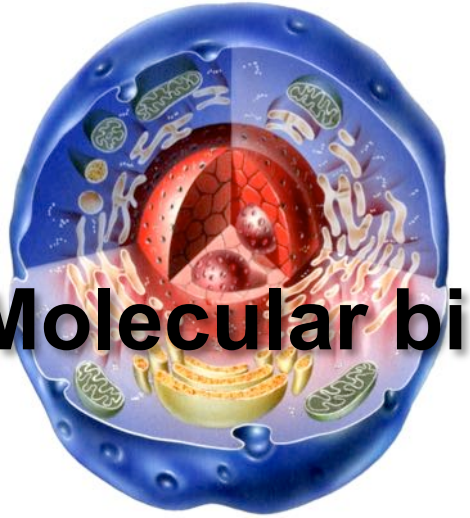


Phenomenological models

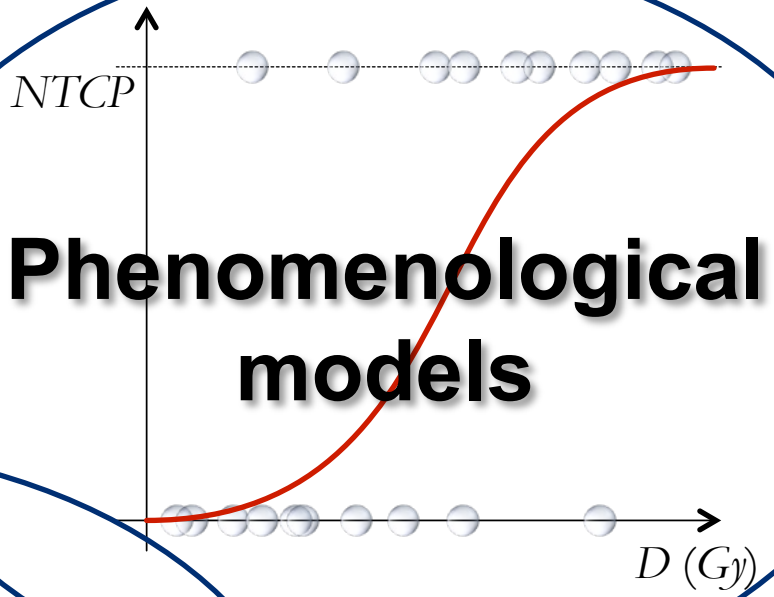


Mechanistic models

From molecular biology to modeling



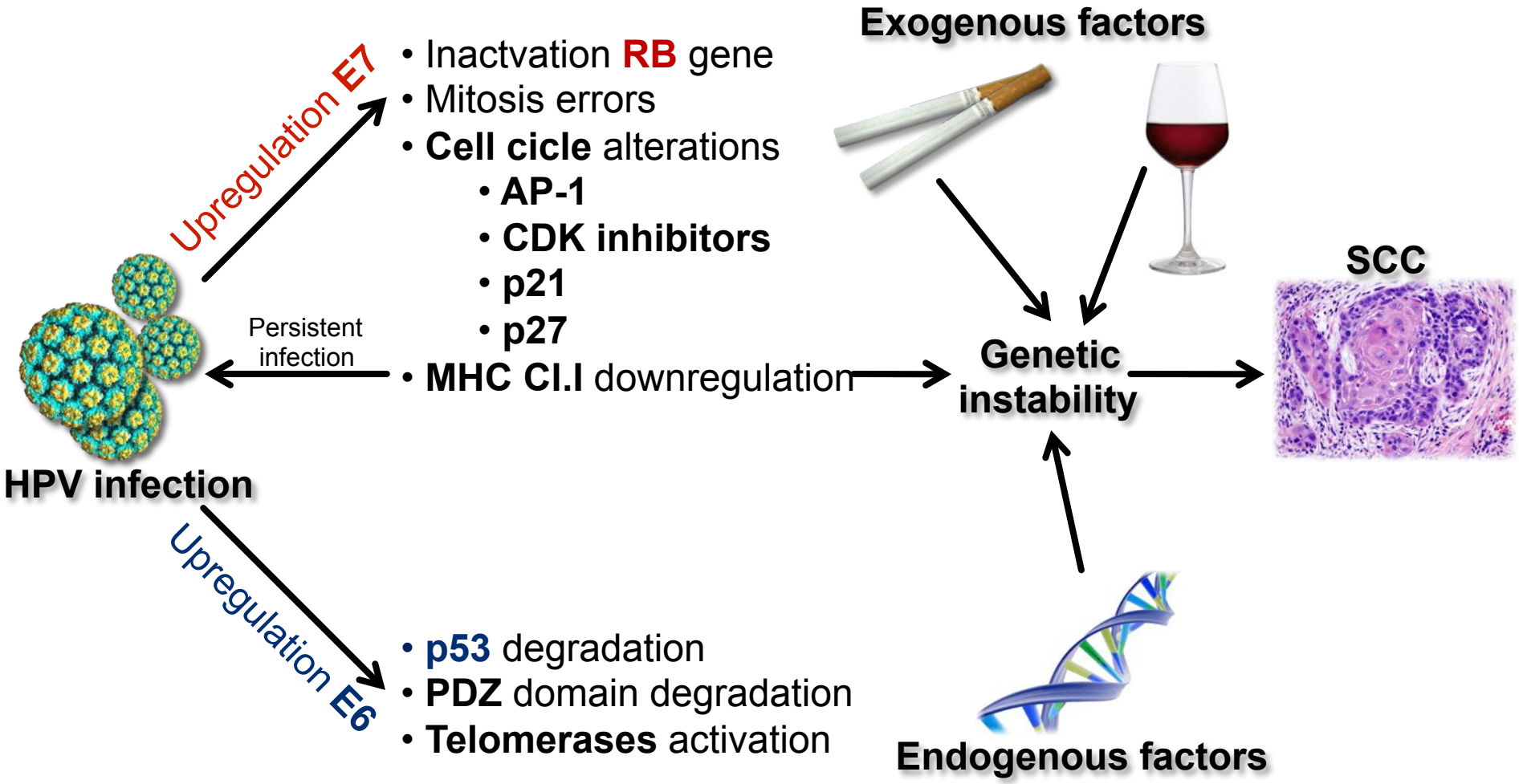
Molecular biology



Phenomenological models

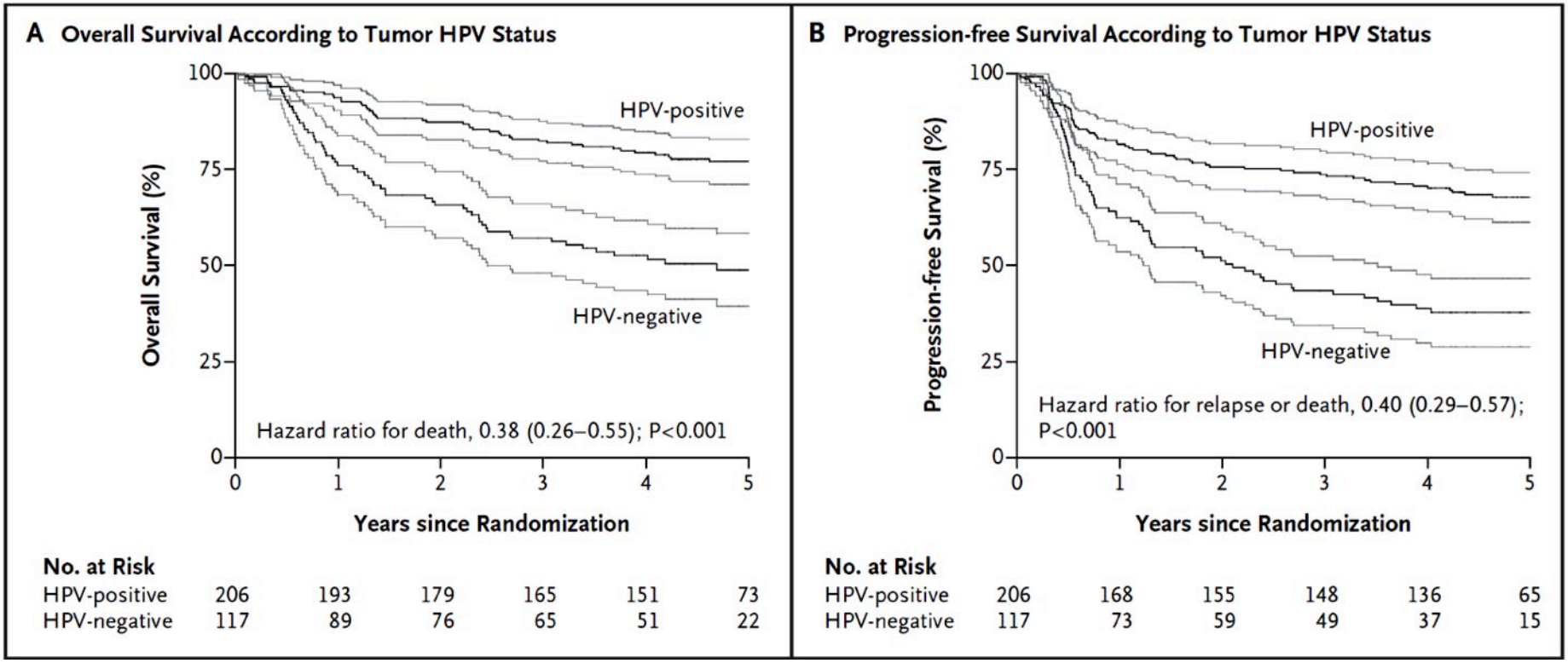
Mechanistic models

Molecular biology: HPV & SCC



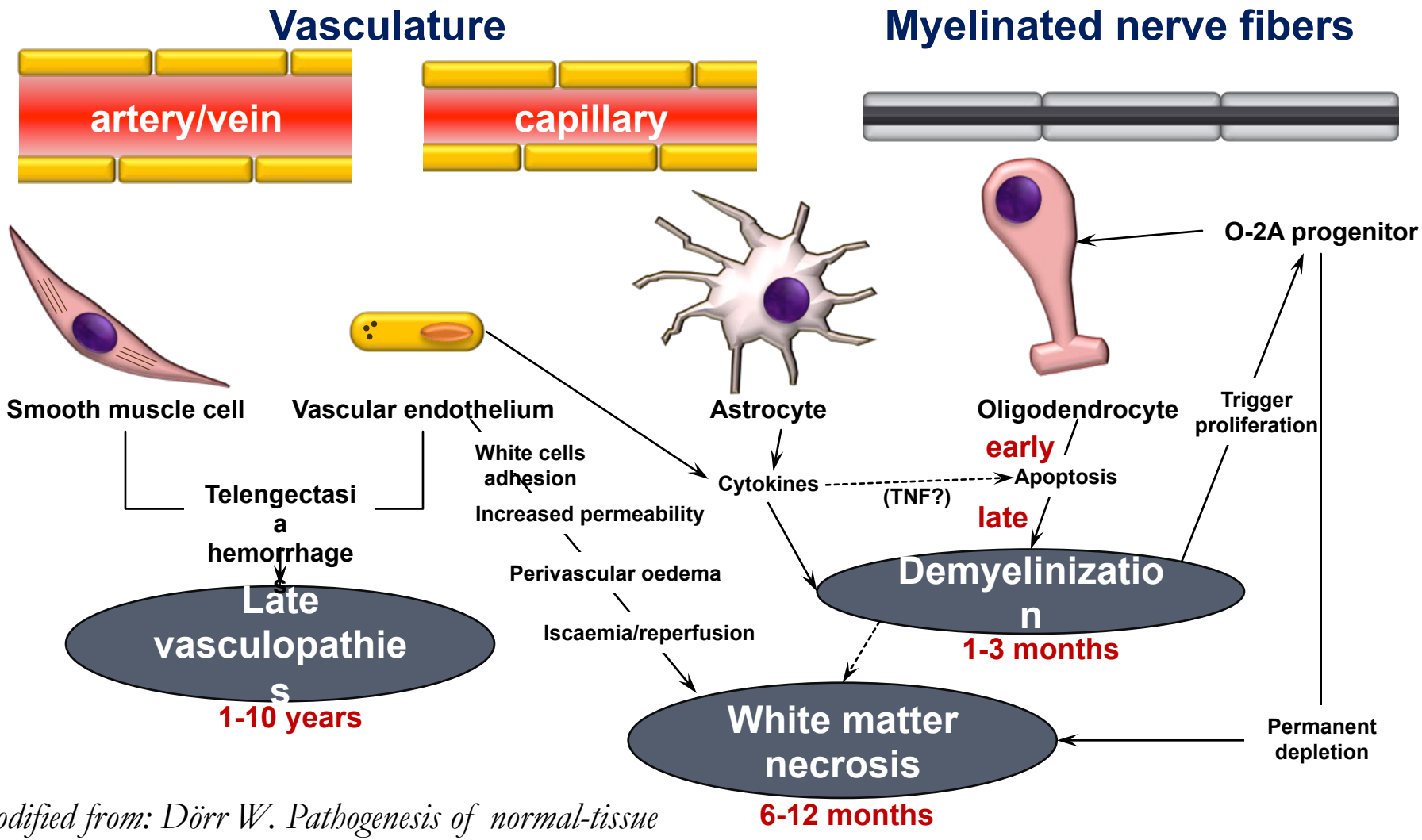
Modified from: L Feller et al. Head & Face Medicine 2010, 6:14

Molecular biology: outcome of oropharyngeal SCC and HPV infection



K Ang et al. New England Journal of Medicine 2010;363:24-35.

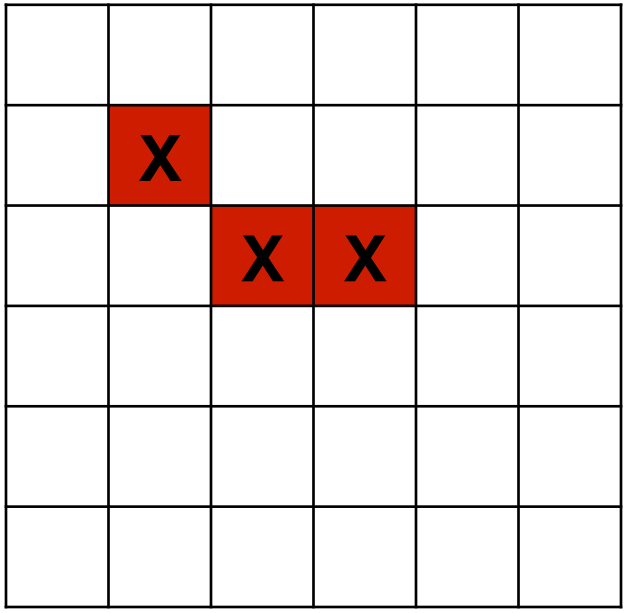
Radiation myelopathy pathophysiology



Modified from: Dörr W. Pathogenesis of normal-tissue side-effects. In "Basic clinical radiobiology" 4th edition. Hodder Arnold. London. 2009.

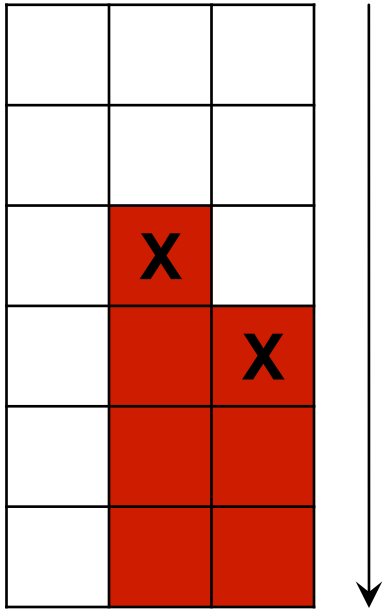
The volume effect

Parallel structure of functional subunits



Parotid glands, mucosa

Serial structure of functional subunits

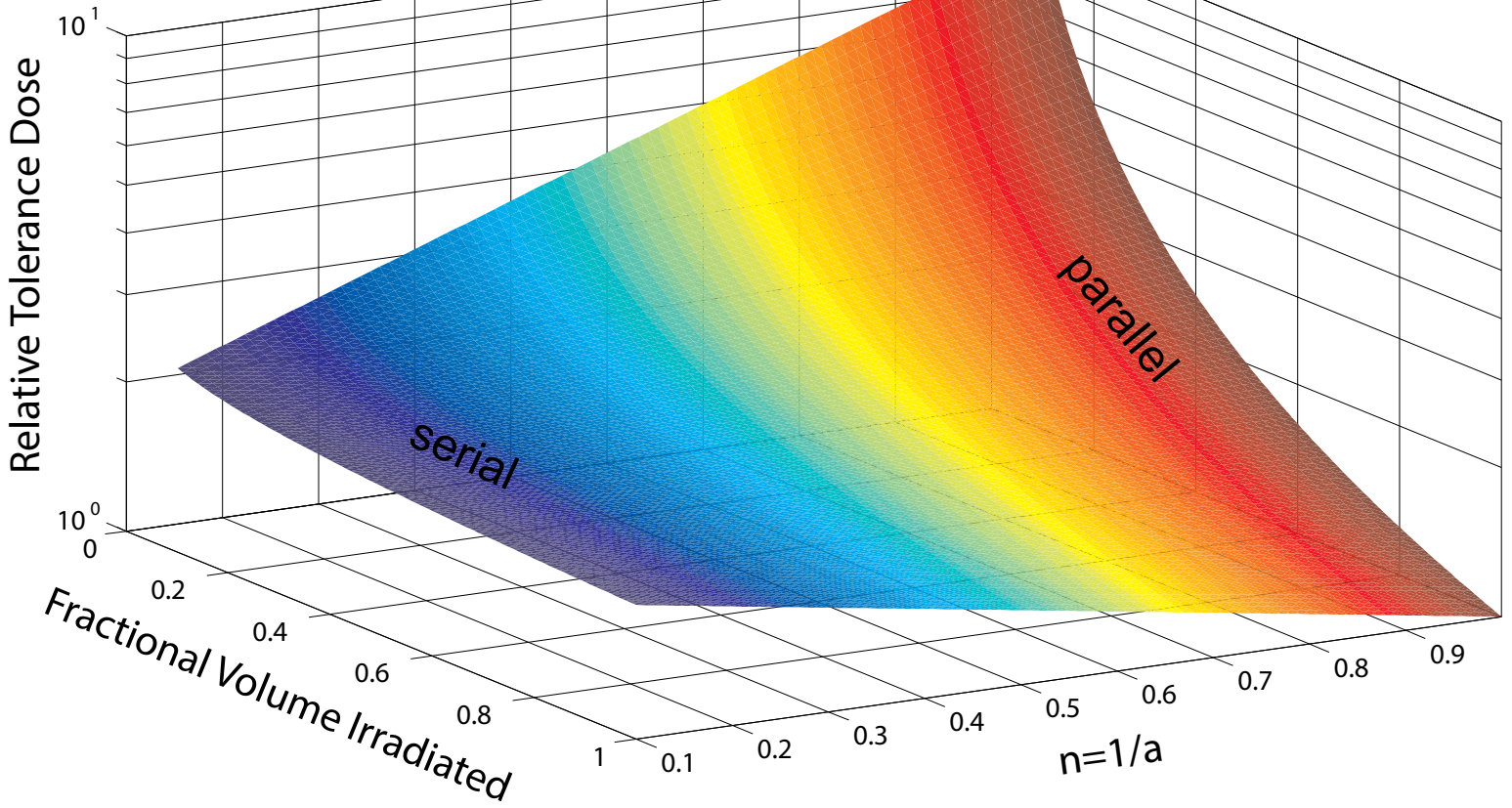


Spinal cord

Withers HR. et al. Treatment volume and tissue tolerance. Int. J. Radiat. Oncol. Biol. Phys. 1988 (14): 751-759.

The n parameter

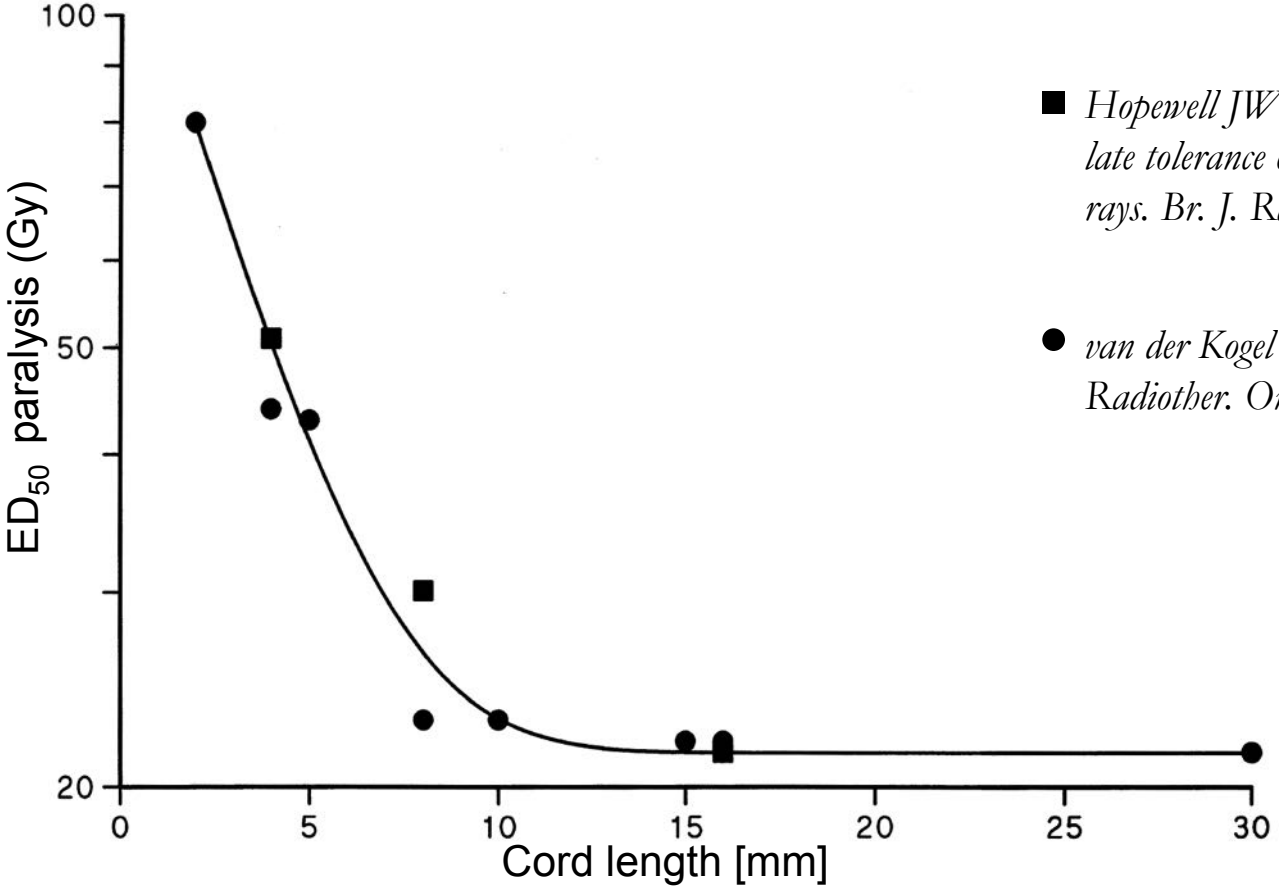
$$D\left(V_{irradiated}\right) = D\left(V_{reference}\right) \cdot \left(\frac{V_{reference}}{V_{irradiated}}\right)^{n}$$



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.*

Spinal cord: the volume effect

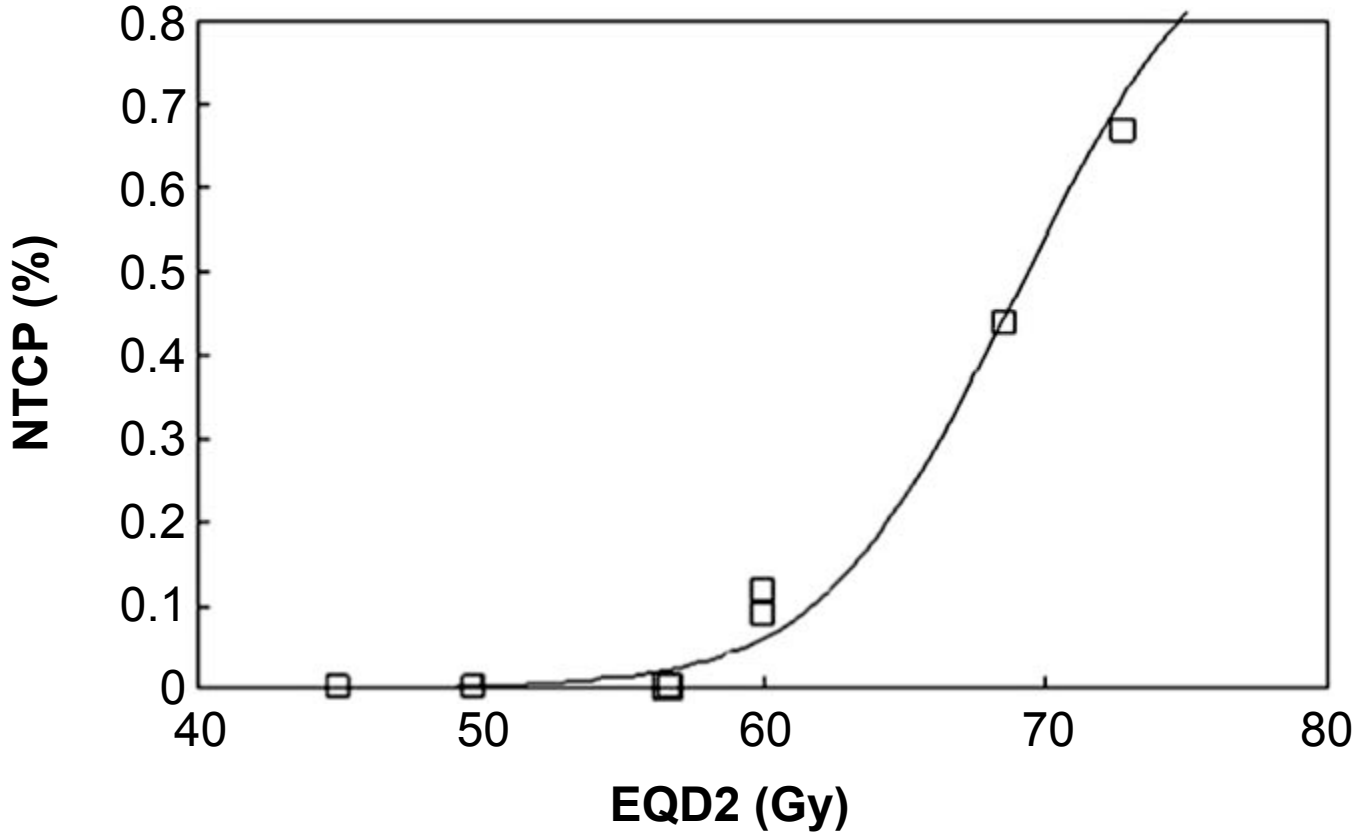
Rat spinal cord: endpoint white matter necrosis



- *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.

QUANTEC: spinal cord modeling



Kirkpatrick JP. Radiation dose-volume effect in the spinal cord. Radiater. Oncol. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S42–S49, 2010

QUANTEC: spinal cord data

Institution		Dose (Gy)	Dose/fraction (Gy)	Cases of myelopathy/ total number of patients	Probability of myelopathy*	2-Gy dose equivalent†
Wake Forest (19)	1989	60	2	1/12	0.090	60.0
		65	1.63	0/24	0.000	56.6
Caen (5)	1978	54	3	7/15	0.622	72.8
Brookhaven (20)	1966	19	9.5	4/13	0.437	68.6
Florida (21)	1990	47.5	1.9	0/211	0.000	45.0
		52.5	1.9	0/22	0.000	49.8
		60	2	2/19	0.118	60.0
Yugoslavia (22)	1991	65	1.63	0/19	0.000	56.6

* Calculated using the percentage of patients experiencing myelopathy corrected for overall survival as a function of time by the method in (18).

† Calculated using $\alpha/\beta = 0.87$ Gy (18).

Quality of data?

1. Dose calculation

2. Treatment technique

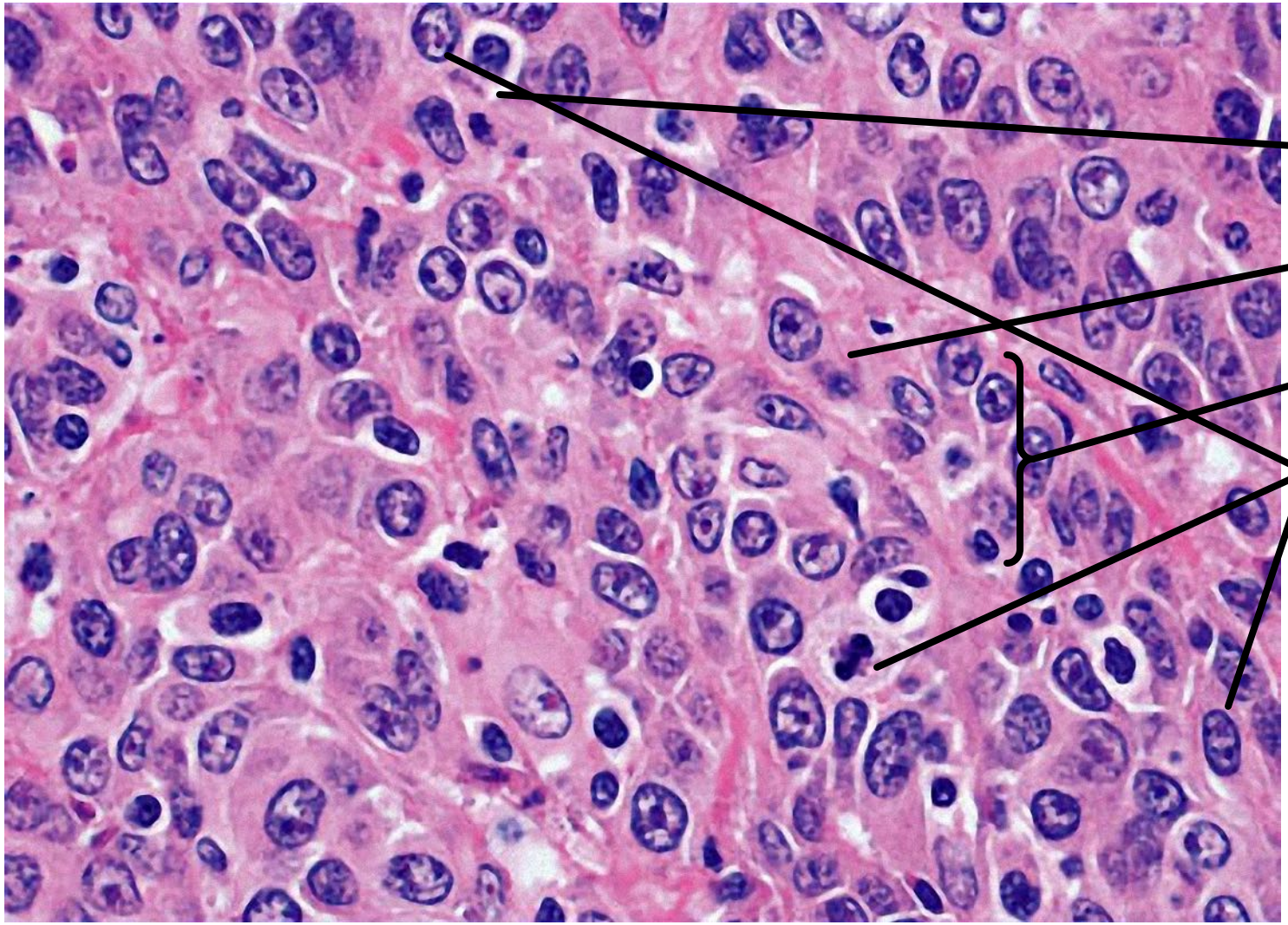
Kirkpatrick JP. Radiation dose-volume effect in the spinal cord. Radiater. Oncol. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S42–S49, 2010

Clinical TCP definition

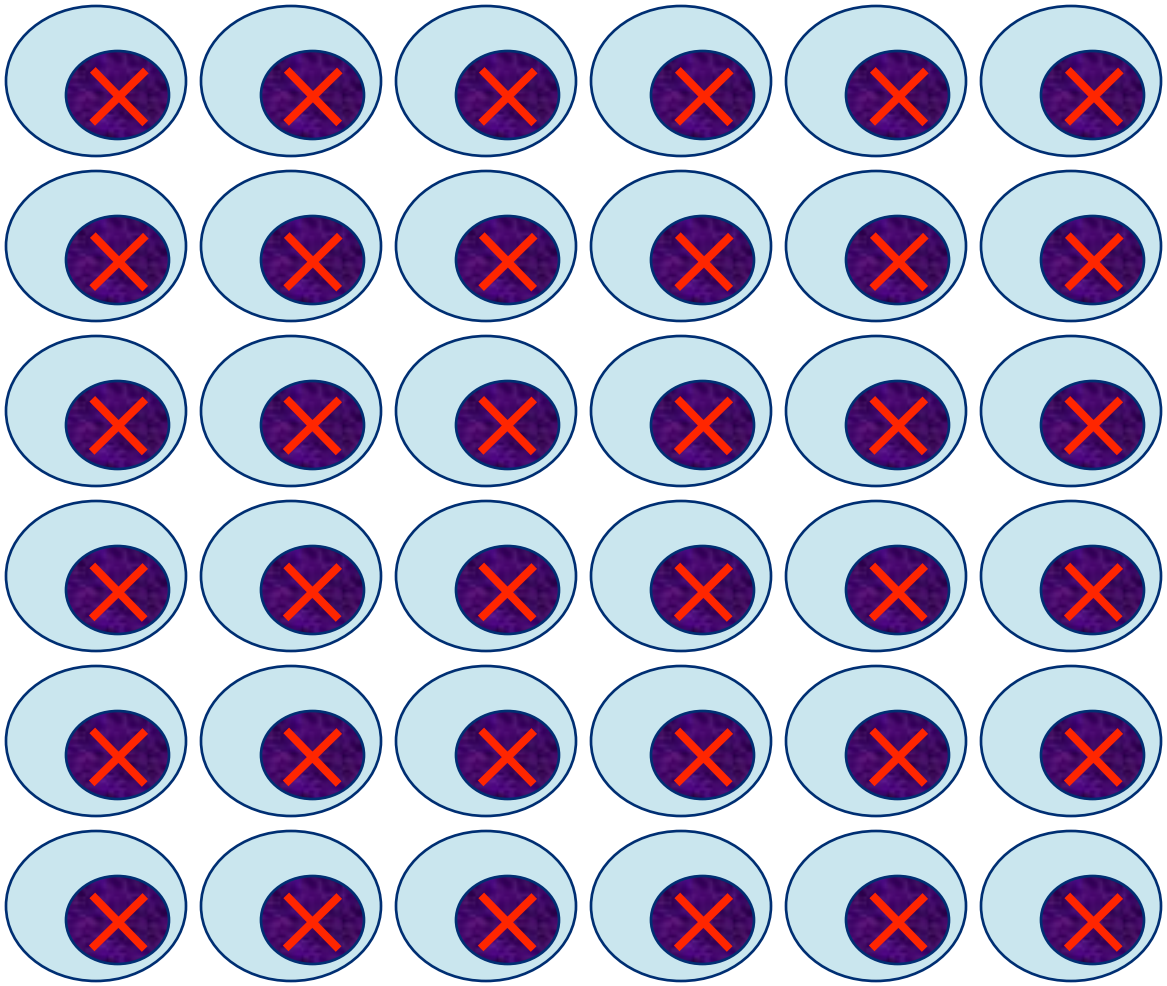
- **Tumor Local Control**: snapshot of an observed patients population at n-years after the first observation of the complete response or the arrest of cancer growth at site of origin.

- The use of the **n-years disease free survival (DFS)** or the **n-years overall survival (OS)** can be affected by other variables that can hide the direct radiation on primary tumor site effect.
    - The DFS can be influenced by the rising of metastases, the use of further anti-cancer treatments (chemotherapy, surgery or both).
    - The OS can be shortened by not tumor caused death of

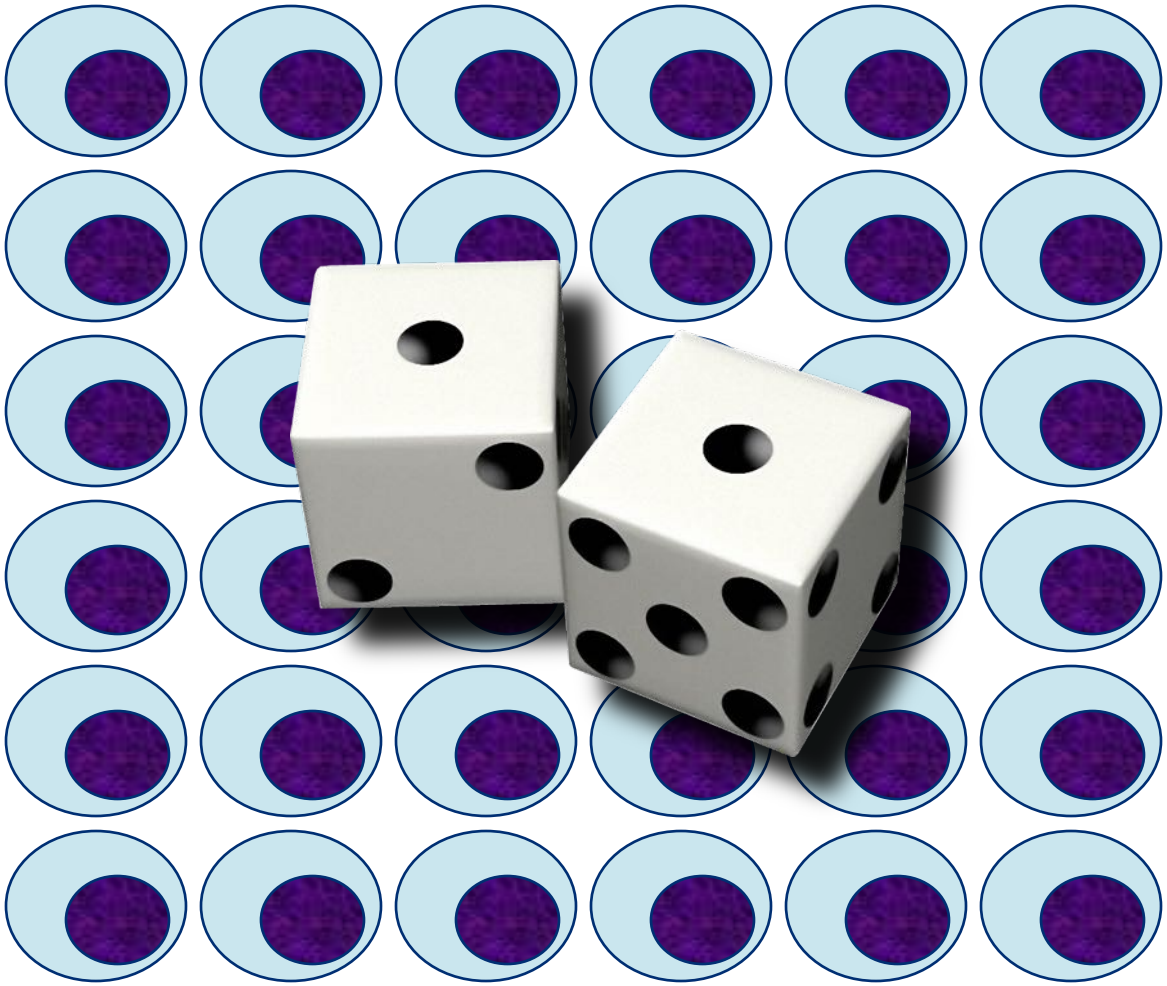
Mechanistic modeling - TCP



Mechanistic modeling - TCP

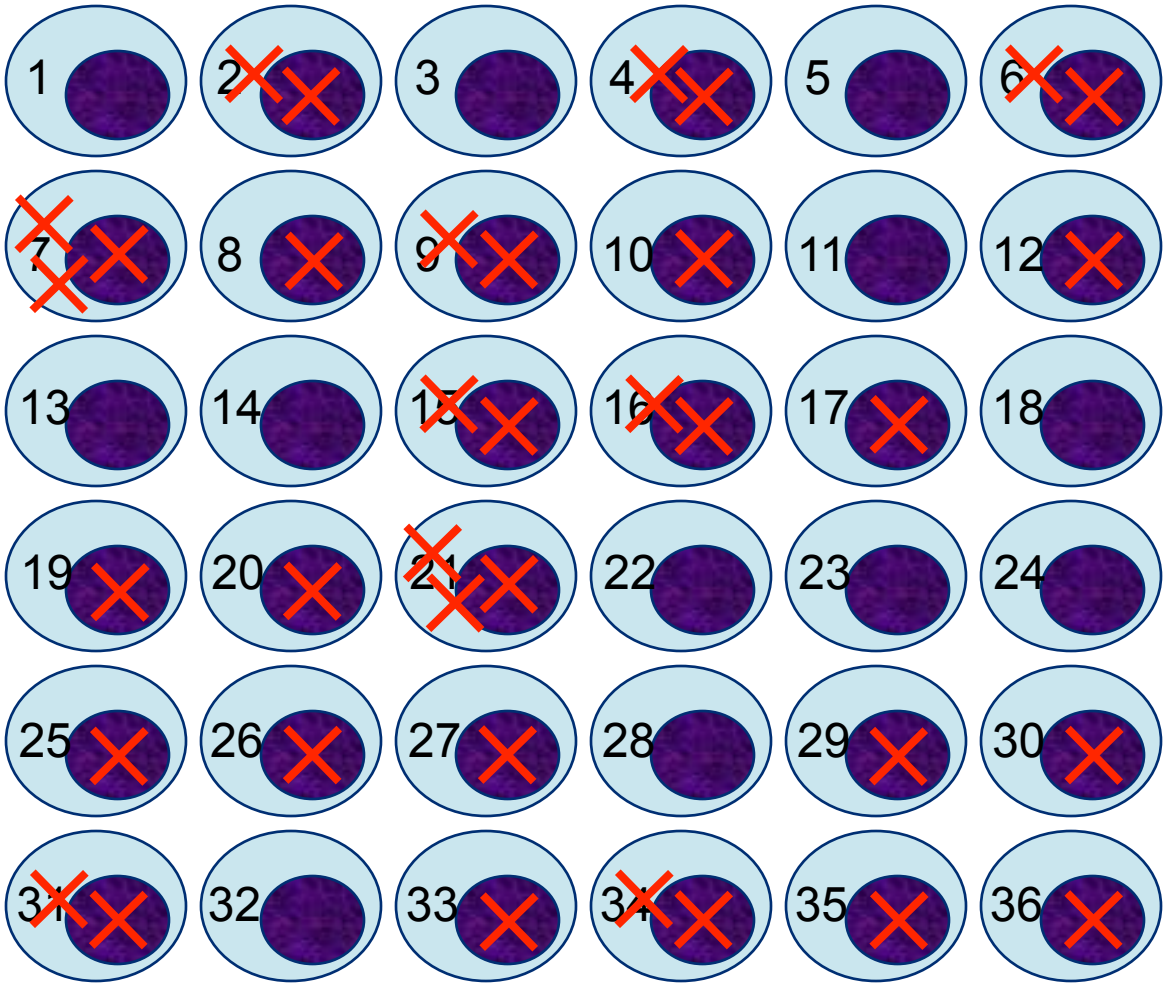


Mechanistic modeling - TCP



Mechanistic modeling - TCP

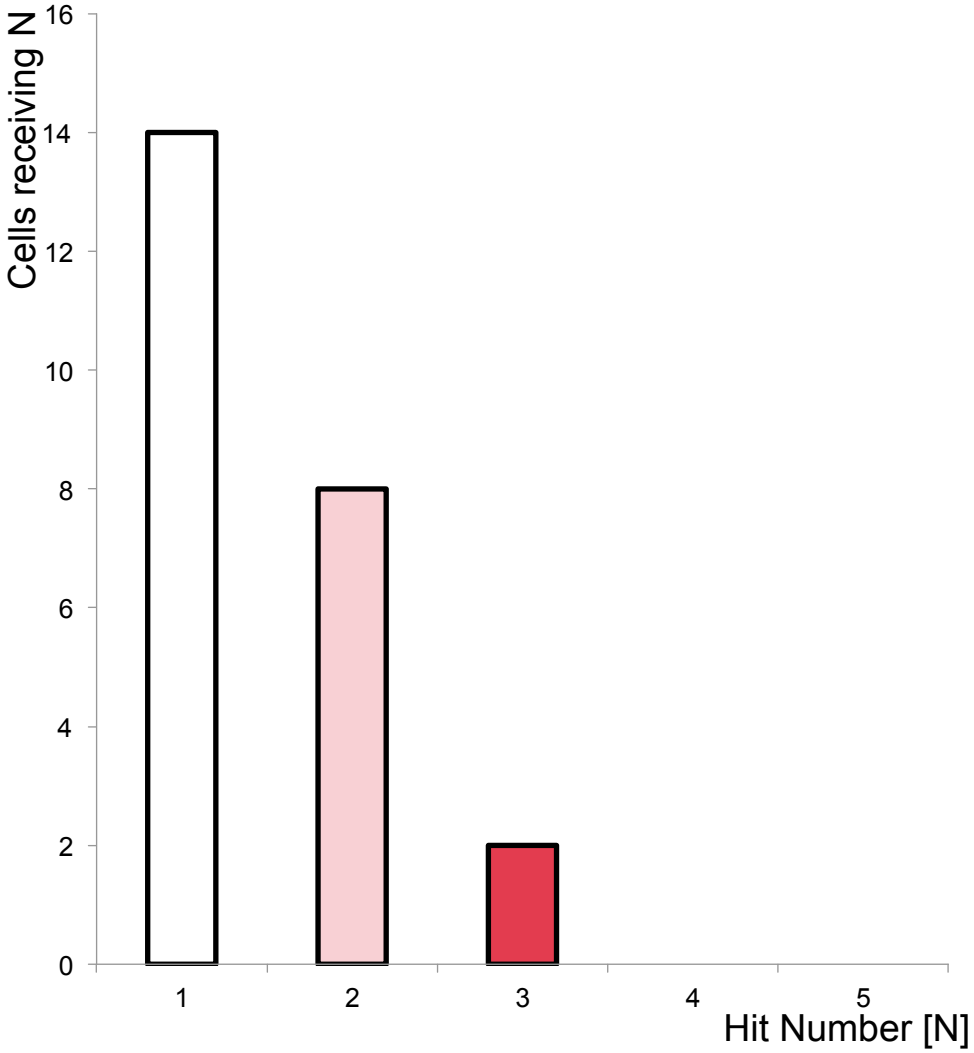
SF: Surviving Fraction



Mechanistic modeling - TCP

2	8	17	29
2	9	19	30
4	9	20	31
4	10	21	31
6	12	21	33
6	15	21	34
7	15	25	34
7	16	26	35
7	16	27	36

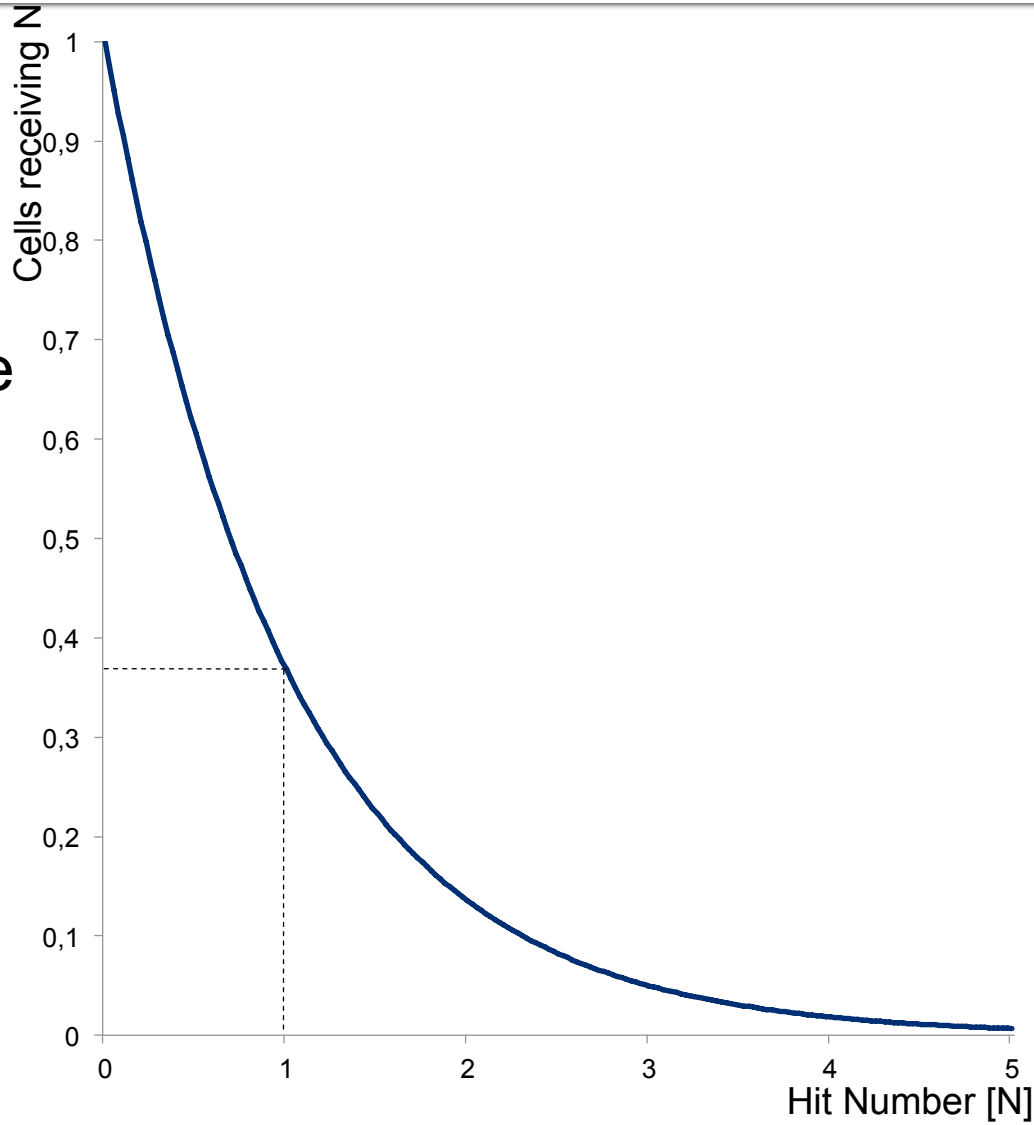
$$SF = \frac{36 - 24}{36} = \frac{12}{36} = 0.3$$



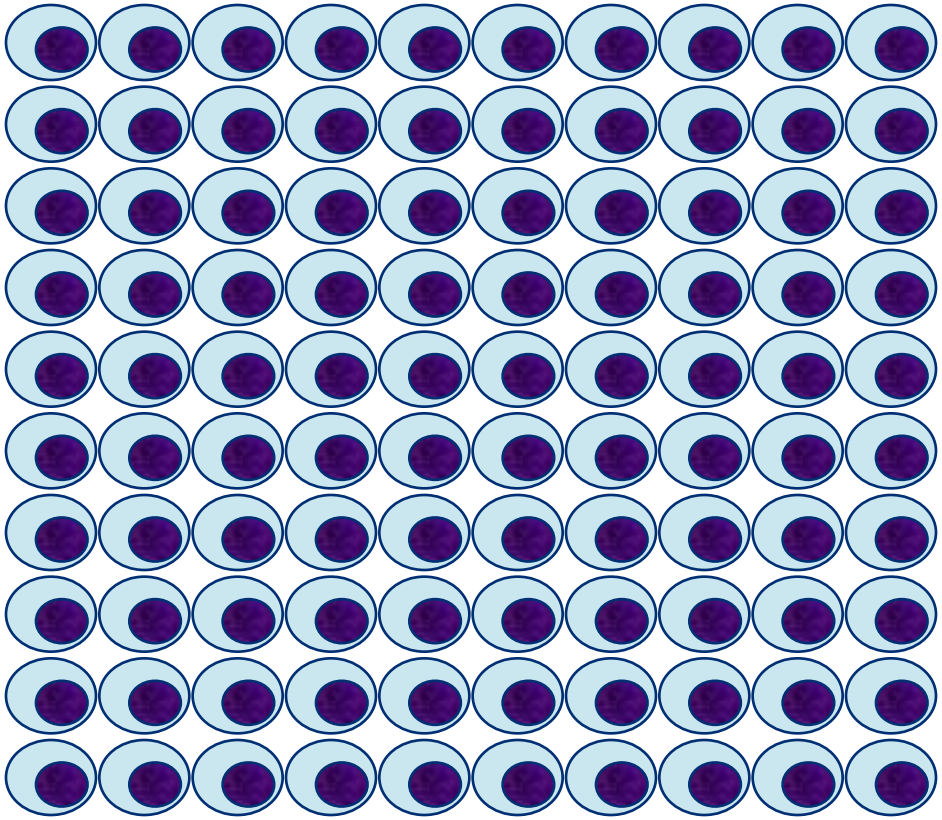
Mechanistic modeling - TCP

- Growing the number of the cells…
- If $m=1$ (one lethal hit per cell)

$$SF=e^{-m}=0.367879\ldots$$



Mechanistic modeling - TCP



$SF = e^{-mN} = 0.$

$N = $

$TCP = 100\text{-}$

Mechanistic modeling - TCP

$$SF = e^{-m \cdot NF}$$

$$N = N_0 \cdot SF$$

$$TCP = e^{-N} = e^{-N_0 \cdot SF}$$

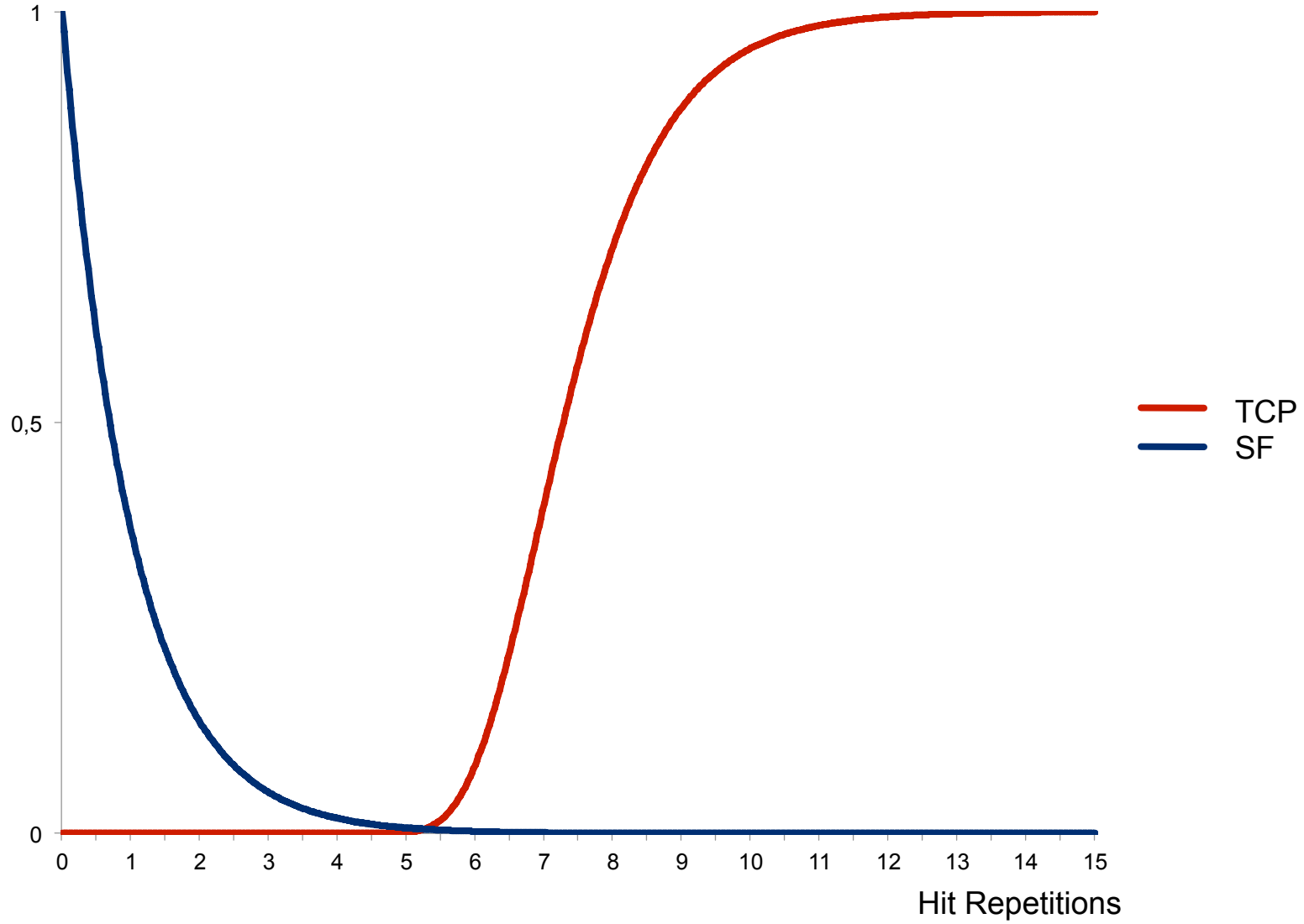
TCP formalism

$m=1$

$SF=e^{-1}$

$N_0=\mathbf{1000}$

$TCP=e^{-N_0 SF}$



TCP formalism

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$SF=e^{-1}$

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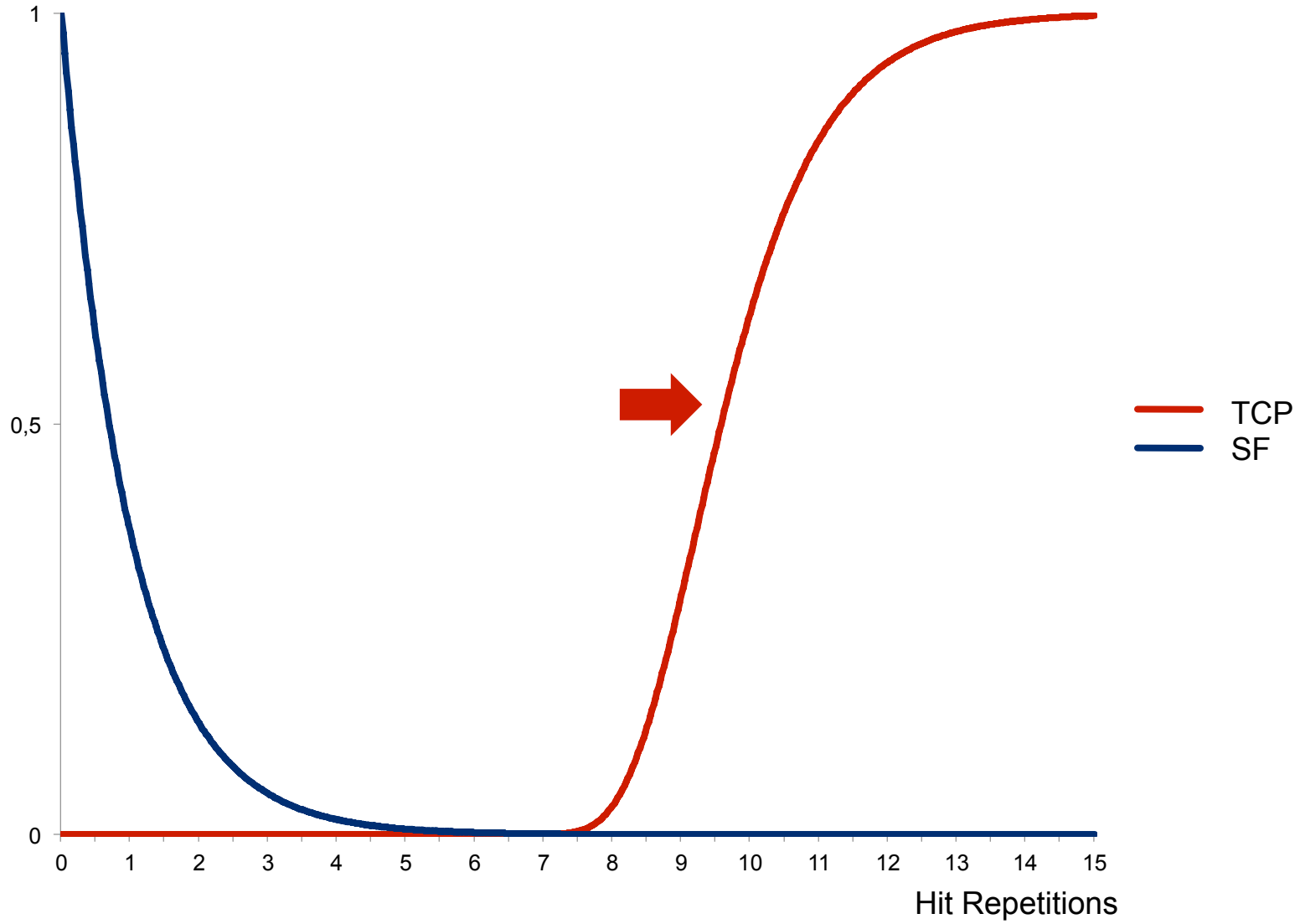
$TCP=e^{-N_0 SF}$



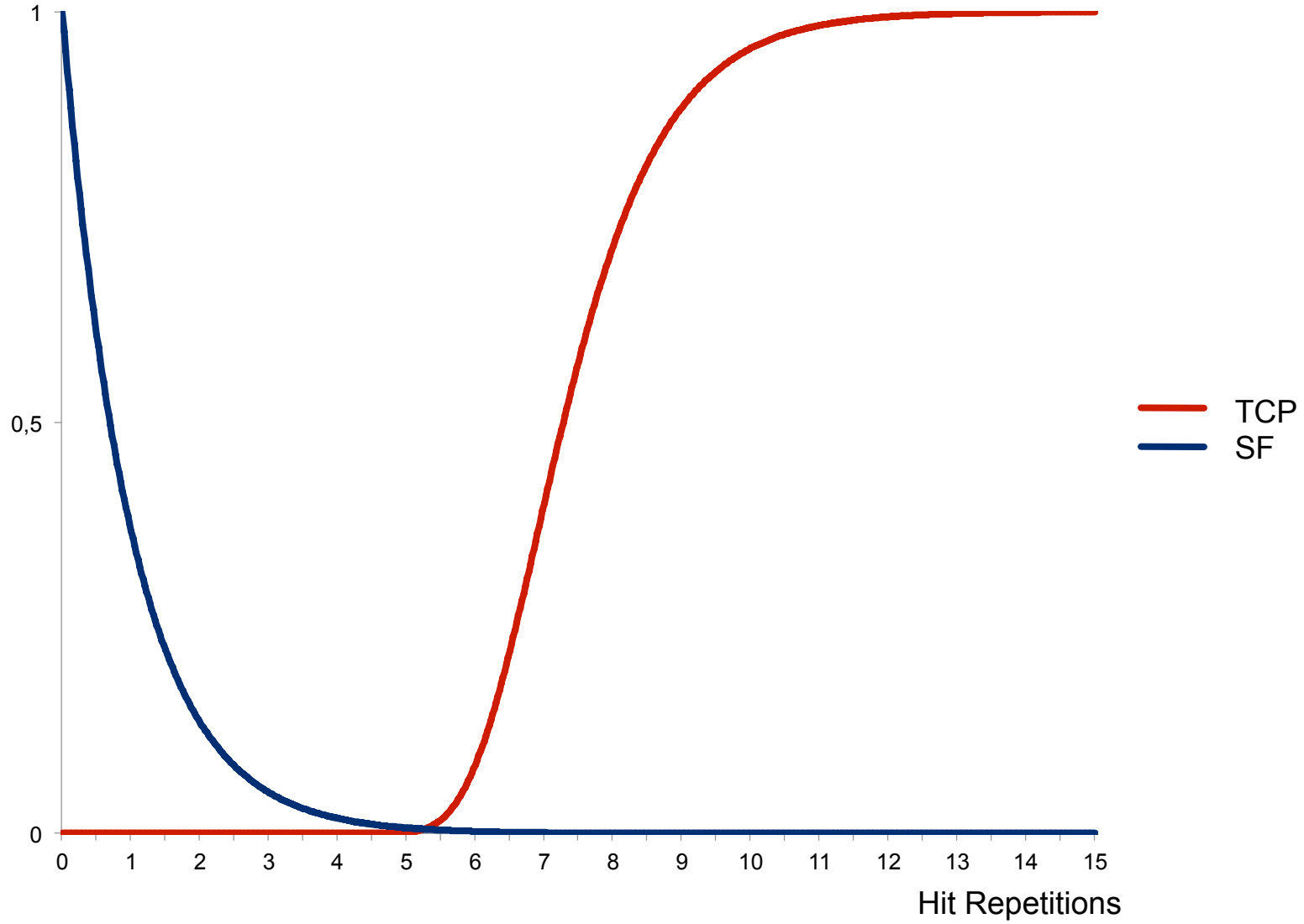
TCP formalism

$m=1$

$SF=e^{-1}$

$N_0=\mathbf{1000}$

$TCP=e^{-N_0 SF}$



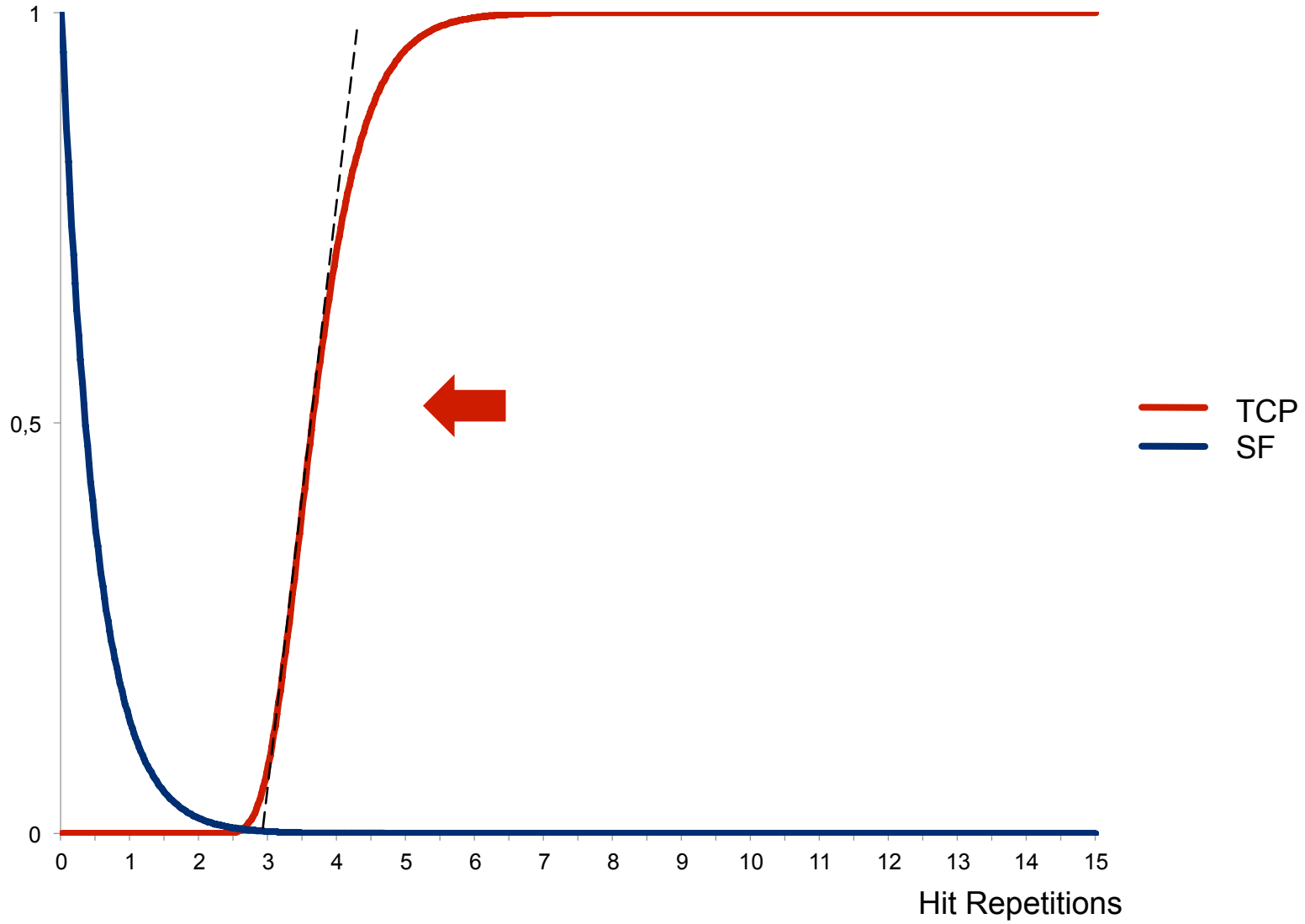
TCP formalism

$m=2$

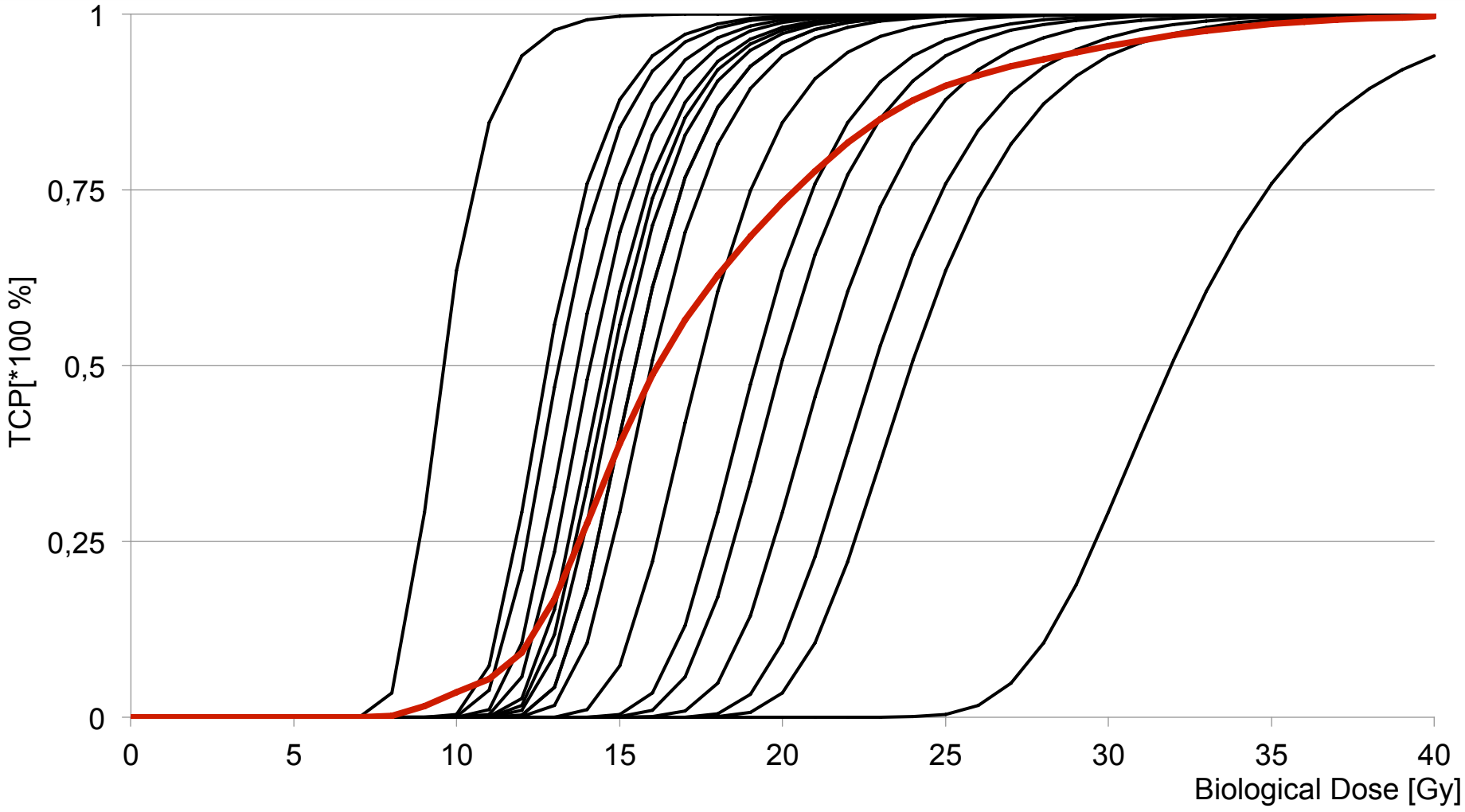
$SF=e^{-2}$

$N_0=1000$

$TCP=e^{-N_0 SF}$



Deriving TCP model from patients series data



Bentzen SM. Radiobiological considerations in the design of clinical trials. Radiother Oncol 32: 1-11. 1994.

TCP phenomenological modeling: choosing a model

- *Poisson*: $TCP = 0.5^{e^{\frac{2\gamma_{50}}{\ln 2}\left(1-\frac{D}{D_{50}}\right)}}$

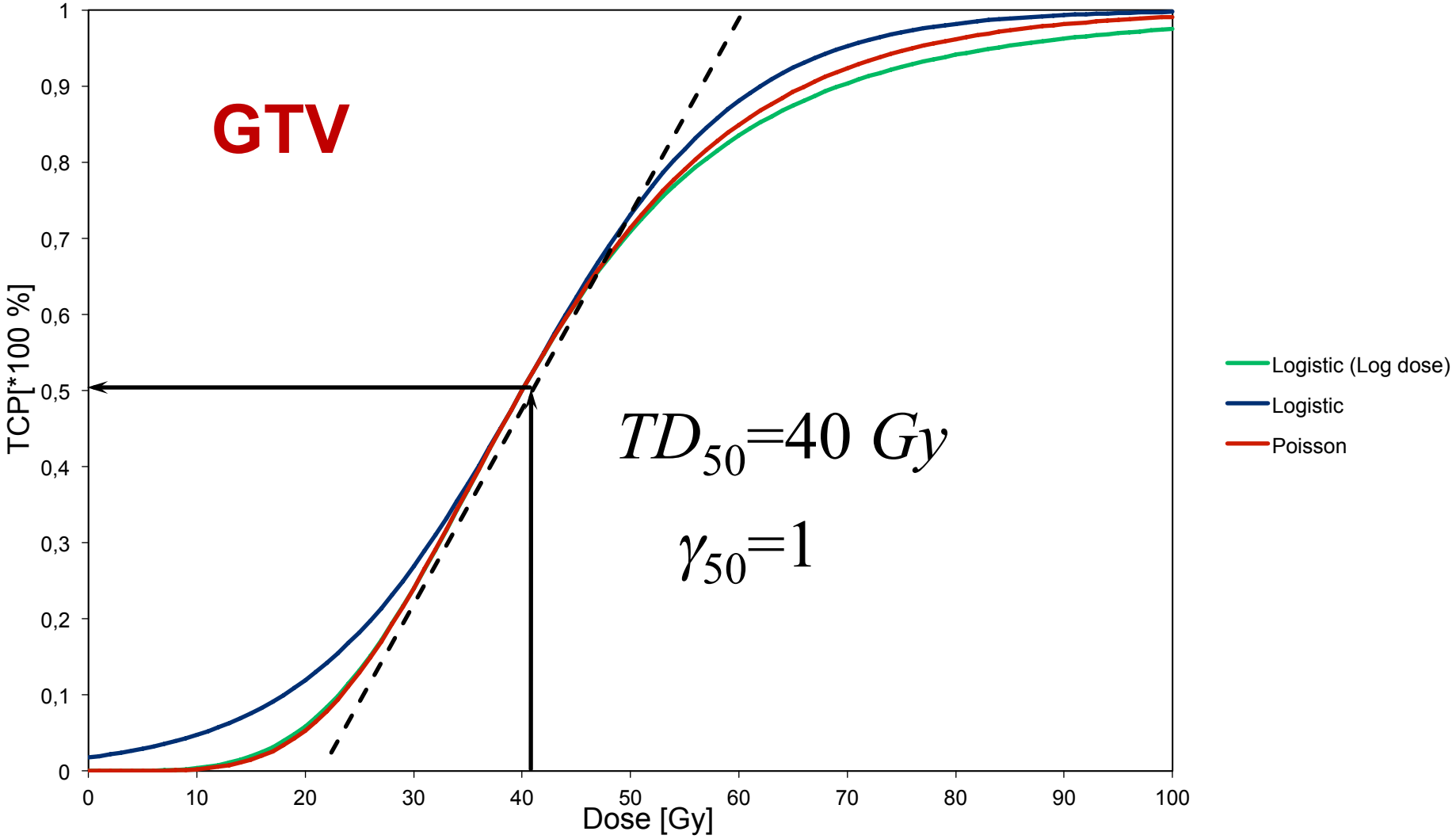
  Munro Gilbert Kallman

- *Logistic:* $$TCP = \frac{1}{1+\exp\left[4\gamma_{50}\left(1-\frac{D}{D_{50}}\right)\right]}$$

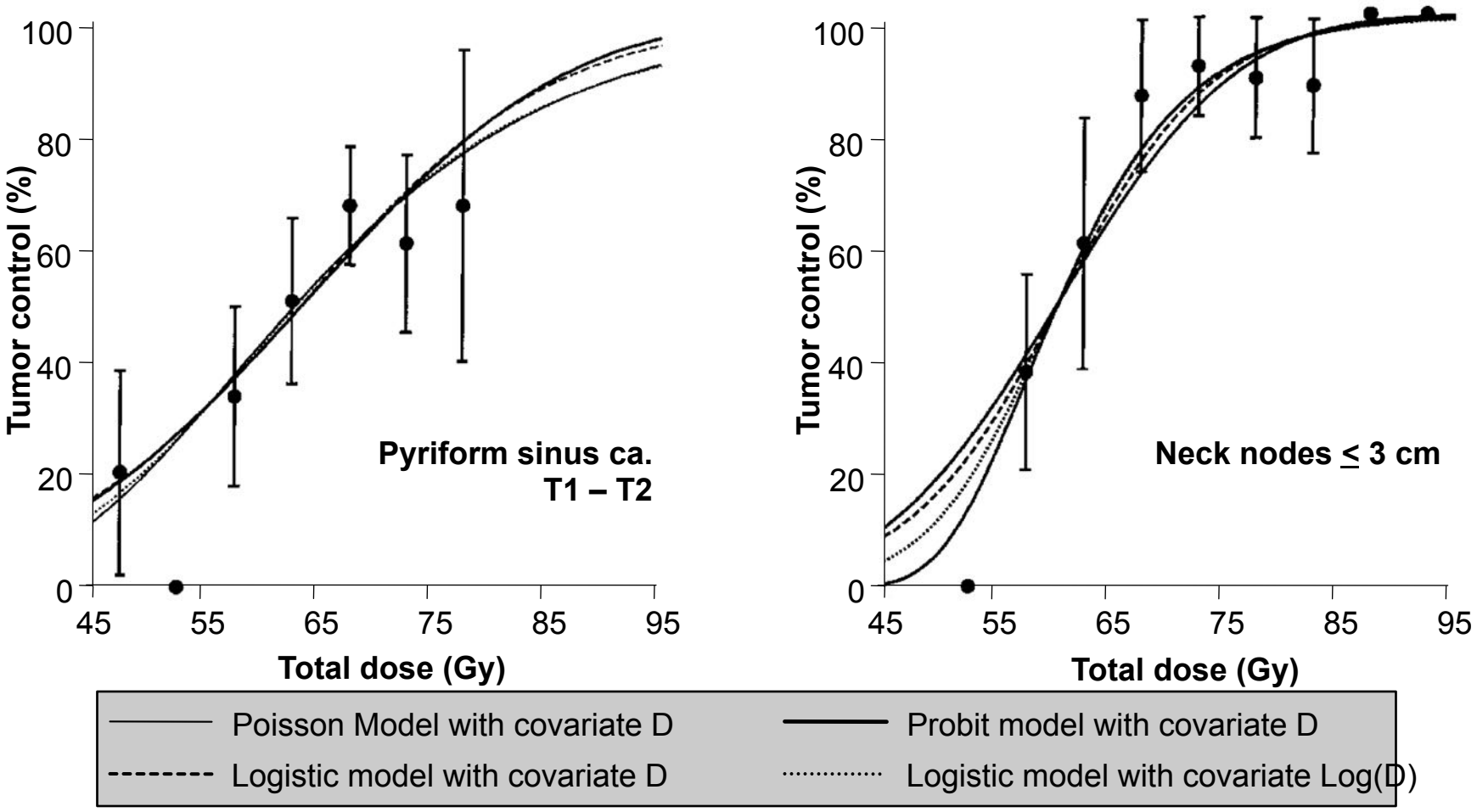
- *Logistict* (log *dose*): $$TCP = \frac{1}{1+\left(\frac{D}{D_{50}}\right)^{4\gamma_{50}}}$$

  Niemierko

TCP for GTV control probability



Deriving TCP models from dose/outcome data



Bentzen SM. Tucker SL. Quantifying the position and steepness of radiation dose-response curves. Int. J. Radiat. Biol. 1997 (71) – 5: 531-542.

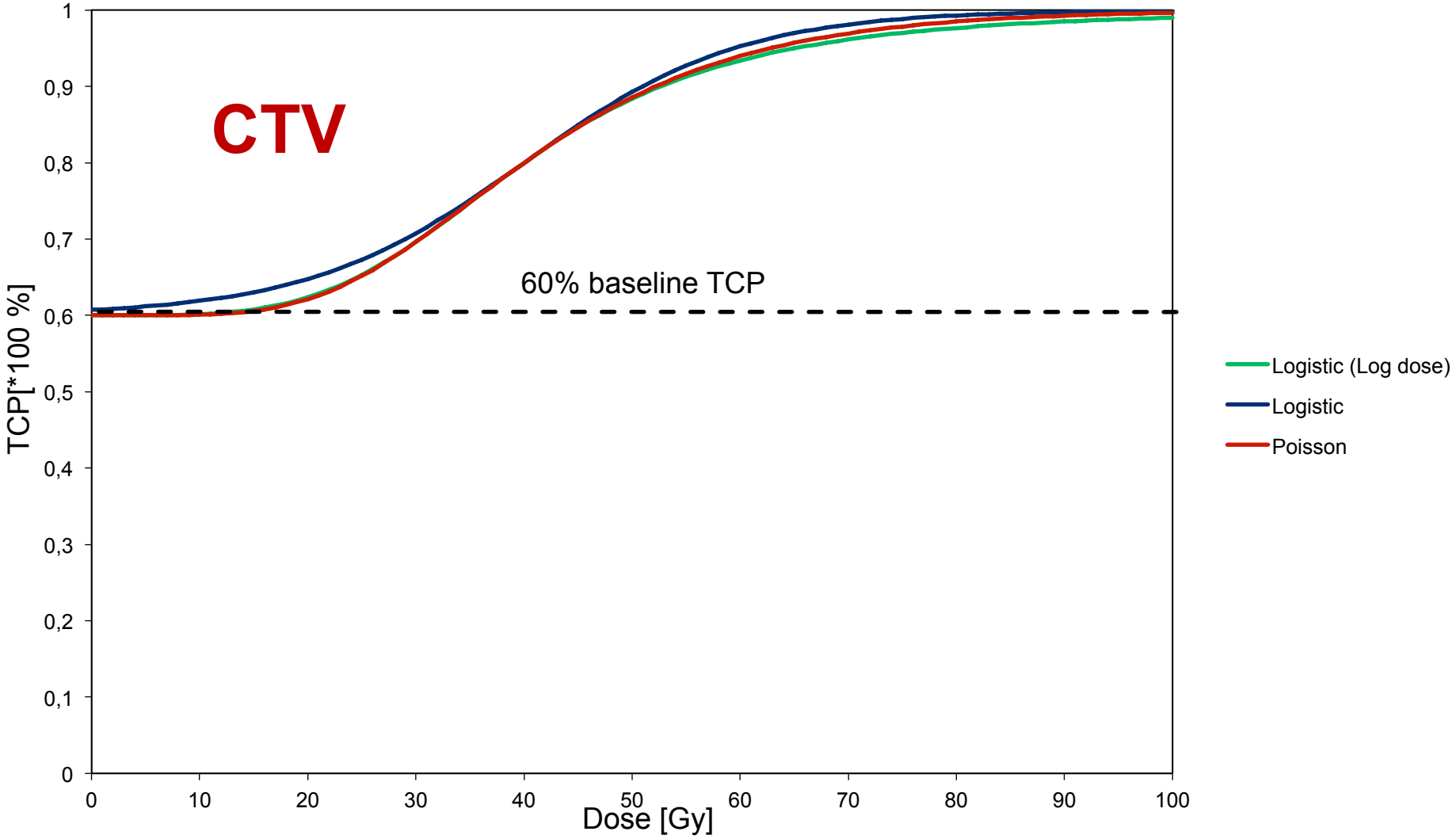
What about CTV?

- A given baseline TCP is given when irradiating clinical target volumes (ex. neck nodes in elective nodal irradiation)

$$TCP_{CTV} = TCP_{base} + \left(1 - TCP_{base}\right) \cdot TCP_{dose}$$

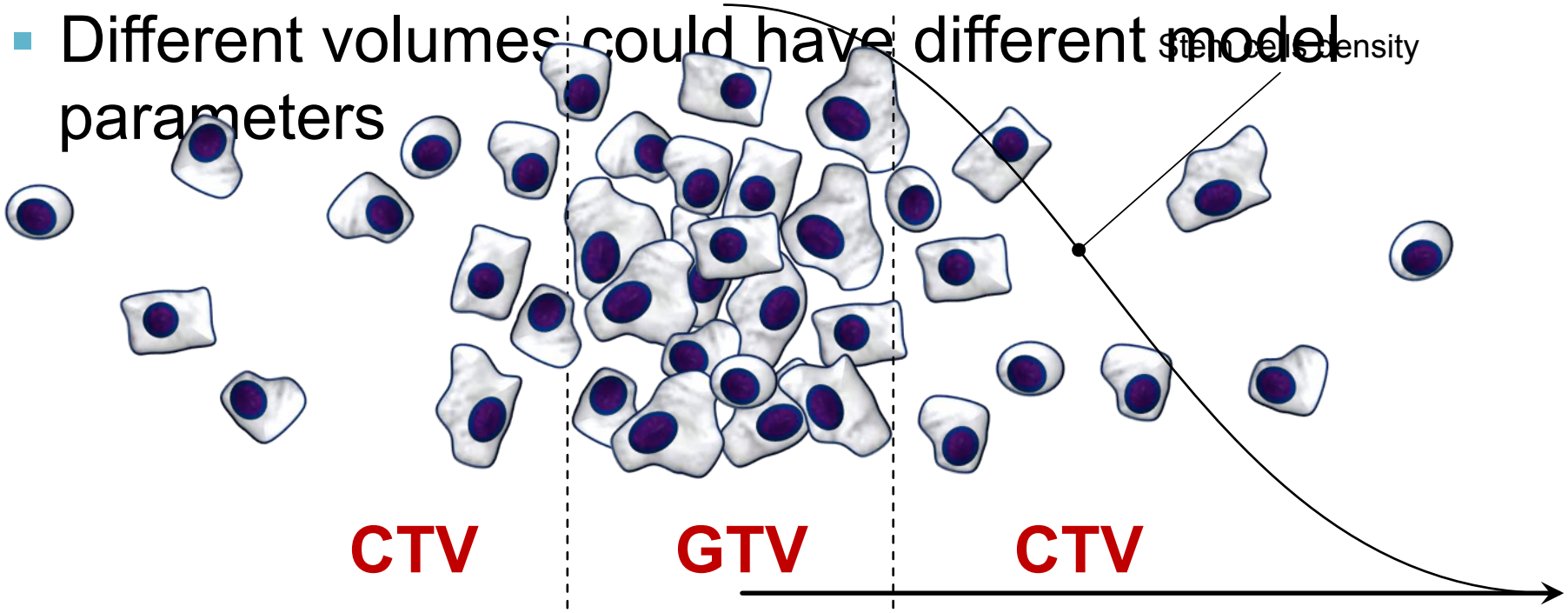
$$TCP_{Total} = TCP_{GTV} \cdot TCP_{CTV}$$

TCP for CTV control probability

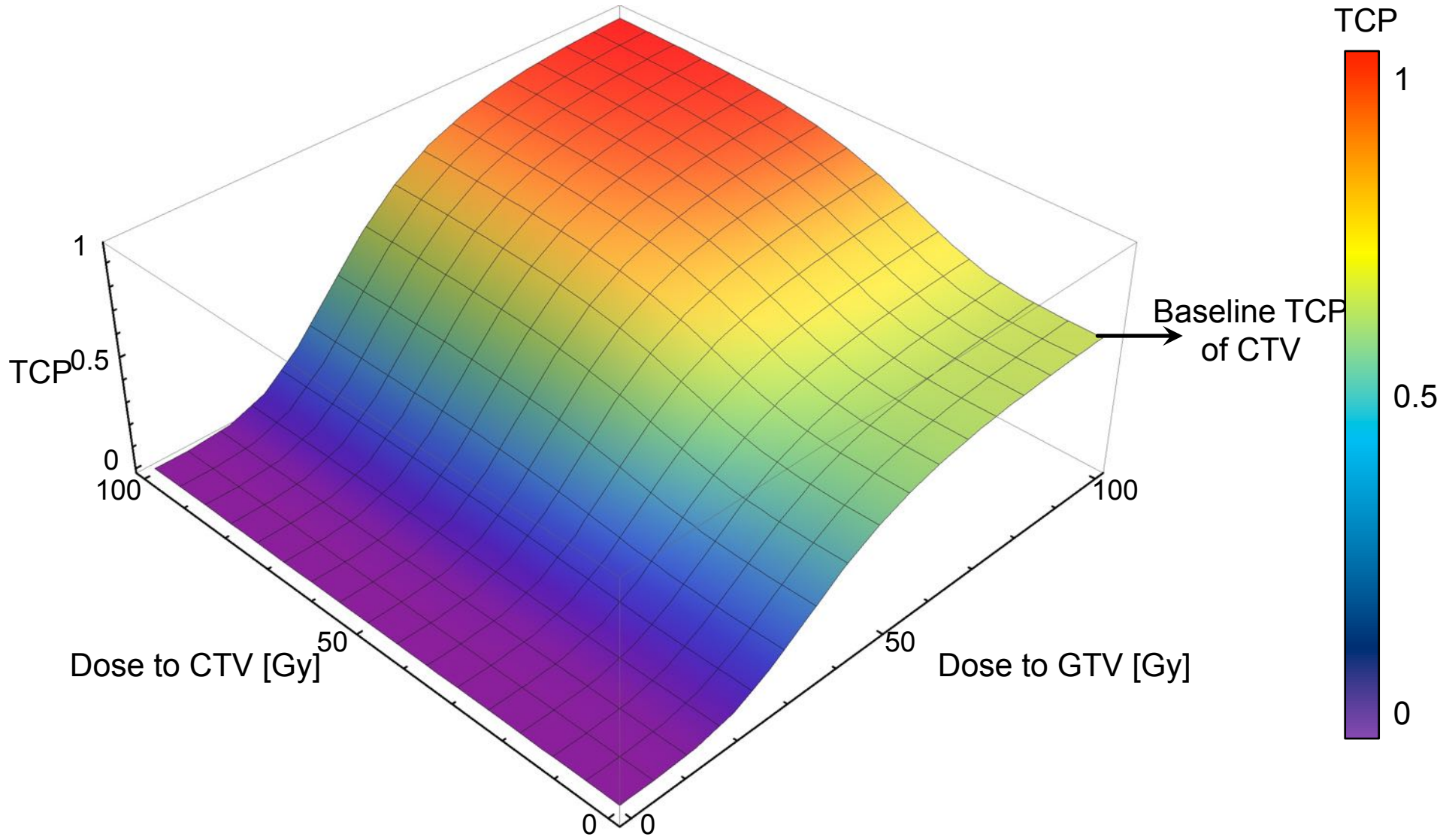


How to combine TCP for GTV & CTV?

- Some assumptions required:
  - The TCP for GTV and CTV are not influenced each other
  - The TCP is homogeneous within a given volume
  - Different volumes could have different model parameters



TCP surface for different volumes

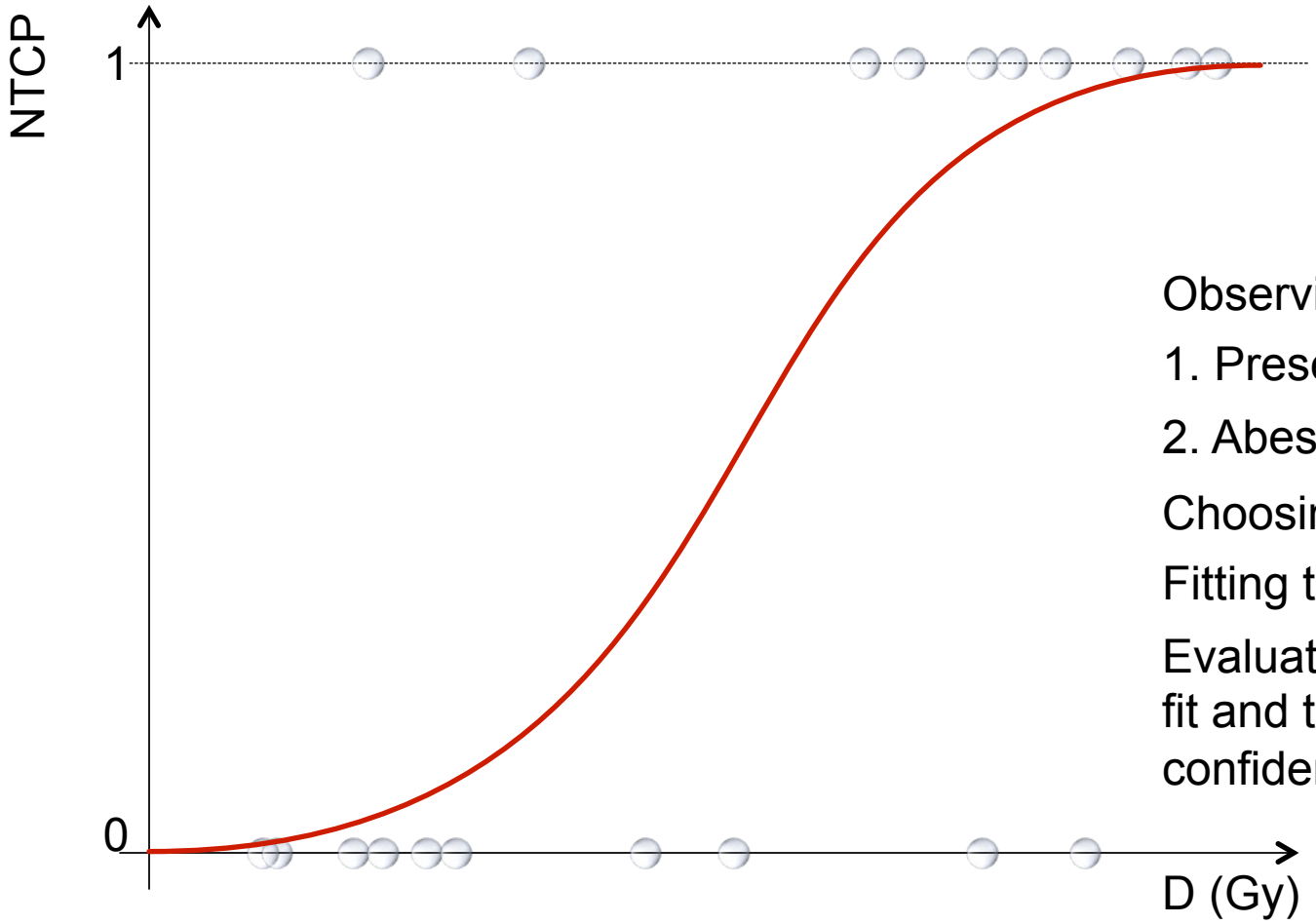


NTCP phenomenological modeling issues

- 1. Clinical definition of the ‘complication’
  - 1. Toxicity scoring system
    - Binary classification of the patients (with- or without-complication)
  - 2.Observation time (usually at a given moment in the follow up history of the patient)
  - 3. Homogeneity of evaluation criteria (intra- or inter-observer evaluation variability)
    - 1.Subjective – a score given by the observer or using patients addressed specific questions
    - 2.Objective – a score obtained by laboratory measures or specific diagnostic procedures

- 2. Reliability of the model
  - 1. Sample size
  - 2.Modeling mathematical procedure
    - 1.Confidence intervals
    - 2.Consistence and practical application of parameters to be used in clinical setting

NTCP phenomenological modeling issues



Observing a binary outcome:

1. Present
2. Abesent

Choosing a model

Fitting the model

Evaluating the goodness of fit and the parameters confidence intervals

NTCP phenomenological modeling: choosing a model

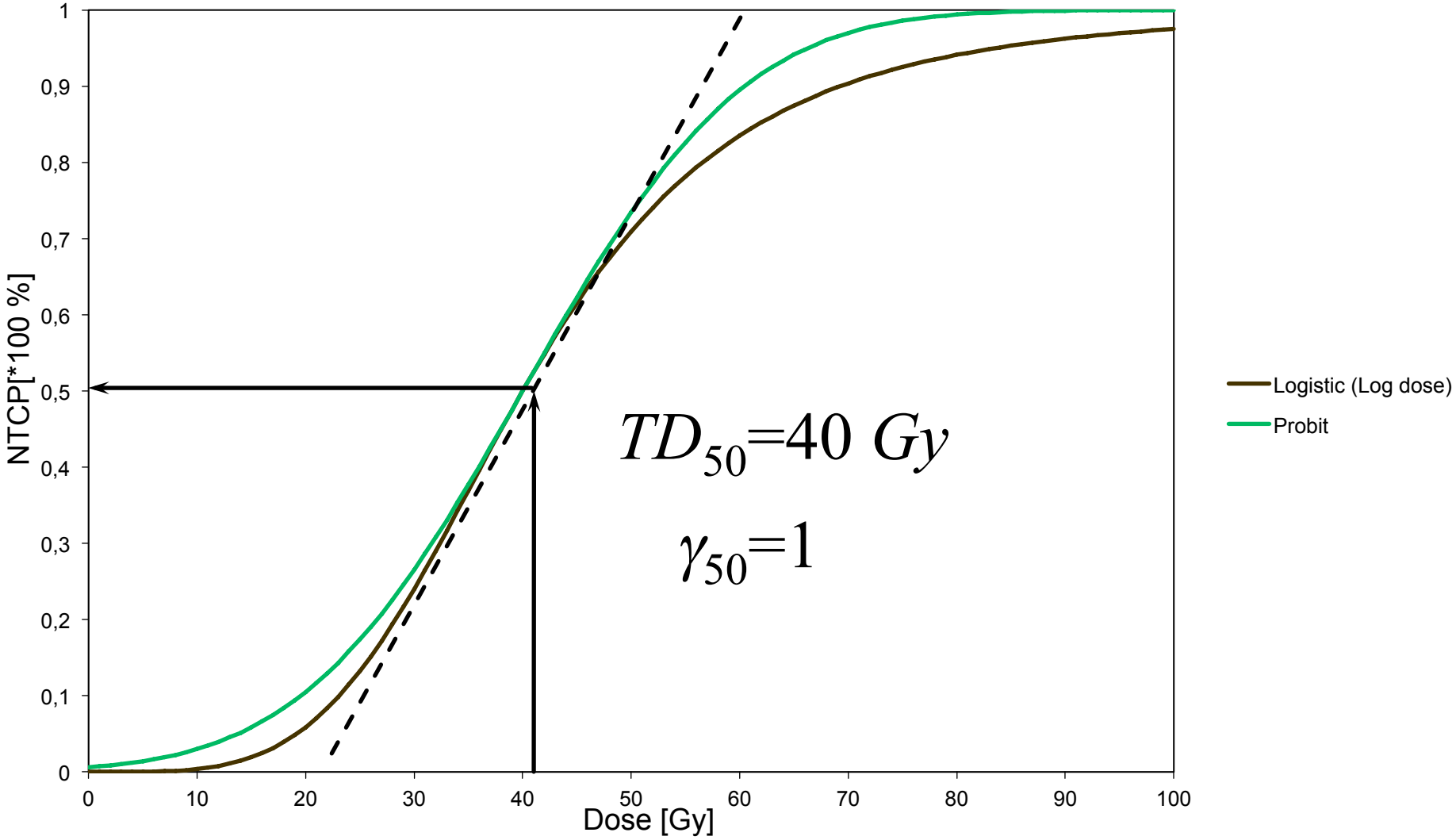
- *Probit*: $NTCP = \frac{1}{2\sqrt{\pi}} \int_{-\infty}^{t} e^{-\frac{x^2}{2}} dx \, , t = \frac{D - D_{50}}{D_{50}} \cdot \left(\gamma_{50} \sqrt{2\pi} \right)$

  Lyman

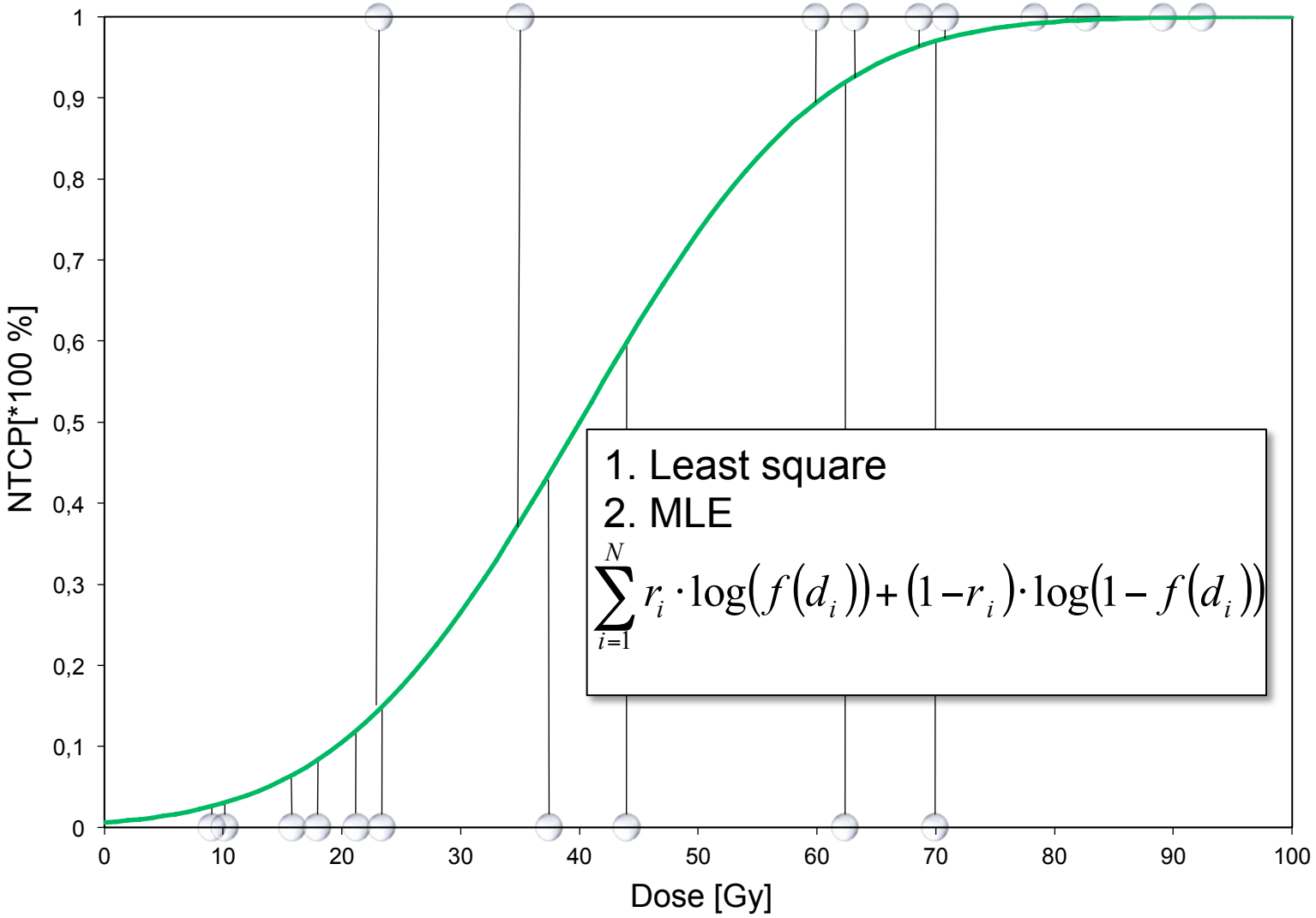
- *Logistic* (log *dose*): $NTCP = \frac{1}{1 + \left(\frac{D}{D_{50}} \right)^{4\gamma_{50}}}$

  Niemierko

NTCP phenomenological modeling: choosing a model



NTCP phenomenological modeling: fitting a model



NTCP phenomenological modeling: evaluating a model

Table 3. Model ranking based on the AIC

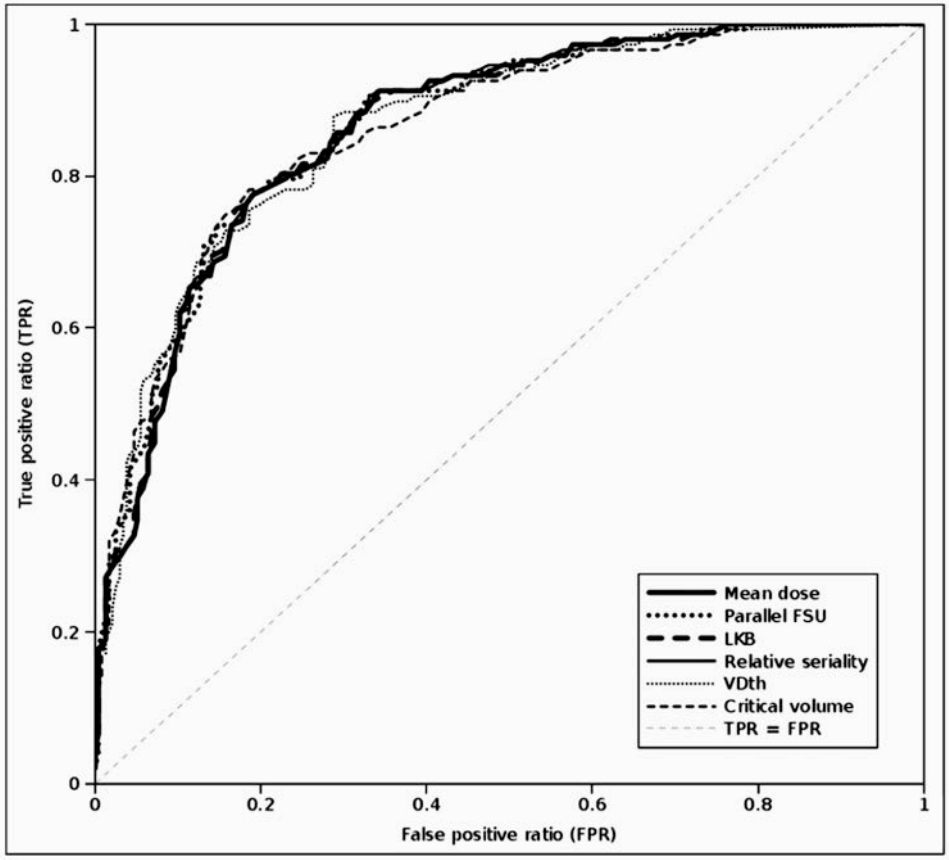
Model	Δ_{LL}	AIC	ROC
Mean dose	339.19	343.22	0.864
Parallel FSU	336.44	344.55	0.867
LKB	340.63	346.70	0.864
Relative seriality	342.56	348.63	0.864
V_{Dth}	342.98	349.04	0.864
Critical volume	357.73	365.83	0.862

Abbreviations: AIC = Akaike's information criterion; Δ_{LL} = deviance; ROC = area under the receiver operacting characteristic curve.

- Δ_{LL}
- AIC

→ Relative score

- ROC → Absolute score



AC Houweling 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.

NTCP phenomenological modeling: evaluating a model

"We combined the parotid gland data of the University Medical Center Utrecht and the University of Michigan Hospital to generate **the largest published dataset of objectively measured parotid gland complications** (384 parotid glands)."

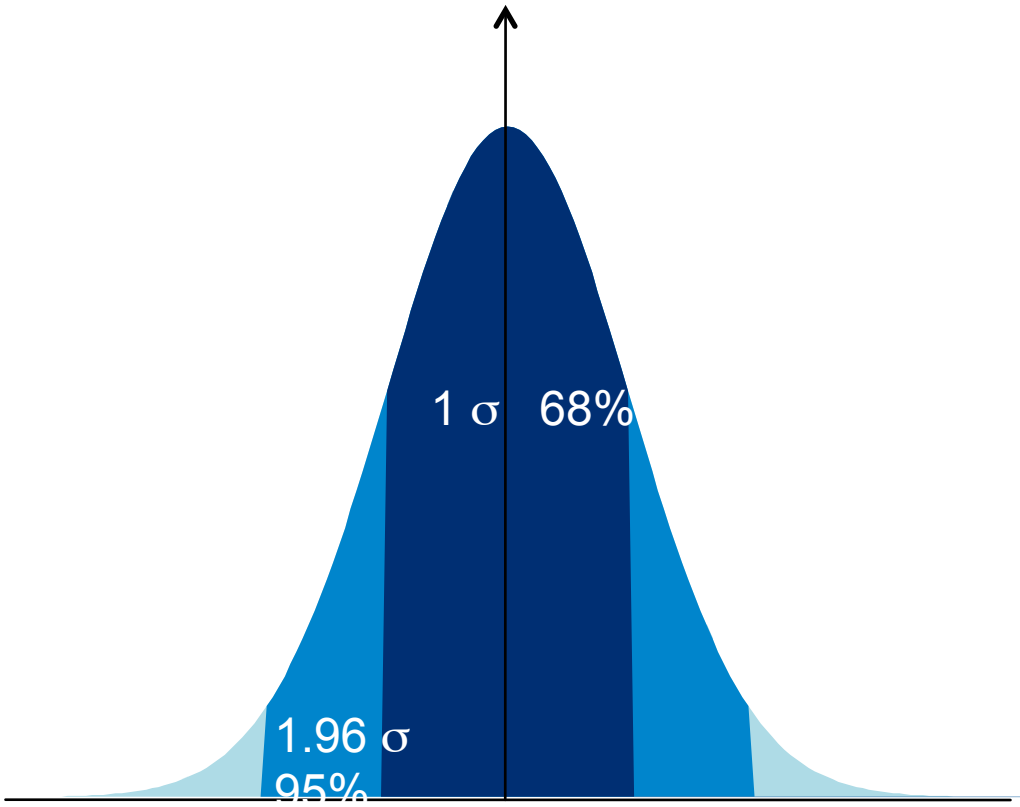
AC Houweling et al. A comparison of dose–response models for the parotid gland in a large group of head-and-neck cancer patients. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 4, pp. 1259–1265, 2010.

NTCP phenomenological modeling: evaluating confidence intervals

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.



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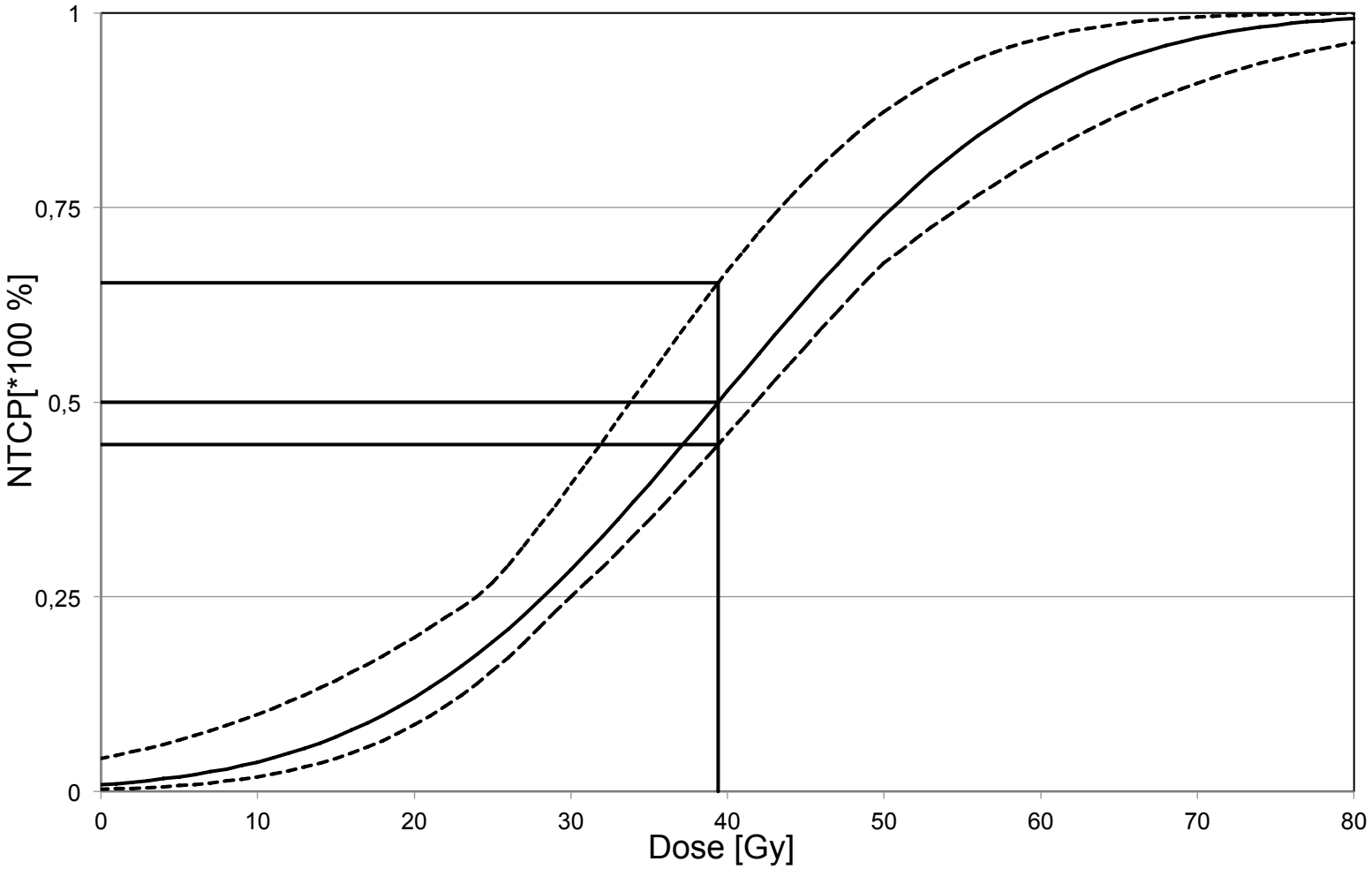
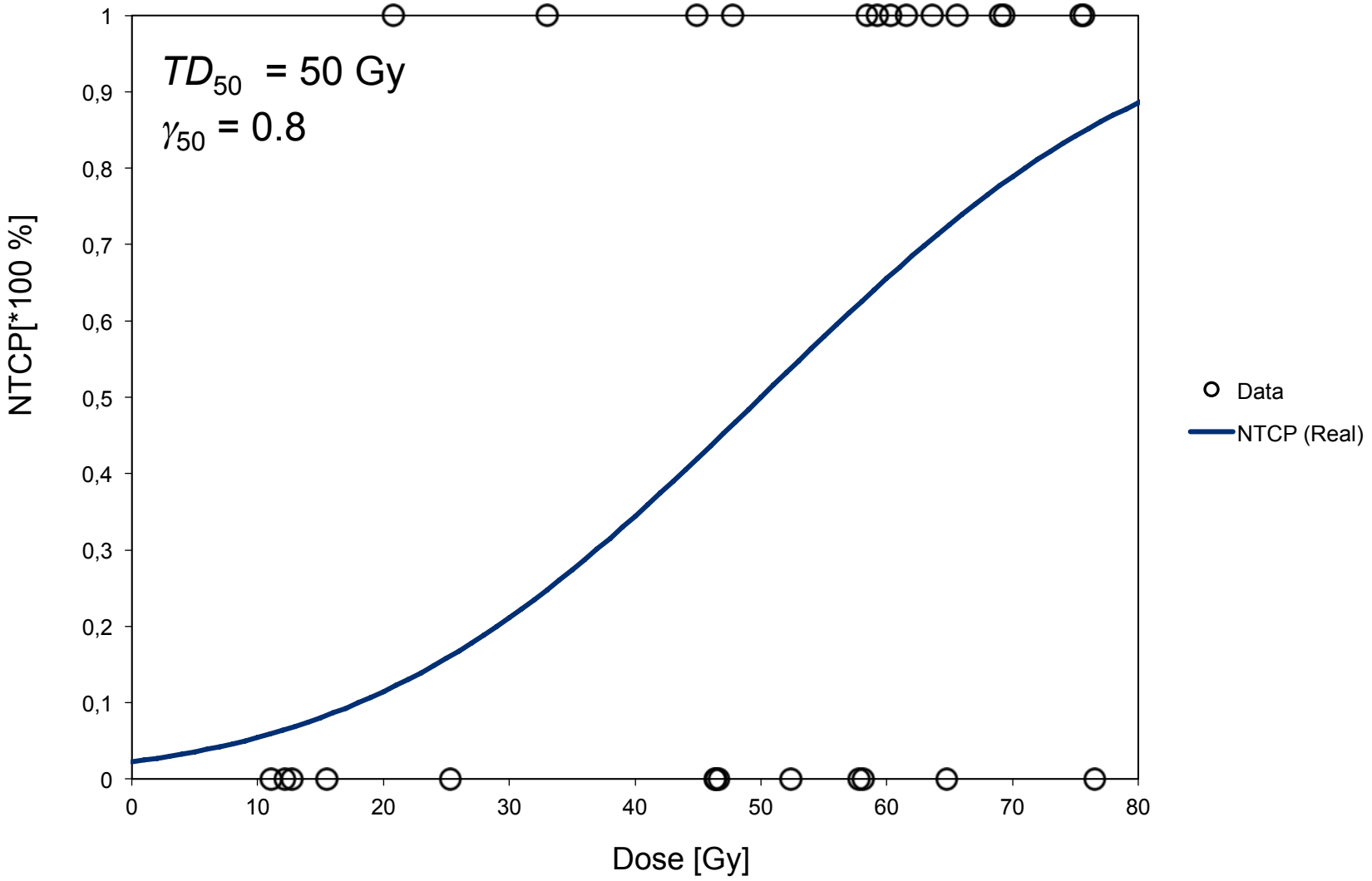
NTCP phenomenological modeling: evaluating confidence intervals

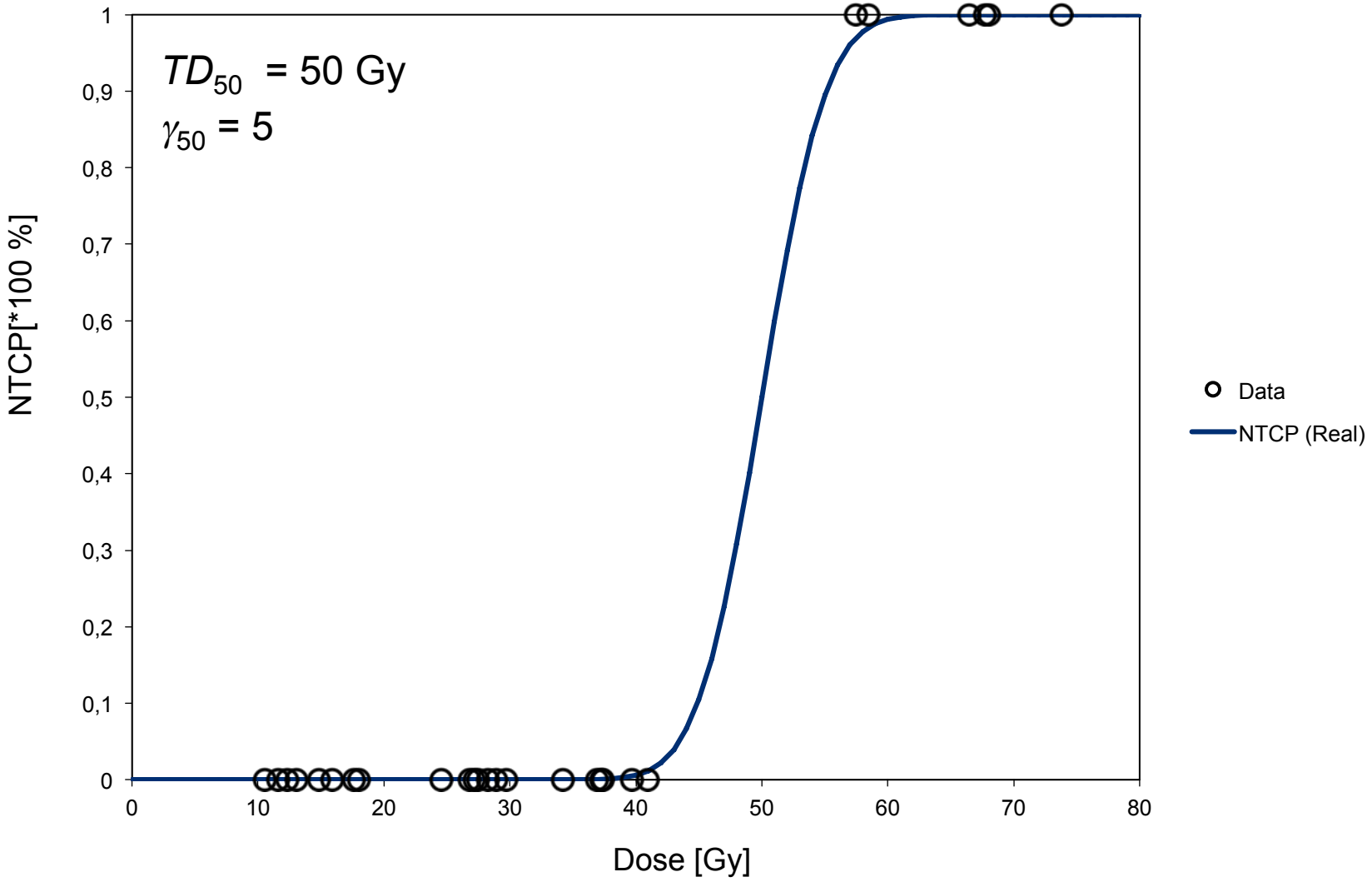


AC Houweling et al. A comparison of dose–response models for the parotid gland in a large group of head-and-neck cancer patients. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 4, pp. 1259–1265, 2010.

NTCP phenomenological modeling: overcoming the uncertainties



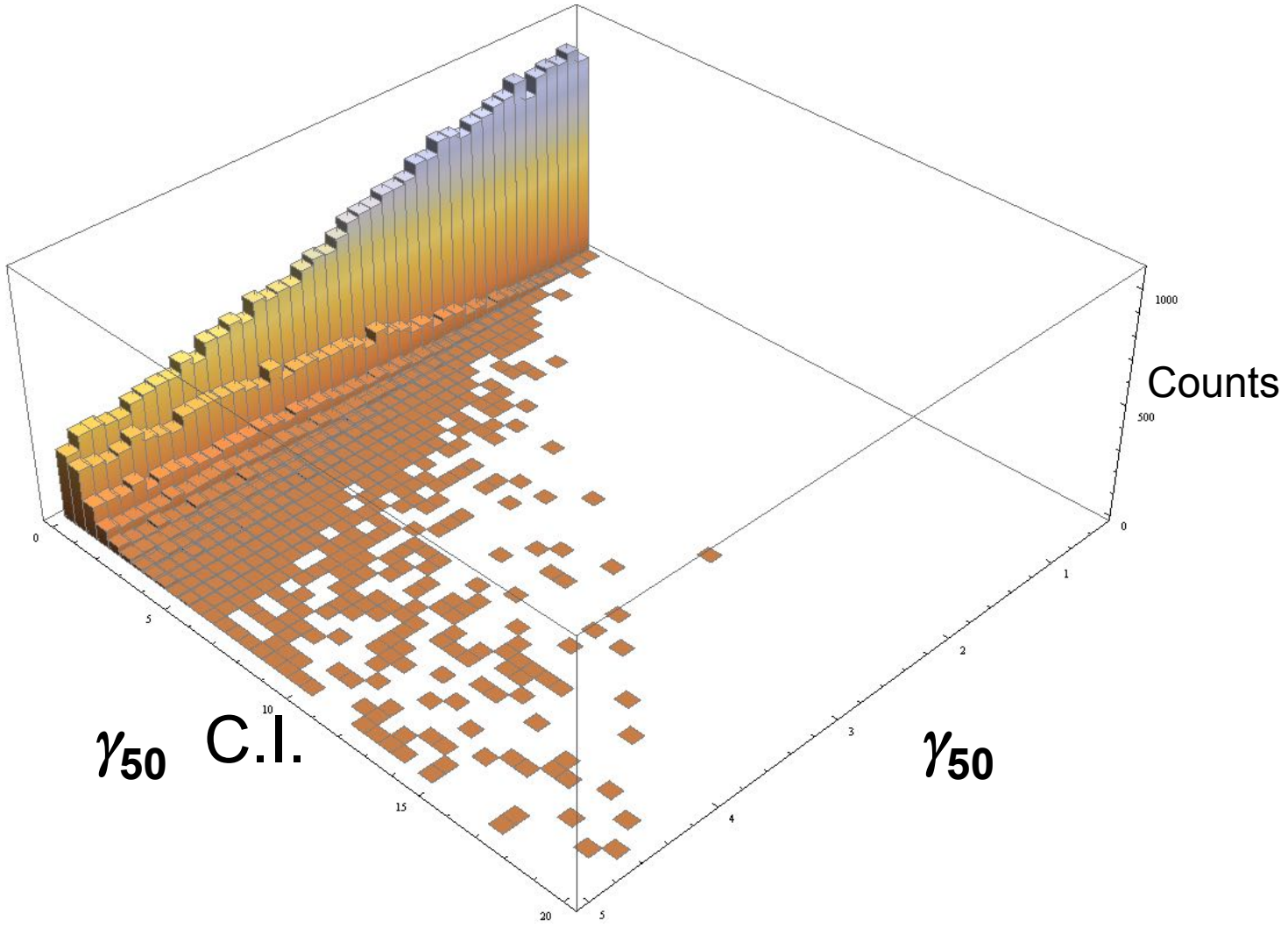
NTCP phenomenological modeling: overcoming the uncertainties



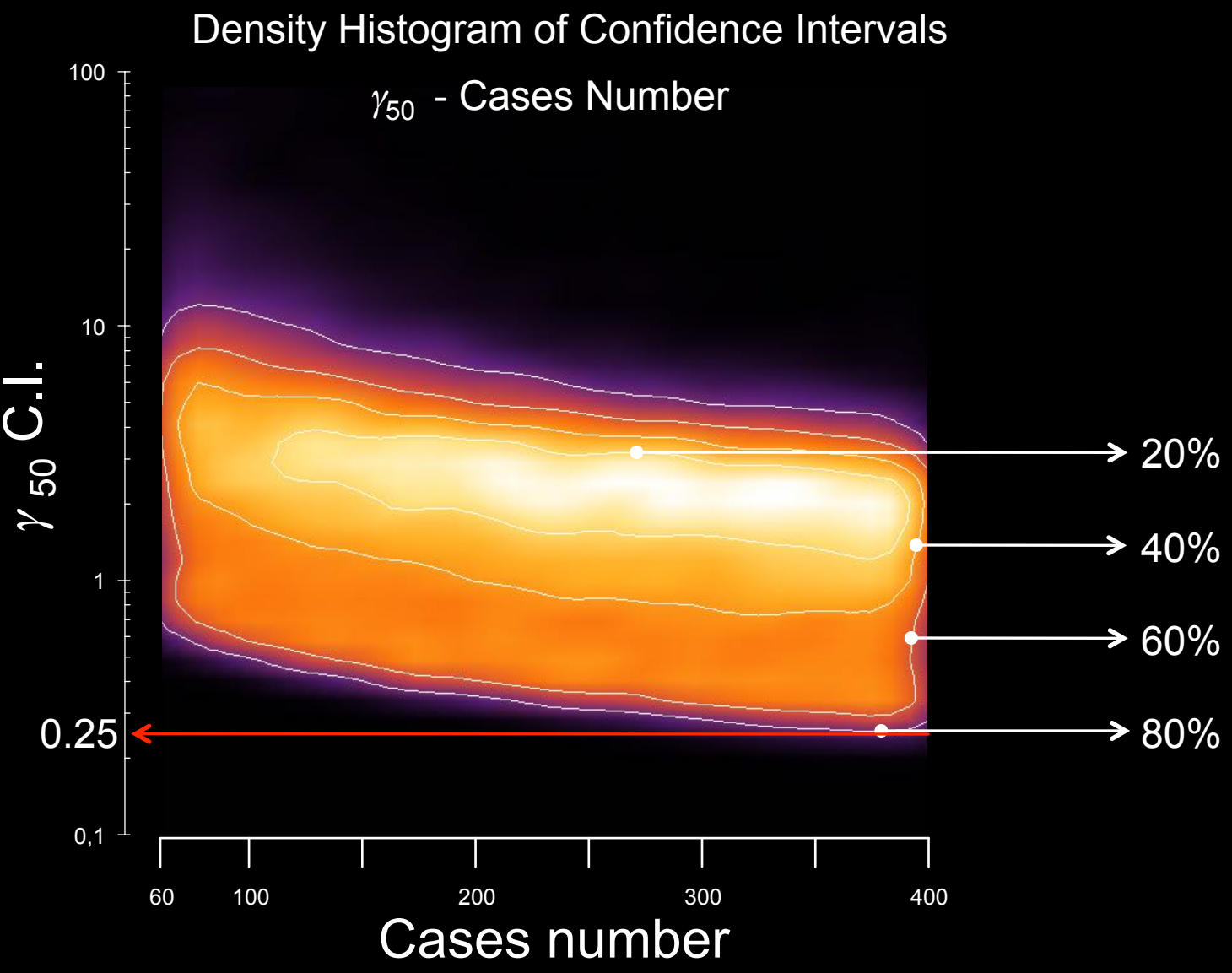
NTCP phenomenological modeling: overcoming the uncertainties

- **Monte-Carlo** approach to simulate almost 10^7 virtual patients, organized in ≈43500 series (avg. 230 pts/series, from 60 up to 400)
- **Randomization** of patients series parameters (TD_{50}, γ_{50}, number of patients per series)
- Simulation of modeling procedures (Maximum Likelihood Estimation) for dose/response prediction
- Evaluation of this modeling approach procedure

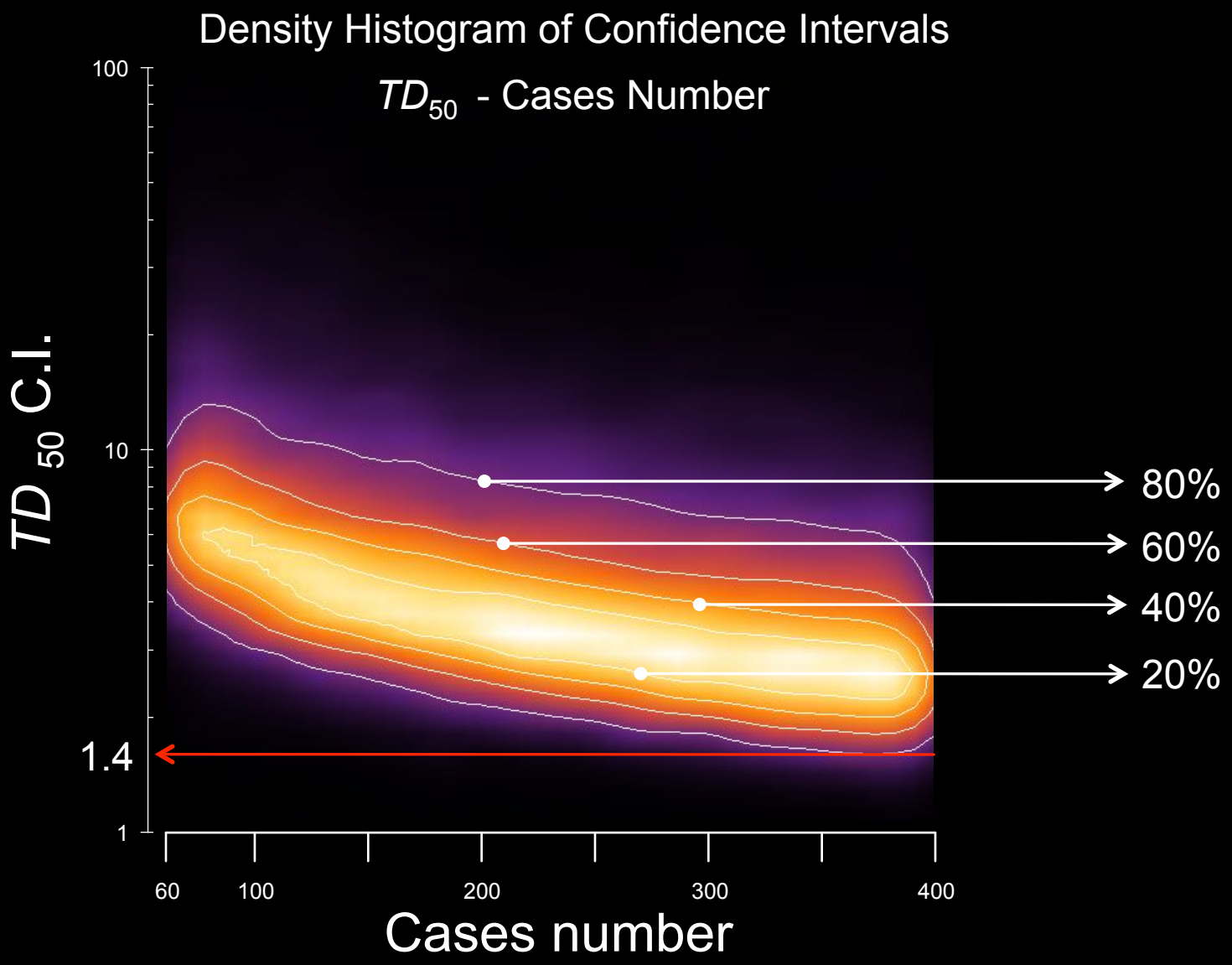
NTCP phenomenological modeling: overcoming the uncertainties



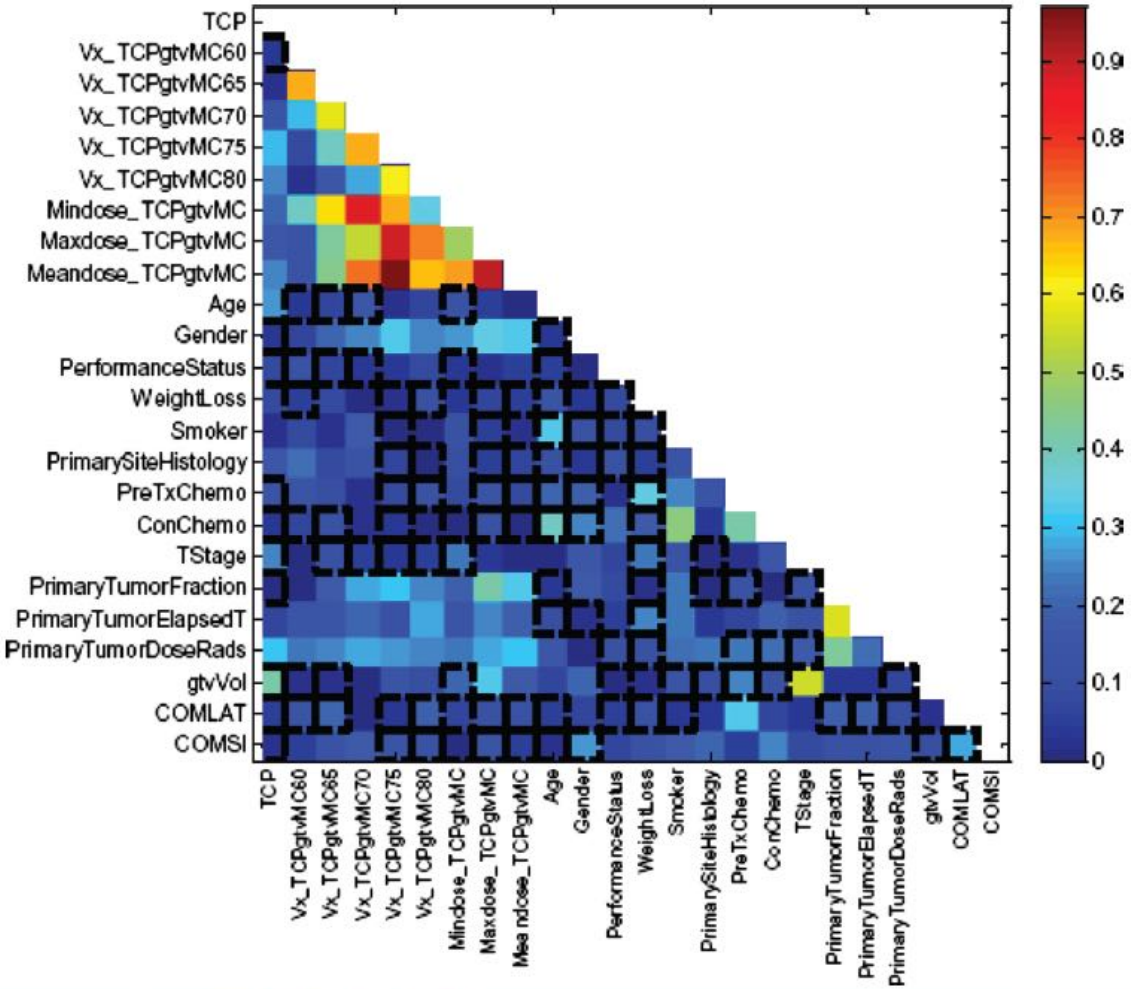
Modeling uncertainties management



Modeling uncertainties management



TCP Modeling uncertainties management



Naqa IE et al. Datamining approaches for modeling tumor control probability. Acta Oncologica, 2010; 49: 1363–1373

NTCP Modeling uncertainties management

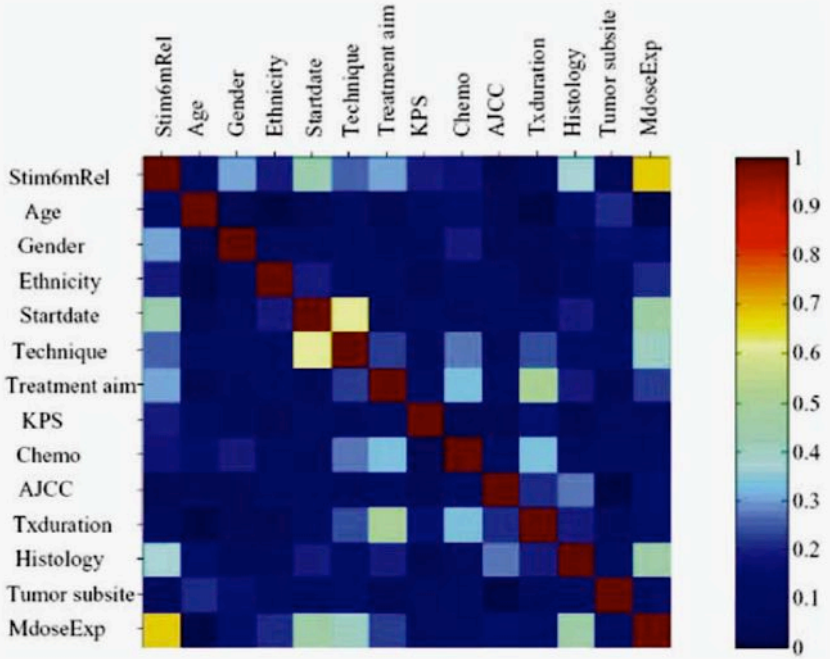


Fig. 3. Spearman's rank correlation coefficient for a selection of dose and clinical factors for relative salivary function at 6 months after radiotherapy (Stim6mRel). Each element's intensity represents the correlation between two factors. A cofactor listed in the *n*th row is also a cofactor in the *n*th column. For example, there is a high correlation between treatment duration and treatment aim (about 0.5), as shown at row 11, column 7; also shown at row 7, column 11 (for color see the online version).

Naqa IE et al. Multivariable modeling of radiotherapy outcomes, including dose-volume and clinical factors.. Int. J. Radiation Oncology Biol. Phys., Vol. 64, No. 4, pp. 1275–1286, 2006.

NTCP Modeling uncertainties management

QUANTEC: VISION PAPER

IMPROVING NORMAL TISSUE COMPLICATION PROBABILITY MODELS: THE NEED TO ADOPT A "DATA-POOLING" CULTURE

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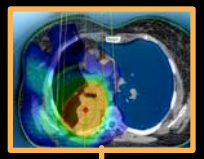
Clinical studies of the dependence of normal tissue response on dose-volume factors are often confusingly inconsistent, as the QUANTEC reviews demonstrate. A key opportunity to accelerate progress is to begin storing high-quality datasets in repositories. Using available technology, multiple repositories could be conveniently queried, without divulging protected health information, to identify relevant sources of data for further analysis. After obtaining institutional approvals, data could then be pooled, greatly enhancing the capability to construct predictive models that are more widely applicable and better powered to accurately identify key predictive factors (whether dosimetric, image-based, clinical, socioeconomic, or biological). Data pooling has already been carried out effectively in a few normal tissue complication probability studies and should become a common strategy.

JO Deasy et al. Improving normal tissue complication probability models: the need to adopt a "data-pooling" culture. Int. J. Radiation Oncology Biol. Phys., Vol. 76, No. 3, Supplement, pp. S151–S154, 2010.

VATE project

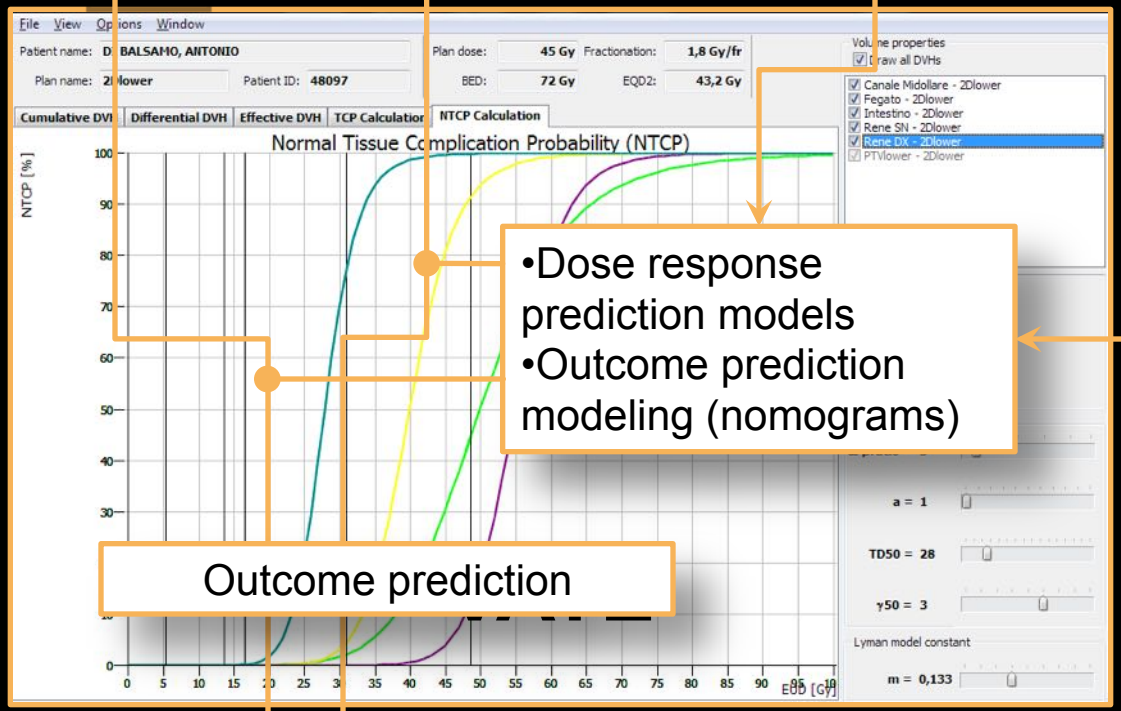
Clinical case data

Physical dose distribution



Single center (on site) database

Multicenter (reference) database



- Dose response prediction models
- Outcome prediction modeling (nomograms)

Outcome prediction

78.5%±3.2% - AUC=0.78

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VARIAN