Radyobiyolojik Tedavi Planlama

(*Radiobiologically Guided Radiotherapy*)

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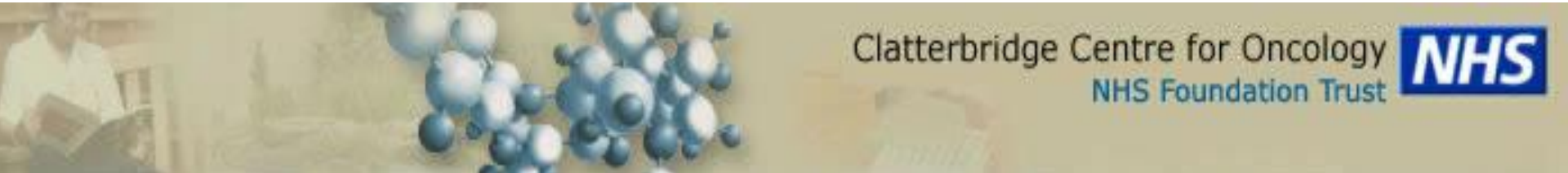
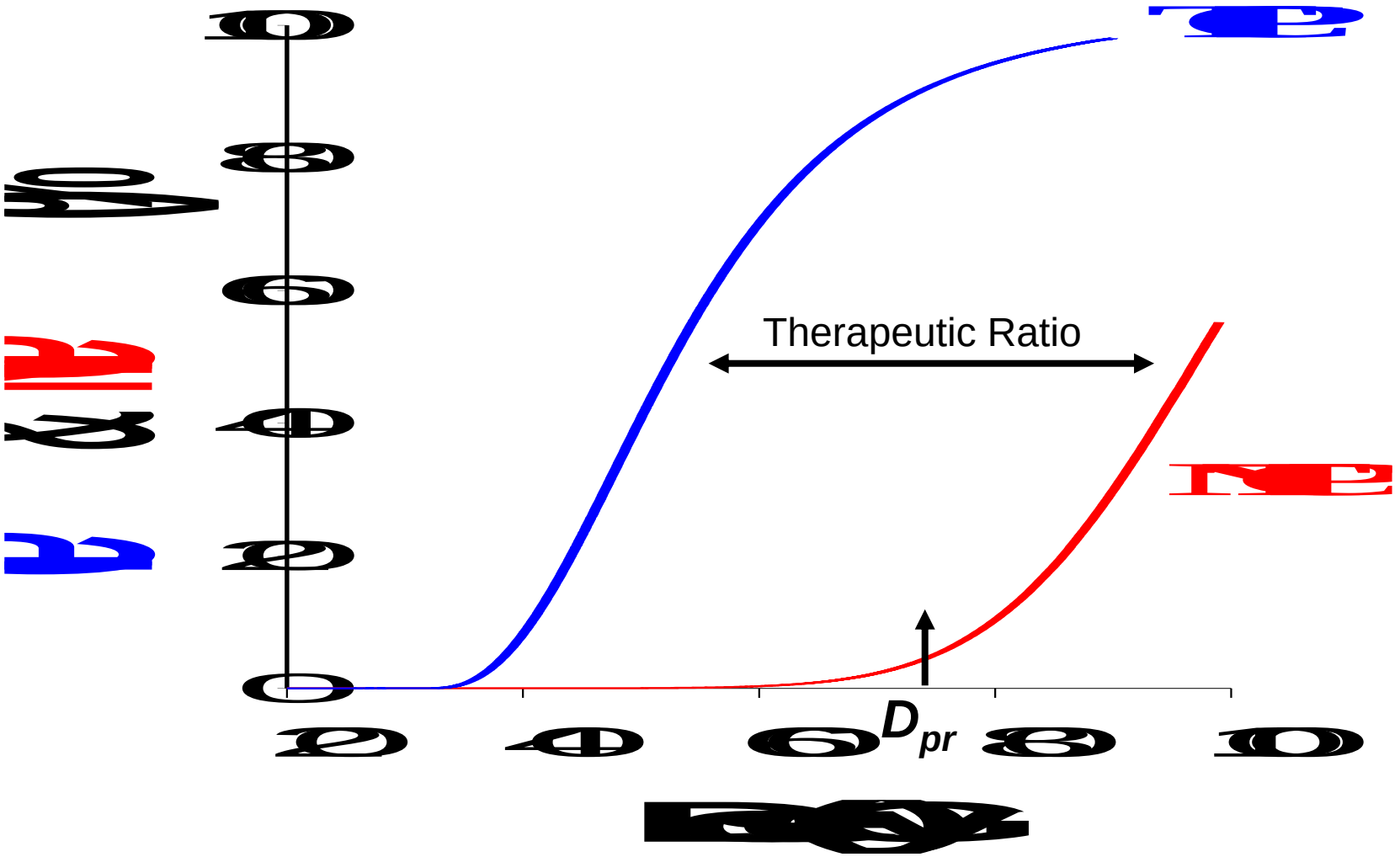
XI. ULUSAL MEDIKAL FIZIK KONGRESI, 14-18 KASIM 2007, CONCORDE HOTEL, ANTALYA



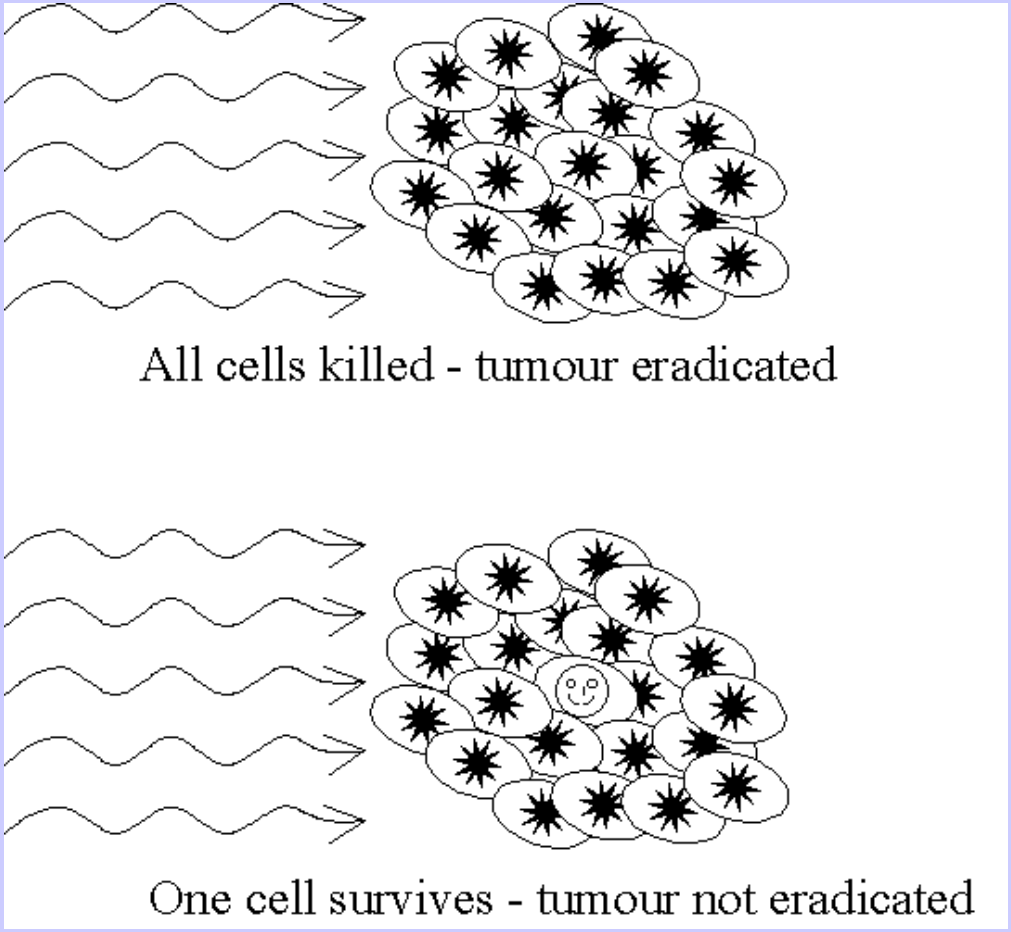


N.B. *for a given fraction size*

What uses might we have for *TCP* and *NTCP* models?

- Analyze clinical+dose-volume data (retrospectively)
- Evaluate treatment plans retrospectively
- Modify treatment plans/Plan the treatment(!)
- Put into an optimization/inverse -planning 'loop'
- Make direct use of clonogen radiosensitivity to improve the prediction of *local control* for an individual patient
- Evaluate/estimate the benefit/harm of
  - Changing the fraction size and total dose
  - '*Dose painting*' (e.g. to mitigate hypoxia 'seen' with PET)
  - Patient movement
  - Dosimetric errors, cold spots, partial tumour boosts etc.

A Mechanistic model for tumour (local) control probability



Poisson-based TCP model

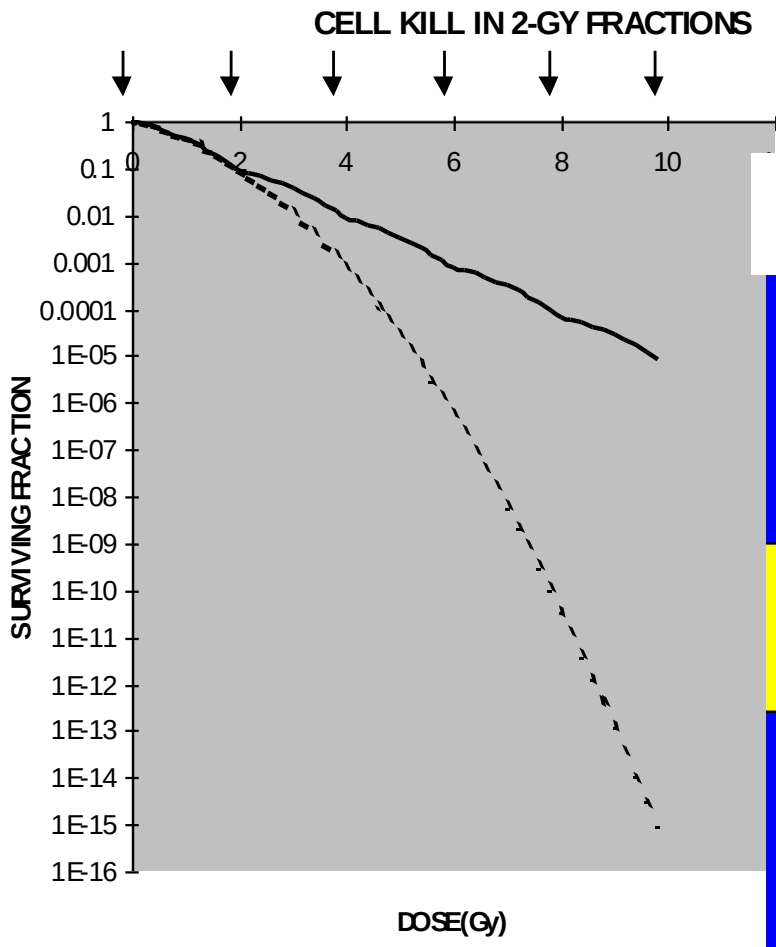
The tumour is "controlled" when

NO SINGLE CLONOGENIC CELL SURVIVES (y = 0)

$$TCP = P(N,0) = e^{-N}$$

where *N* is the average value of the final number of clonogens

What do we know about cell killing by radiation?



The Linear-Quadratic Model:

Clonogenic cells after *n* fractions is given by

***n* times**

$$N = N_0 \cdot e^{-\left(\alpha \cdot d + \beta \cdot d^2\right)} \cdot e^{-\left(\alpha \cdot d + \beta \cdot d^2\right)} \cdots e^{-\left(\alpha \cdot d + \beta \cdot d^2\right)}$$

***N* after 1st fraction**

***N* after 2nd fraction...**

NB the LQ expression assumes that the doserate is HIGH (cf. LDR brachy) and may be invalid below ≈ 0.8 Gy (low-dose hypersensitivity: HRS)

Poisson-statistics-based TCP model

No. of cells surviving after *n* fractions (*D* = total dose = *d* * *n*):

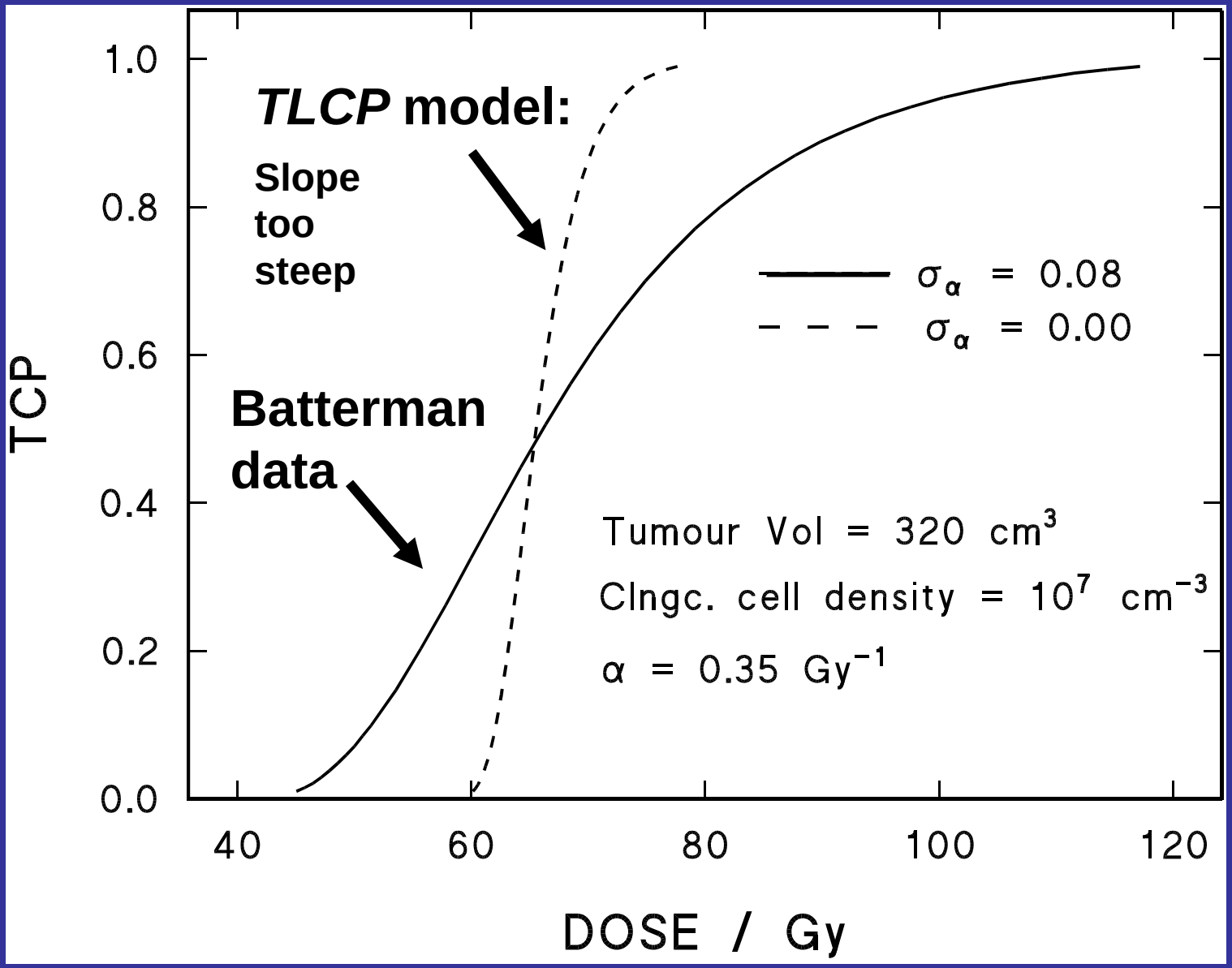
$$N_s = N_o \exp\left[-\alpha D\left(1+\frac{\beta}{\alpha}d\right)\right]$$

Thus the expression for TCP is

$$TCP = \exp\left\{-N_o \exp\left[-\alpha D\left(1+\frac{\beta}{\alpha}d\right)\right]\right\}$$

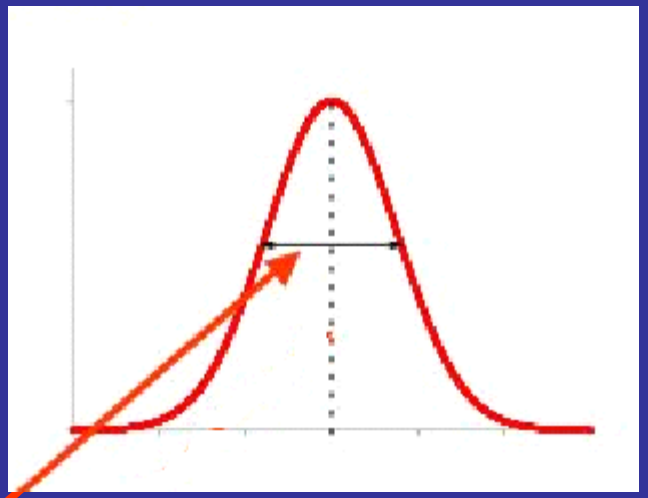
for total dose *D* delivered in *n* equal fractions of size *d* [final term 0 as $\beta/\alpha \rightarrow 0$]

Fitting the Batterman *et al* ca. bladder data (Nahum and Tait 1992)



Building inter - patient heterogeneity into the *TLCP* model

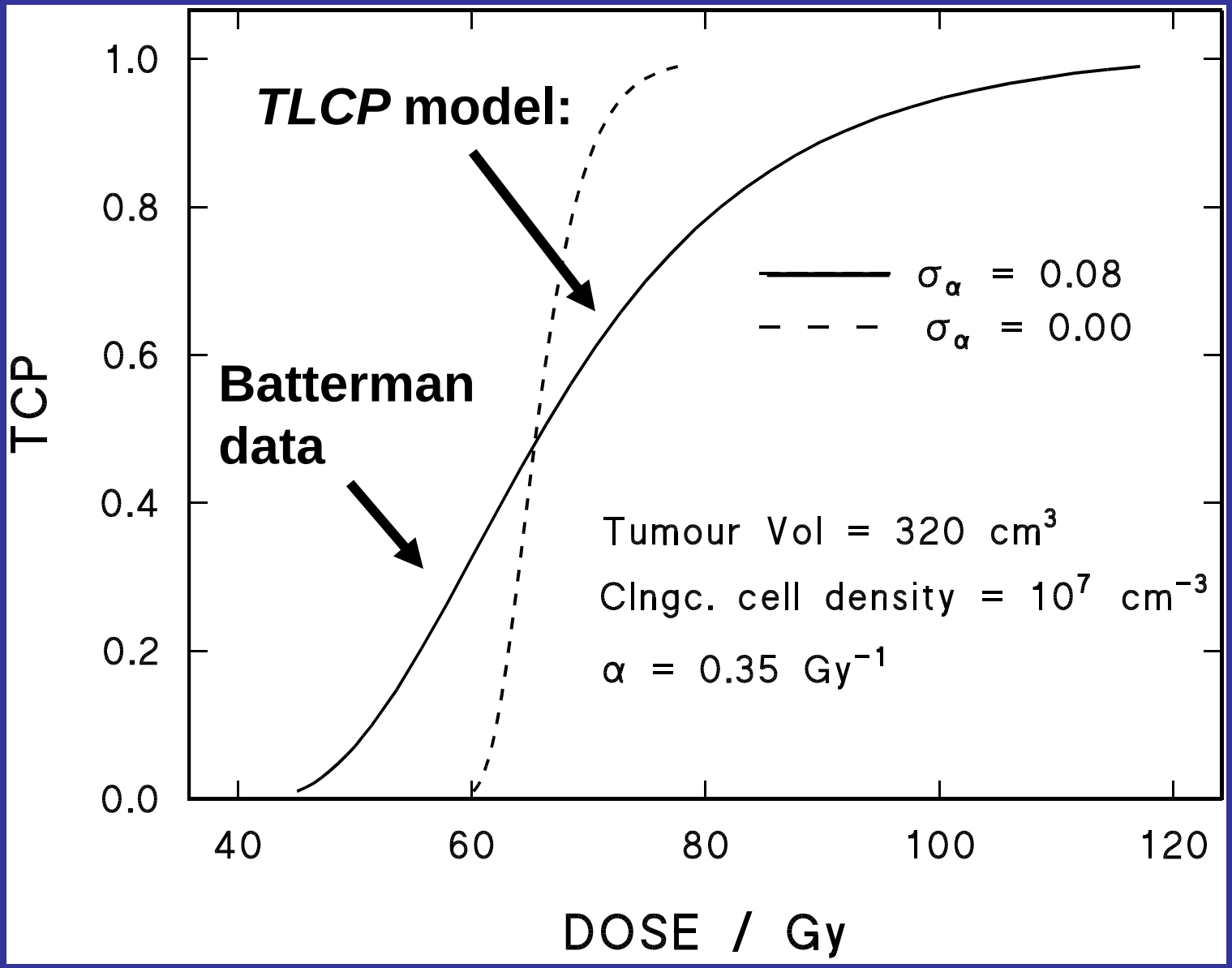
It is assumed that radiosensitivity α is normally distributed over the patient population with SD = σ_α



$$TCP(D,\alpha_i) = \exp\left\{-N_o \exp\left[-\alpha_i D\left(1+\frac{\beta}{\alpha}d\right)\right]\right\}$$

$$TCP(D,\bar{\alpha},\sigma_\alpha) = \sum_i g_i(\sigma_\alpha)\cdot TCP(D,\alpha_i)$$

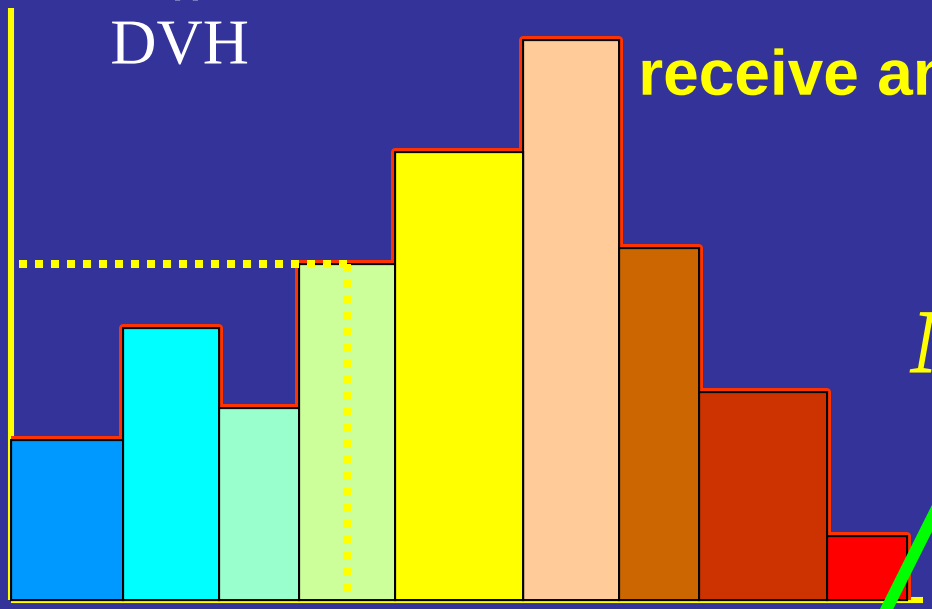
Fitting the Batterman *et al* ca. bladder data (Nahum and Tait 1992)



Inhomogeneous dose distributions

But … not all the cells receive the same dose

DVHs summarise the dose distributions in a convenient way



Cells in each single dose bin *i*

receive an ≈ uniform dose D_i

$$N_{o,i} = \rho_C \cdot v_i$$

Clonogen density

$$-\alpha \cdot D_i \left(1 + \frac{\beta}{\alpha} \cdot D_i\right)$$

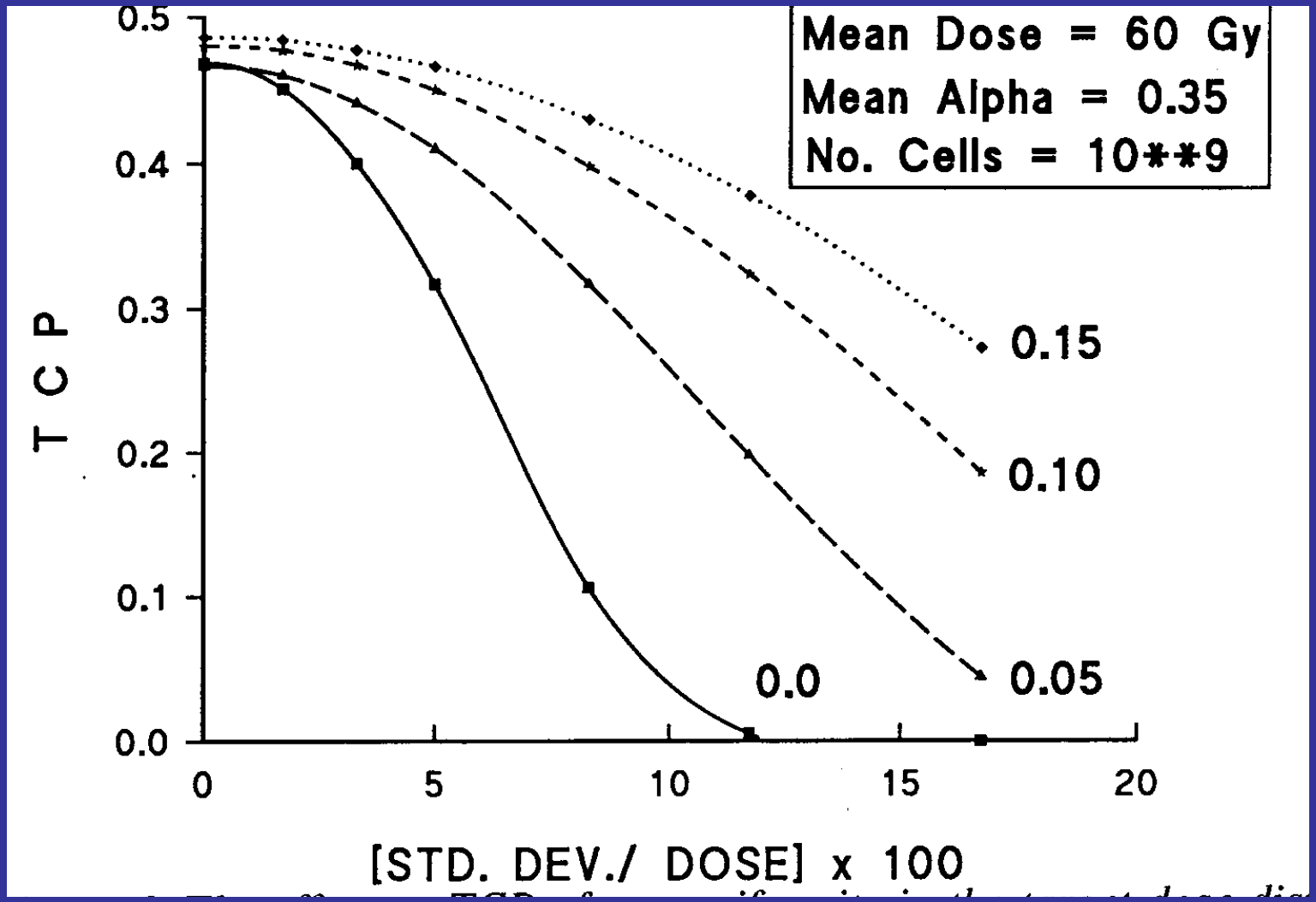
Total no. surviving cells

$$N = \sum_i N_i = \sum_i N_{o,i} \cdot e$$

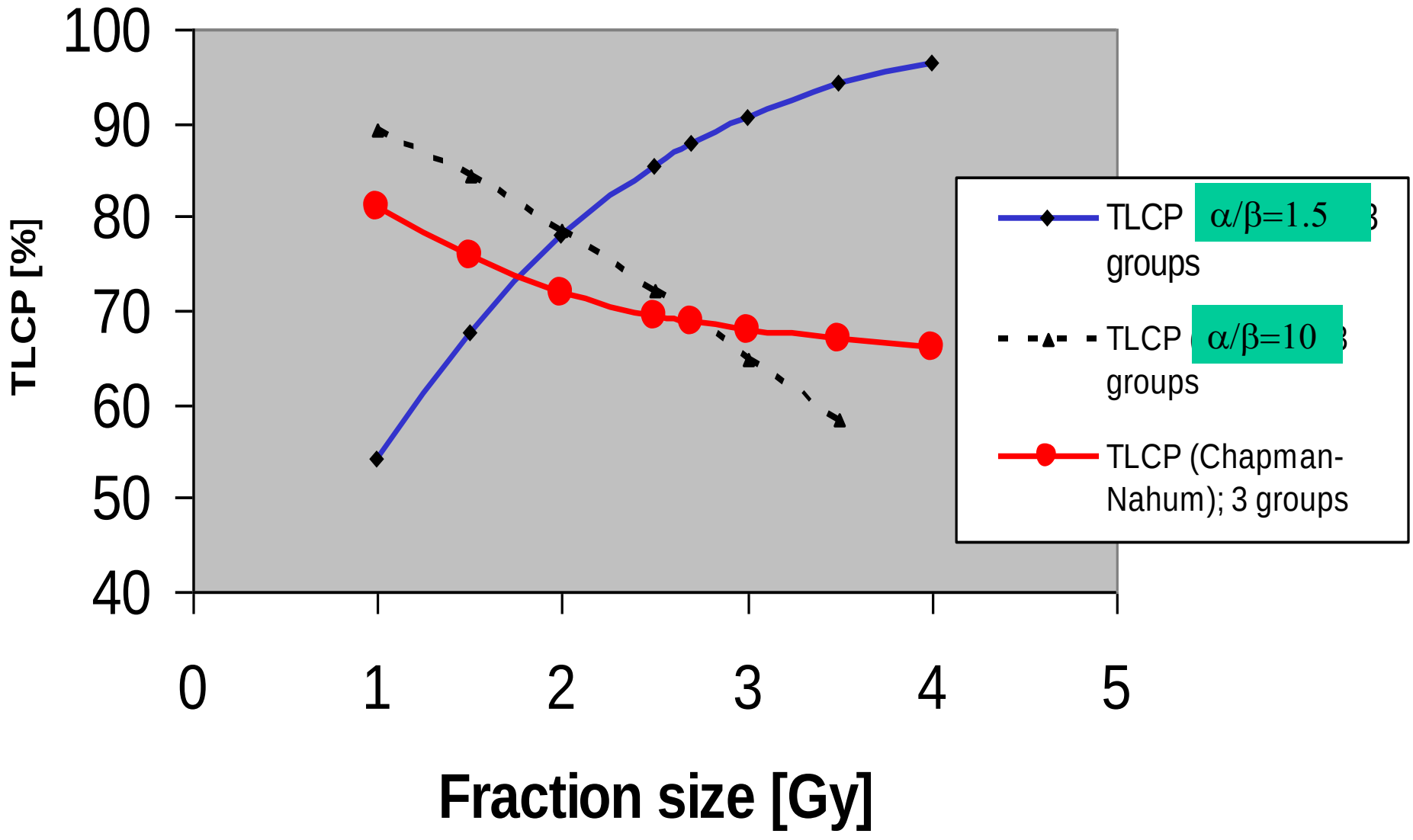
Effect of dose non-uniformity on TCP

- Tumour dose distribution (diff DVH) normally distributed with varying width but constant mean dose of 60 Gy.

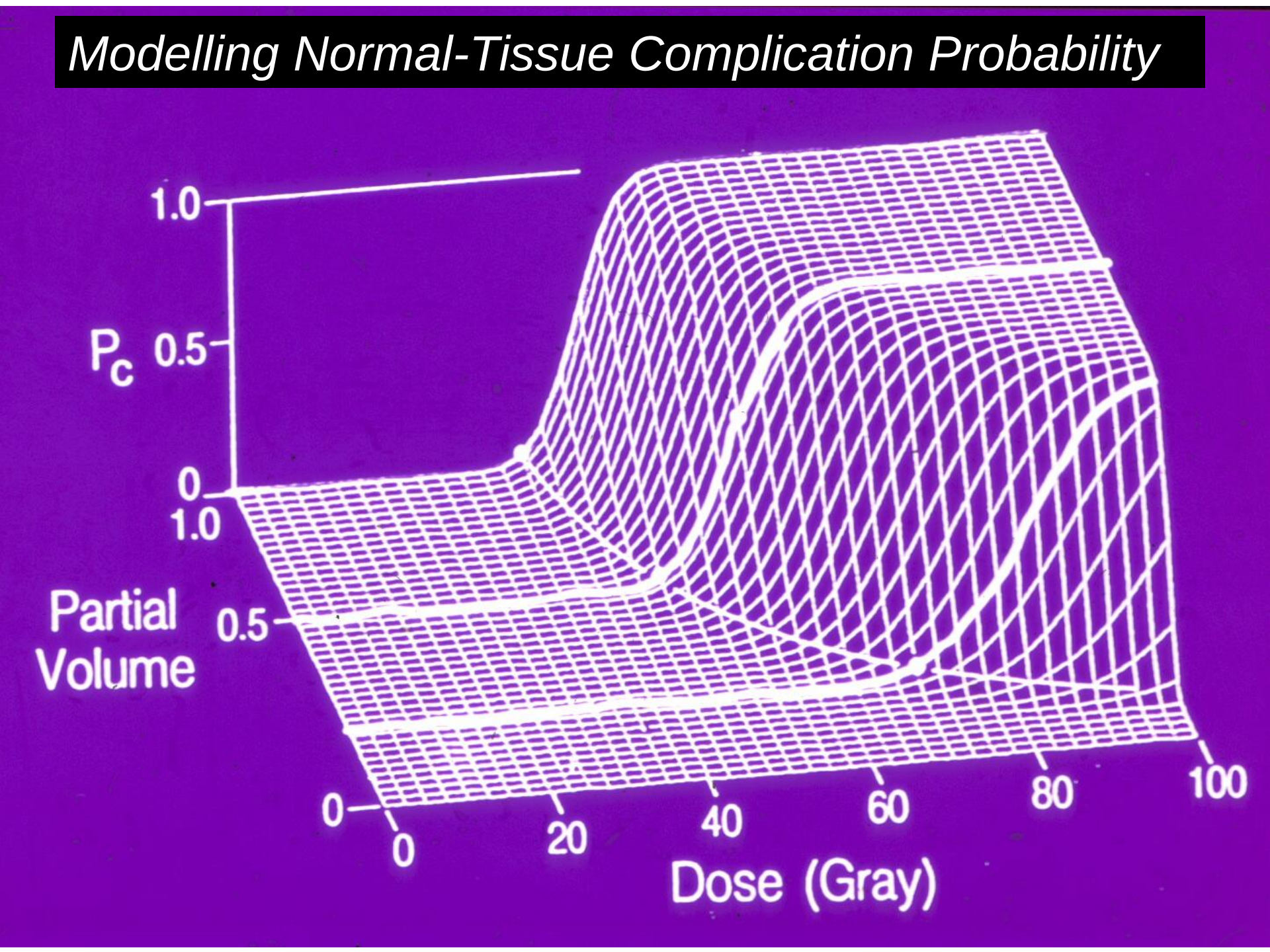
- inter-patient radiosensitivity σ_α varied from 0 to 0.05 to 0.10 to 0.15



TLCP as f'n of fraction size for N-T isoeffect (α/β=3)



Modelling Normal-Tissue Complication Probability



Lyman NTCP model (1985)

Basic assumptions:

- sigmoid- shape dose response curve (error function)
- power law relationship for tolerance doses.

  It can be applied independently to each volume element of the organ

- a ‘single step’ DVH represents the case of uniform irradiation of a partial volume (of the organ/tissue)
- extension to non-uniform irradiation through an algorithm (“DVH reduction”)

- **Formal Equations (Lyman-Kutcher-Burman)**
  for uniform partial irradiation: (with dose D of the partial volume *v*)

$$NTCP = \frac{1}{\sqrt{2\pi}} \int_{-\infty}^{t} \exp\left(-t^2/2\right) dt$$

- Error function
- Doesn't exhibit a "threshold" effect

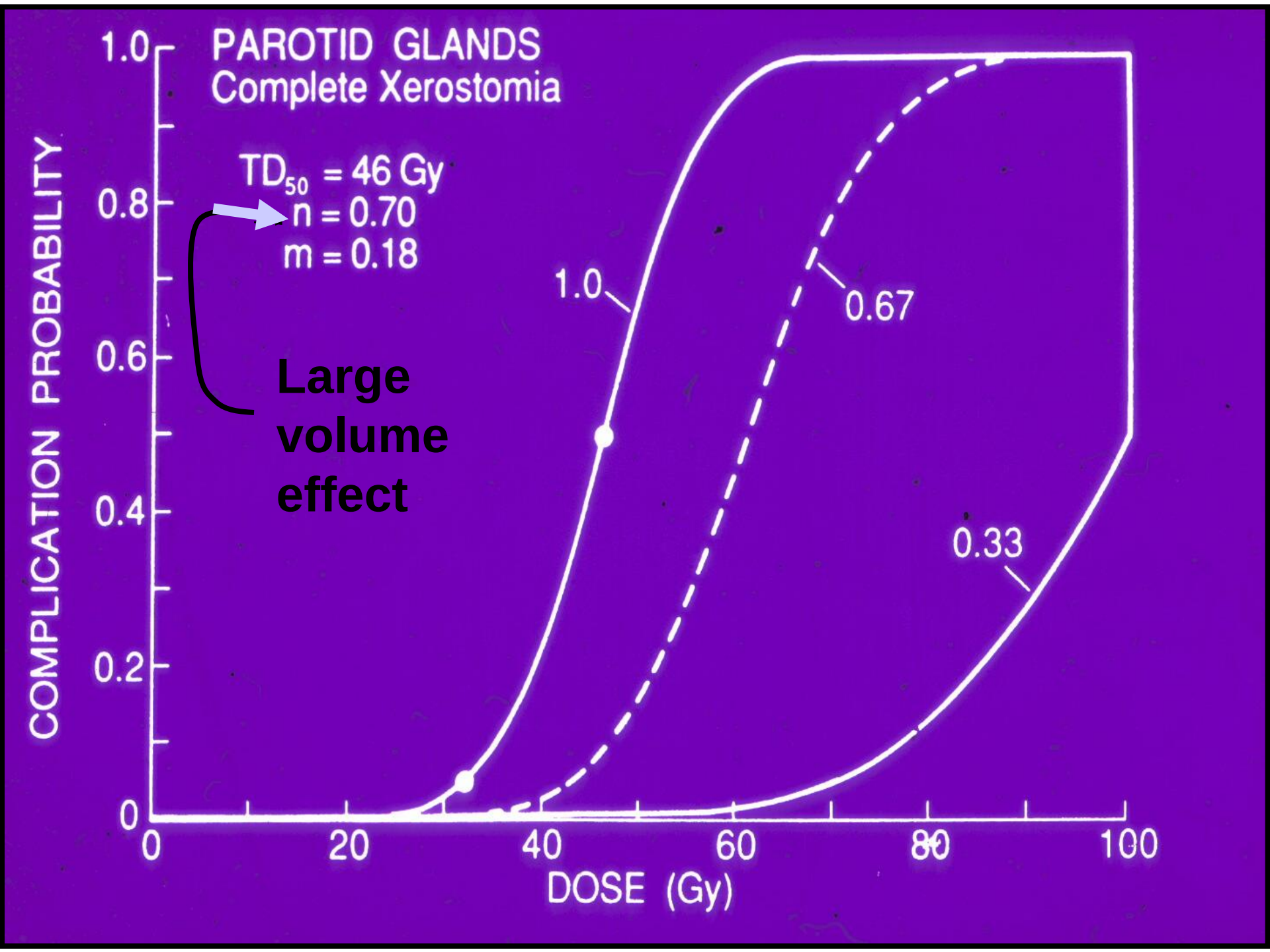
$$t = \frac{D - D_{50}{}^{v}}{m * D_{50}{}^{v}}$$

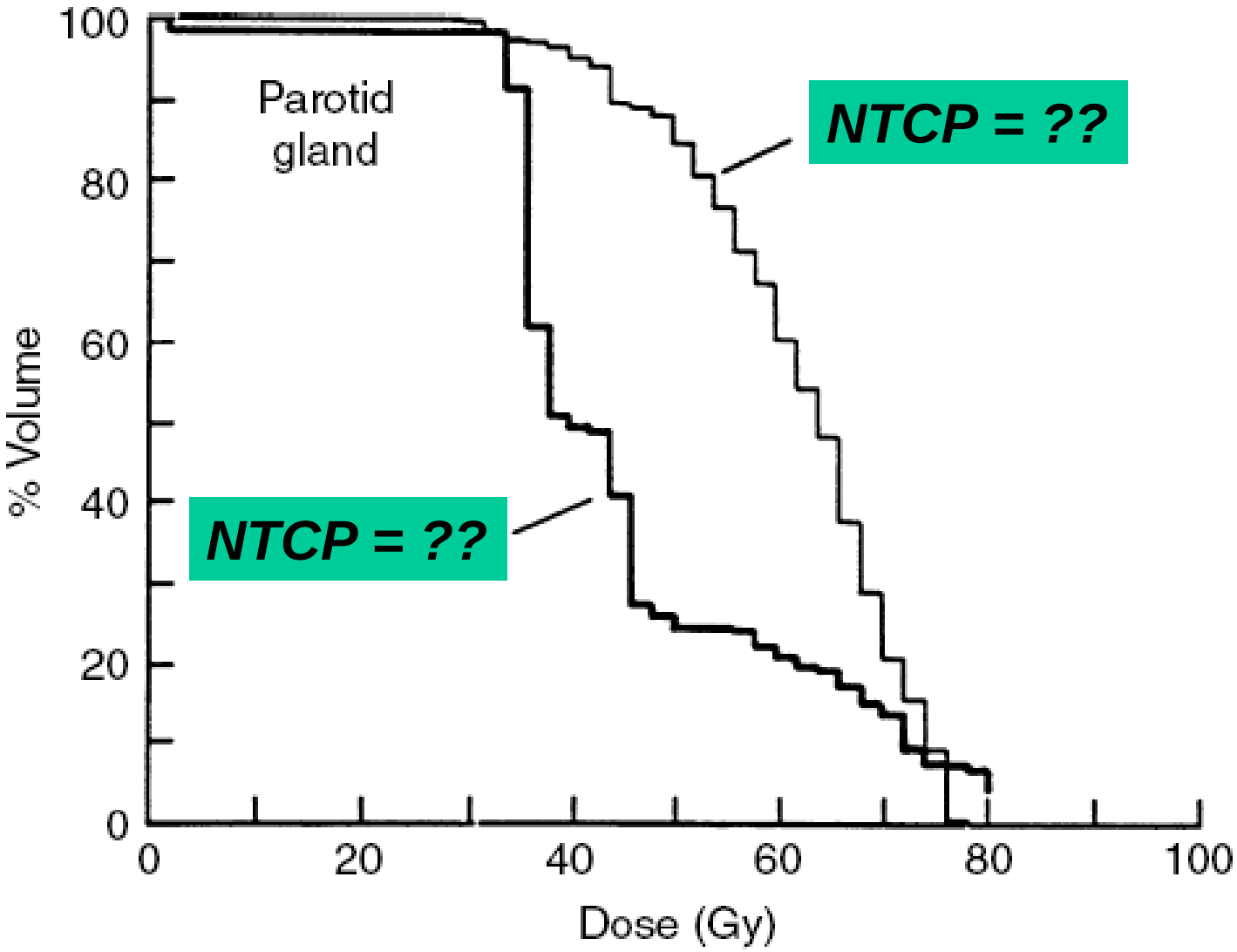
$$D_{50}(1) = D_{50}(v) * v^{n}$$

- **Parameters**: D_{50} dose to the whole organ ⟶ 50% NTCP

  m steepness

  n volume exponent
  (volume effect : n=1 large, n=0 small)


PAROTID GLANDS
Complete Xerostomia
TD_{50} = 46 Gy
n = 0.70
m = 0.18
Large volume effect
1.0
0.67
0.33
COMPLICATION PROBABILITY
1.0
0.8
0.6
0.4
0.2
0
0
20
40
60
80
100
DOSE (Gy)


Parotid gland
NTCP = ??
NTCP = ??
% Volume
Dose (Gy)
0
20
40
60
80
100

- **Histogram reduction methods**

  CRT / IMRT dose distributions are unlike partial irradiation : therefore one has to convert the DVH to an *equivalent partial irradiation*

  – Effective volume method [Kutcher 1991]
    - a certain partial volume v_{eff} receives the max Dose (D_{max})

$$\mathbf{v_{eff} = \sum_i v_i * \left(D_i / D_{max} \right)^{1/n}}$$

  – Equivalent Uniform Dose [Niemierko 1999]
    - the entire volume (V_{tot}) receives a certain equivalent uniform dose (*EUD*)

$$\mathbf{EUD = \left(\sum_i v_i * (D_i)^{1/n} \right)^n}$$

$$\mathbf{v_{eff} * D_{max} = V_{tot} * EUD}$$

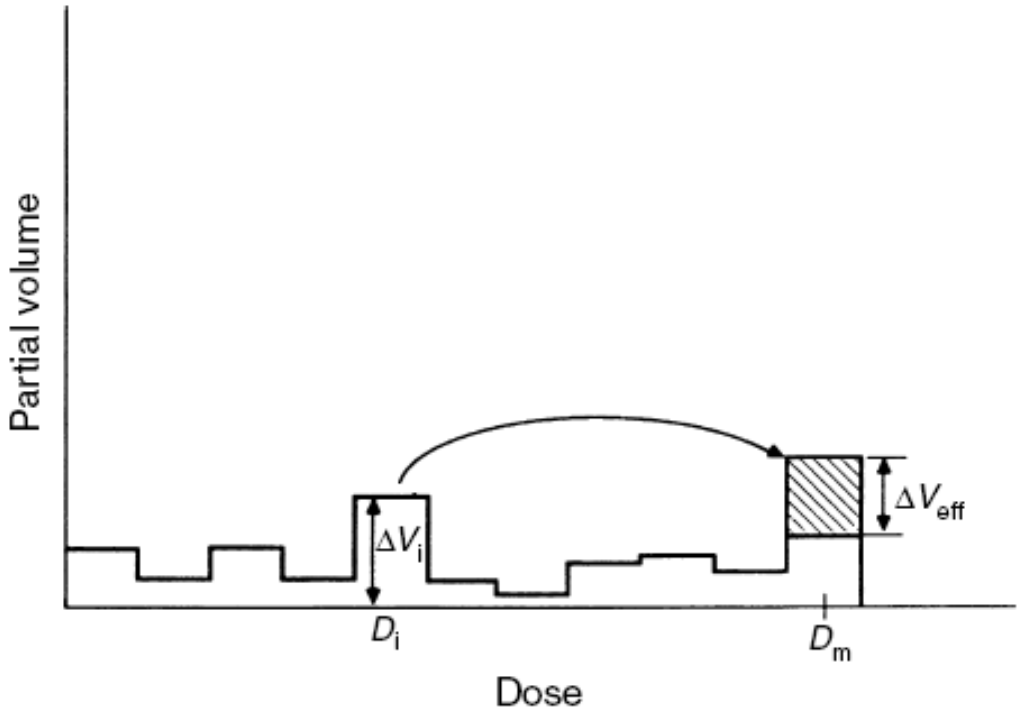
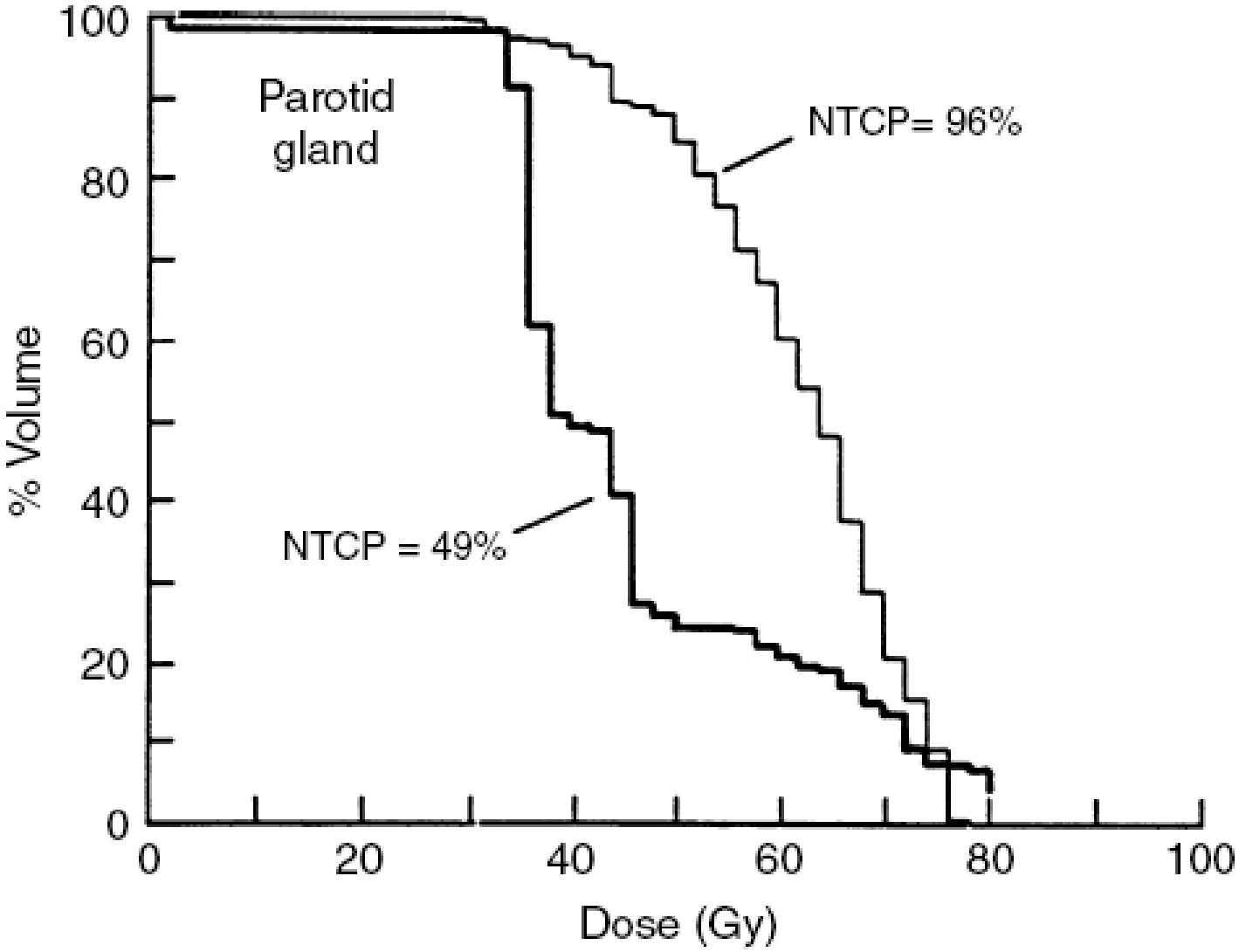


FIGURE 36.15
Illustration of *dose-volume histogram reduction* using the *effective volume* method; the DVH shown is in differential form, as opposed to the more familiar cumulative version. (From Kutcher, G. J., Burman, C., Brewster, L., Goitein, M., and Mohan, R., *Int. J. Radiat. Oncol. Biol. Phys.*, 21, 137–146, 1991. With permission.)


100
80
60
40
20
0
% Volume
Parotid
gland
NTCP= 96%
NTCP = 49%
0
20
40
60
80
100
Dose (Gy)

Parotid glands – xerostomia

Clinical criteria: **mean dose** **≤ 25Gy**

Available data: **mean dose threshold** **24 – 26 Gy**
(suppression of salivary flow)
mean dose (no thereshold) **35 – 45 Gy**
(decreased salivary flow)

LKB model	TD_{50}	m	n
Emami (1991) No 3D - retrosp.	46 Gy	0.18	0.7
Eisbruch (1999) 88 pts – prosp.	28.4 Gy (25 – 34.7)	0.18 (0.10 – 0.33)	1 (fixed)
Reisink (2001) 180 pts – prosp. 95% CI	39 Gy (34 - 44)	0.45 (0.33 - 0.65)	1 (fixed)

Lung – Grade-2 pneumonitis

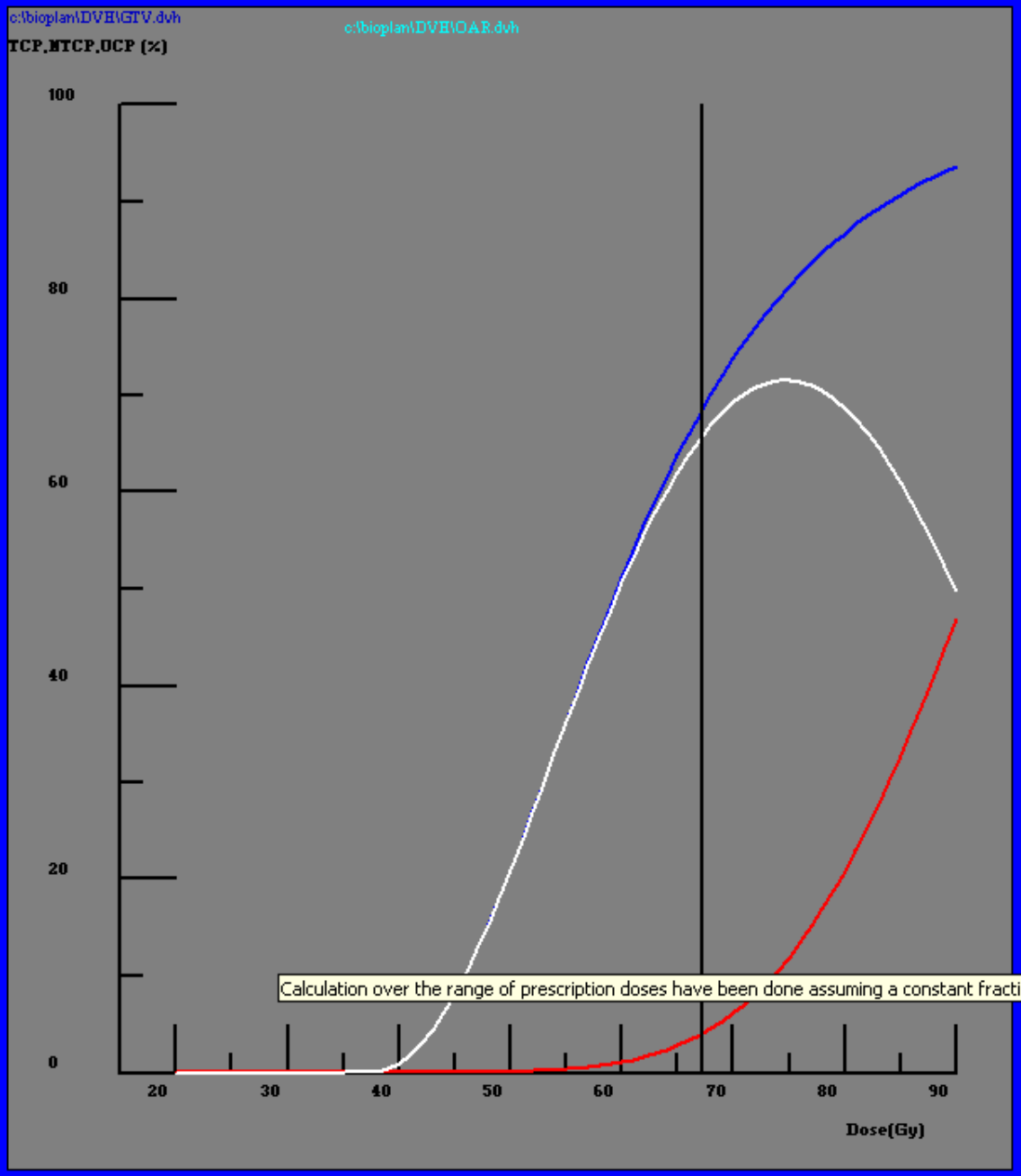
L-K-B model	TD_{50}	m	n
Emami (1991) No 3D - retrosp.	24.5 Gy	0.18	0.87
Seppenwolde (2003) 382 pts–retrosp.- both lungs as paired organ (95%CI)	30.8 (23 – 46)	0.37 (0.28 – 0.56)	0.99 (0.8 – 1.6)

Relative Seriality (RS) model	D_{50}	γ	s
Gagliardi (1998) 68 pts–retrosp-1 lung 68%CI	30.1 (27-32.53)	0.97 (0.77 – 1.21)	0.01 (at limit; 0.16)
Seppenwolde (2003) 382 pts–retrosp- 2 lungs 95%CI	34	0.97	0.06

TREATMENT PLAN OPTIMISATION

through

CONFORMAL RADIOBIOLOGY



TCP	68.17
NTCP	03.89
UCP	65.52
Dose (Gy)	67

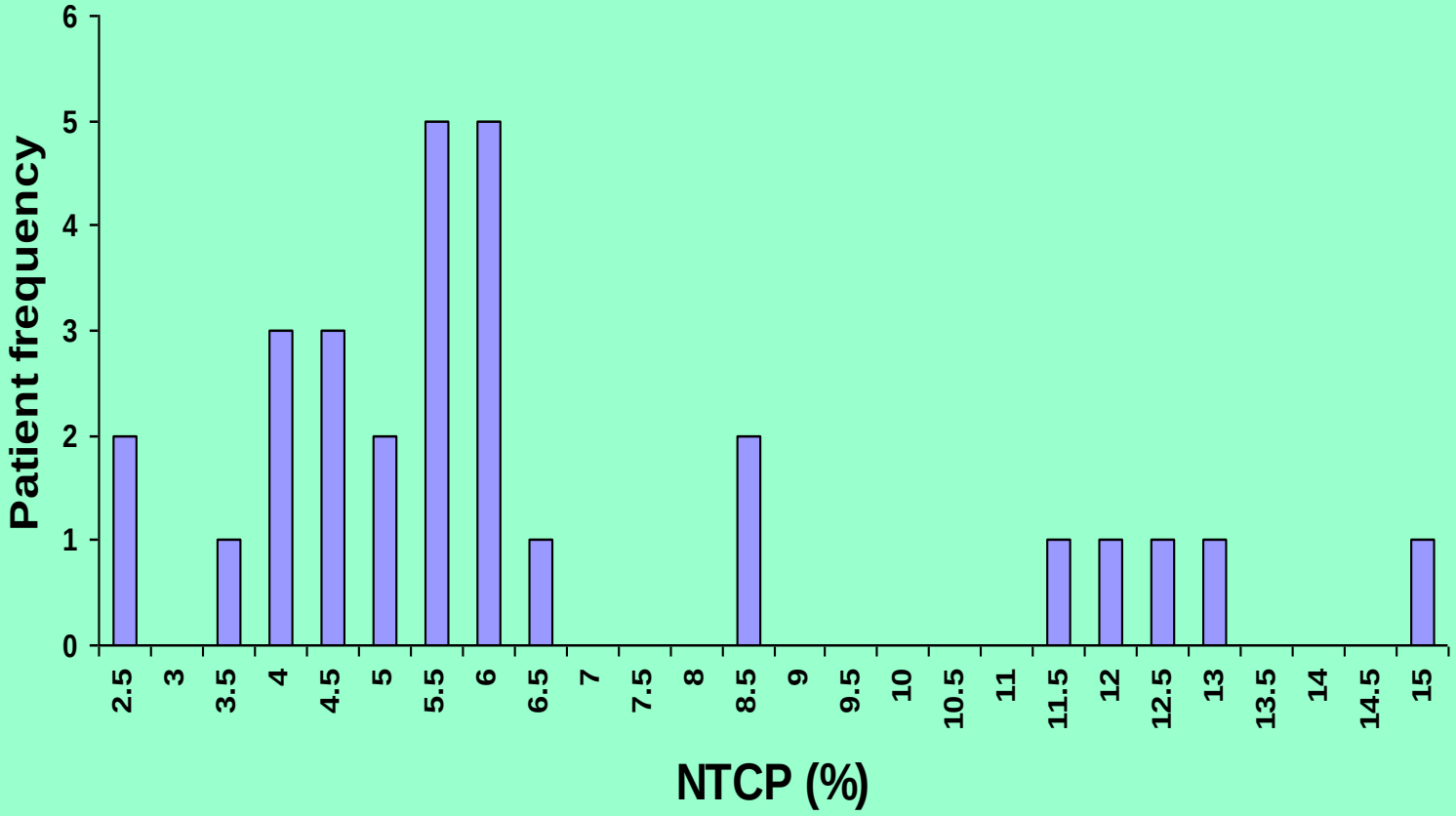
Calculation over the range of prescription doses have been done assuming a constant fraction size at the prescription point

Malik Z, Eswar Vee C, Dobson J, Fenwick J and Nahum A E

Biomathematical-model-based analysis of a standard UK dose and fractionation lung-tumour radiotherapy protocol; **4th UK Radiation Oncology Conference 19-21 March 2007, Edinburgh**

CCO protocol: 55 Gy in 20 fractions

NTCP calculated (using L-K-B model)



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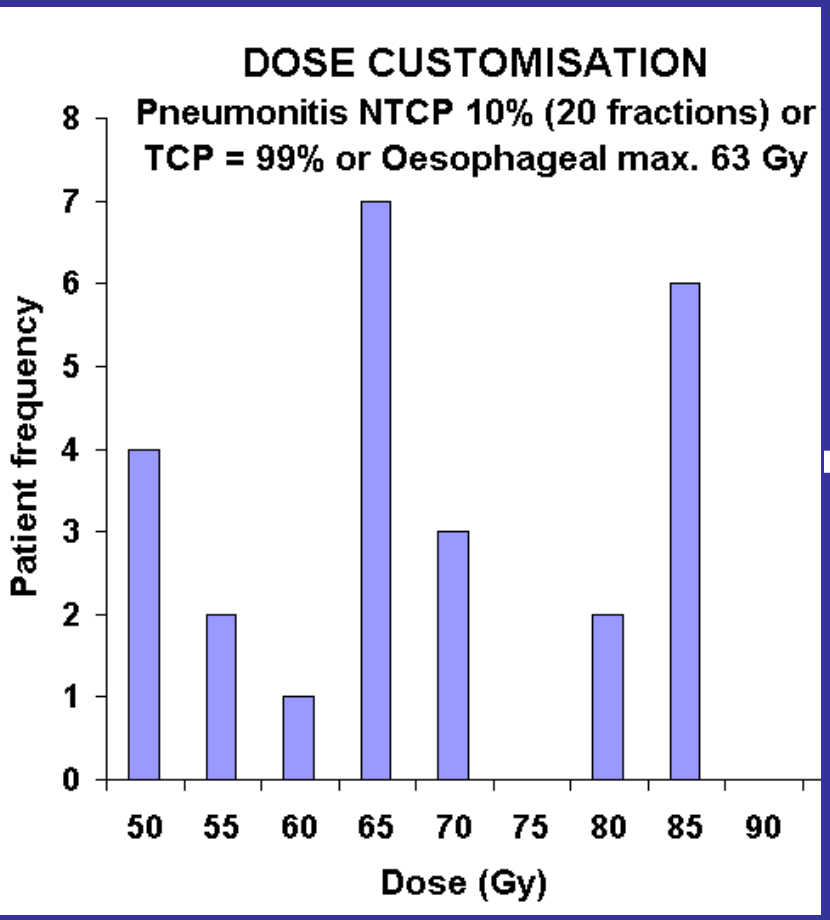
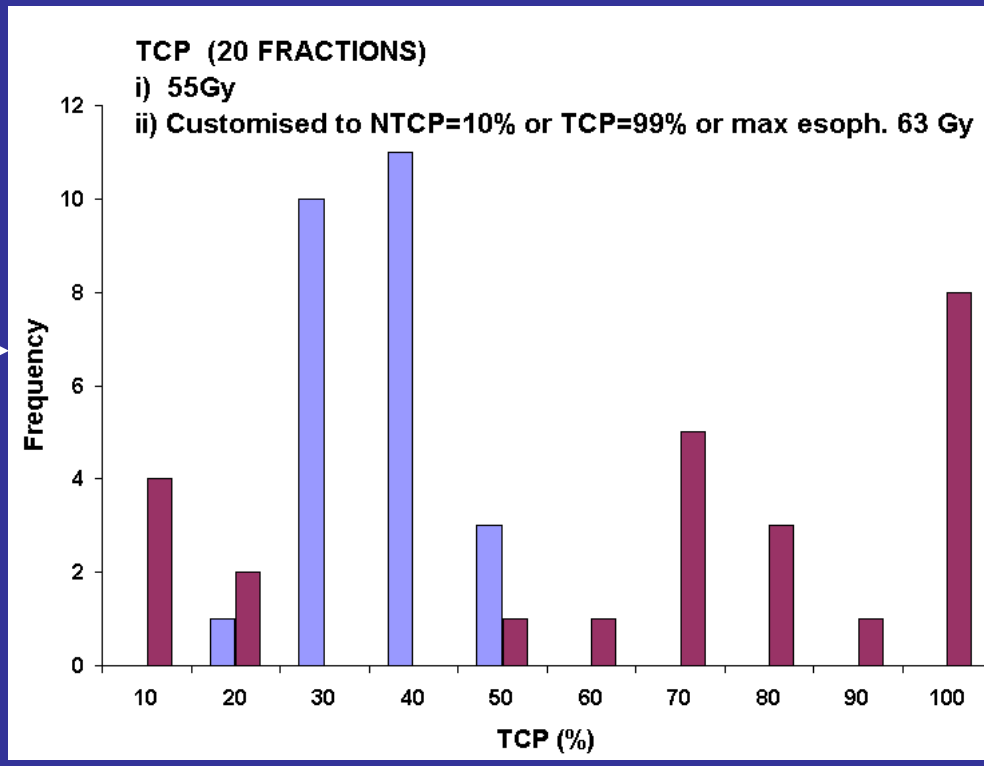


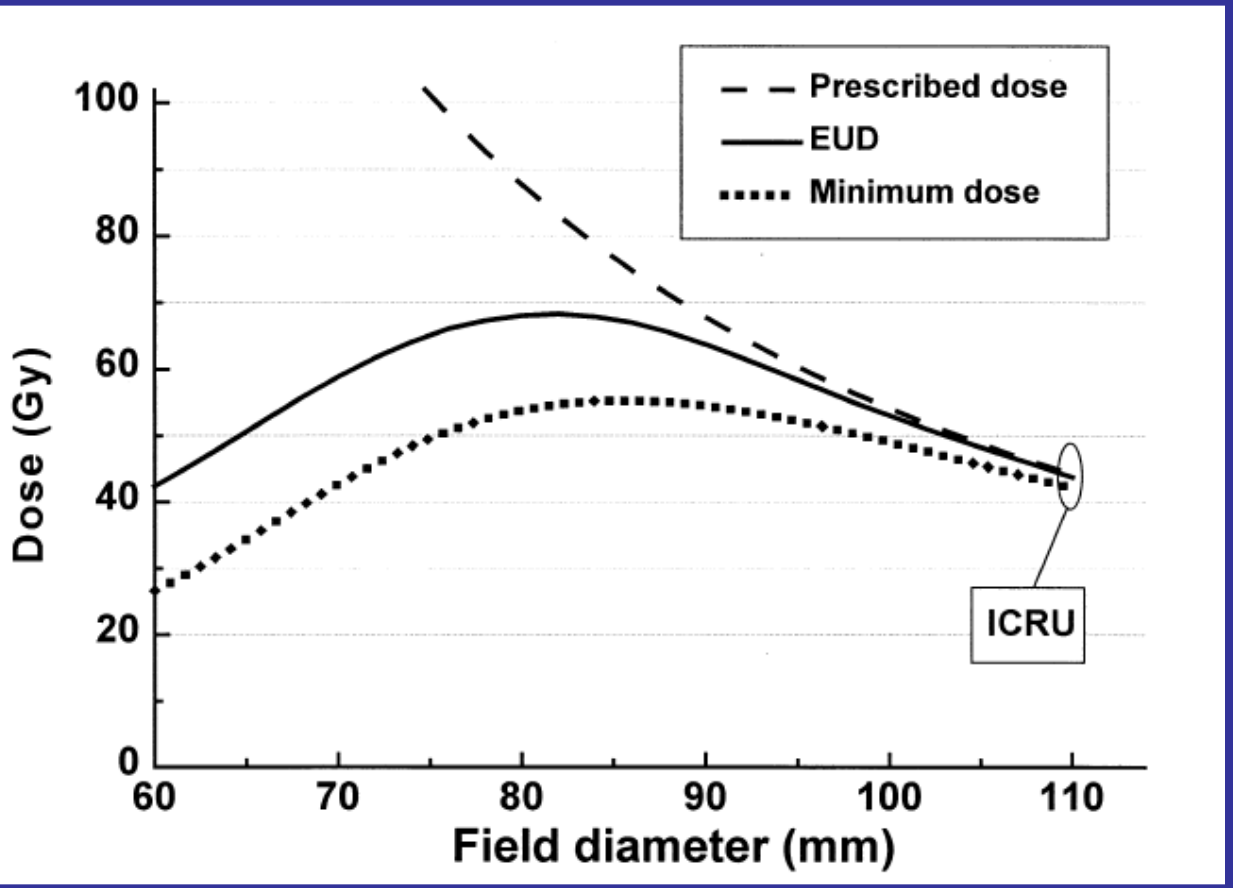


Local Control almost doubled

FIELD SIZE REDUCTION ENABLES Iso-NTCP ESCALATION OF TUMOR CONTROL PROBABILITY FOR IRRADIATION OF LUNG TUMORS

MARTIJN ENGELSMAN, M.SC., PETER REMEIJER, PH.D., MARCEL VAN HERK, PH.D.,
JOOS V. LEBESQUE, M.D., PH.D., BEN. J. MIJNHEER, PH.D., AND EUGÈNE M. F. DAMEN, PH.D.

Int. J. Radiation Oncology Biol. Phys., Vol. 51, No. 5, pp. 1290–1298, 2001



Prescribed dose, EUD of the CTV, and minimum dose in the CTV as a function of field size for an AP-PA irradiation of a phantom simulating a tumor located centrally in a lung. ***The mean lung dose is 20 Gy for each field size***. ***The ellipse*** indicates the field size for which the ***minimum dose in the CTV is 95% of the prescribed dose*** (ICRU Report 50 recommendation).

The message – Biological models must be "inside" the optimisation process/inverse planning

LEVEL-II OPTIMISATION

‘*Biologically motivated’ optimization*:

Use expressions for NTCP and TCP directly in the ‘objective function’ of the inverse-planning process, thus allowing the mathematical and radiobiological properties of the models to drive the search for the optimum plan (e.g. Hoffmann, Larsson *et al* 2004; Peñagarícano *et al* 2005).

What should the objective be?

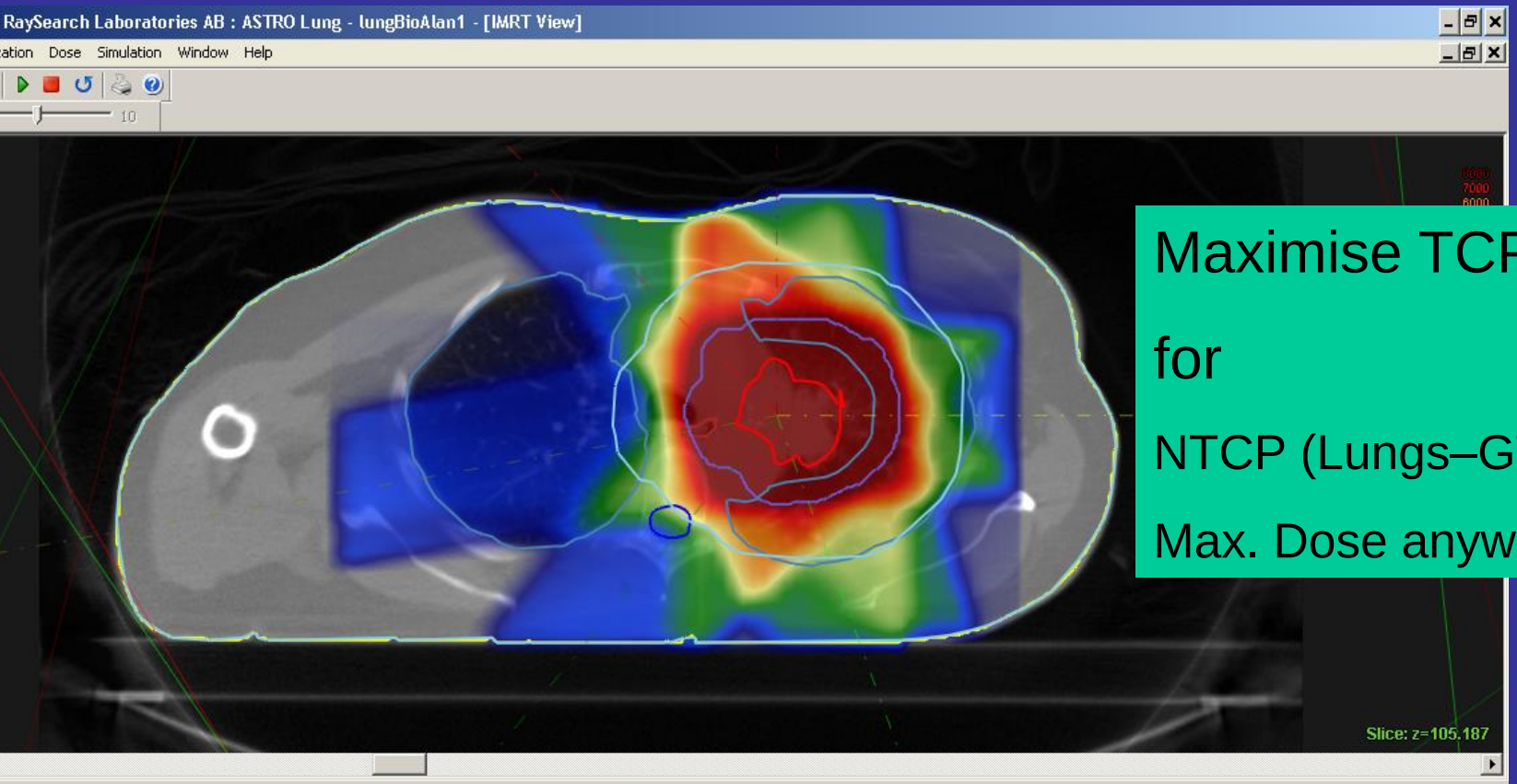
Maximise *TCP* for fixed *NTCP (e.g. 4%)*

OR

For fixed *TCP (e.g. 80%)*, minimise *NTCP*

ORBIT (RaySearch Laboratories)

Biologically optimised lung-tumour IMRT plan



Maximise TCP

for

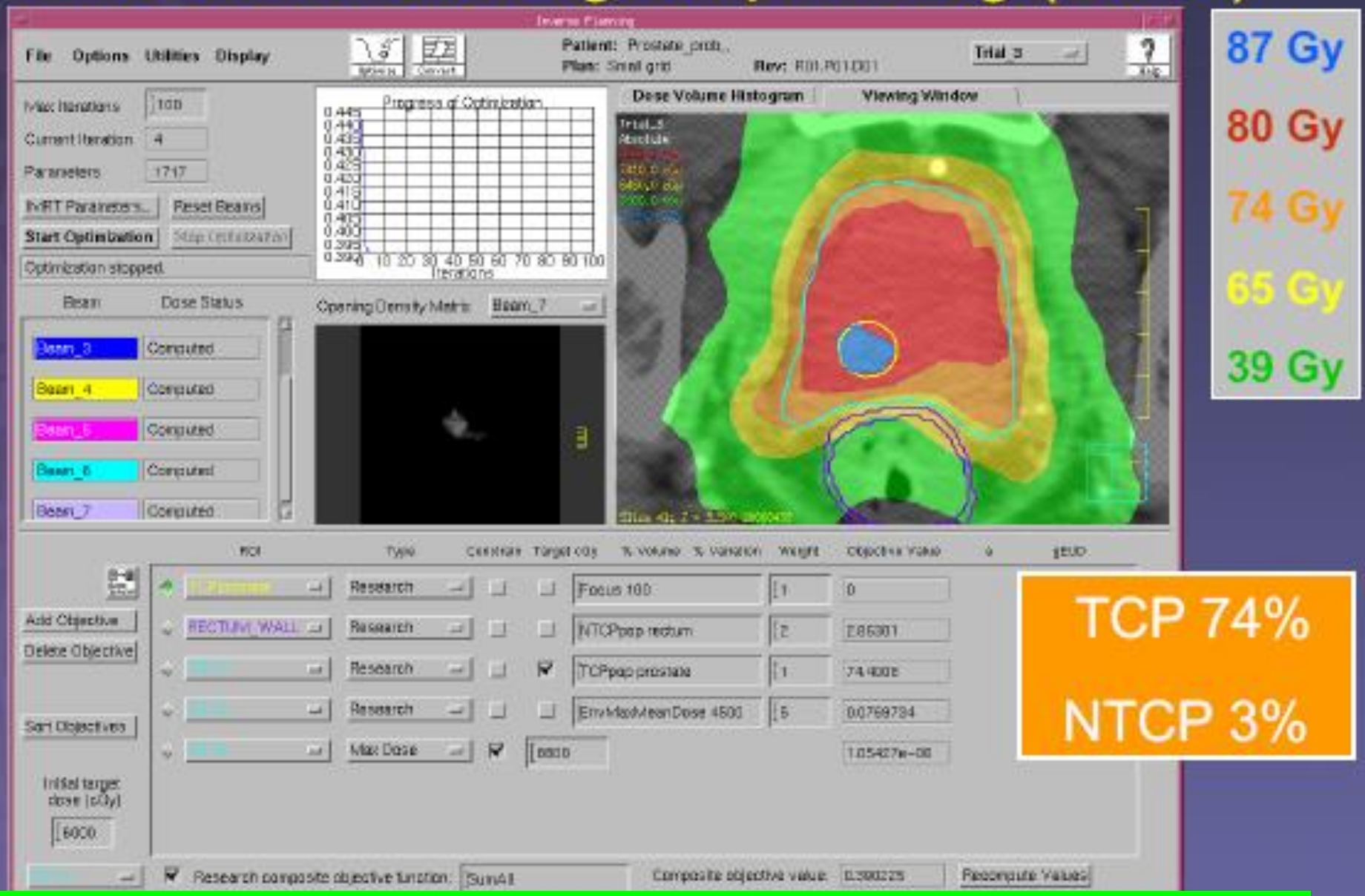
NTCP (Lungs–GTV) <= 3%

Max. Dose anywhere 90 Gy

Beam name	Group	MU	Nr segments	Gantry (deg)	Couch (deg)	Collimator (deg)	SSD (cm)	X (cm)	Y (cm)	Z (cm)
0	0	100...	0	0.00	0.00	0.00		28.03	-27.70	104.28
45	0	90.47	0	45.00	0.00	0.00		28.03	-27.70	104.28
100	0	79.46	0	100.00	0.00	0.00		28.03	-27.70	104.28
270	0	78.59	0	270.00	0.00	0.00		28.03	-27.70	104.28
140	0	119...	0	140.00	0.00	0.00		28.03	-27.70	104.28
200	0	98.96	0	200.00	0.00	0.00		28.03	-27.70	104.28

ROI	Function Description	Function Value	Dose Value (cGy)
PTV	TCP d50 4920.0 cGy, Gamma 1.0, Alpha/beta 10.0, Weight 1.00	0.96399725	
lungs-PTV	Constraint NTCP d50 2600.0 cGy, Gamma 1.7, Alpha/beta 3.0, Seri...	0.03009476	
External	Constraint Max Dose 9000 cGy	0.00000010	Max Dose: 9091.3

Probabilistic biological planning (focus)



Courtesy of Marnix Witte, Netherlands Cancer Institute, Amsterdam.

Fraction size?

- What is the scope for increasing the therapeutic ratio by changing the fraction size? (depends on the α/β ratio)

- Is there a connection between the degree of conformality of the treatment and the ‘fractionation sensitivity’?

BIOPLAN

Freeware, runs on PCs (Beatriz Sanchez-Nieto)

Calculates:

i. *TLCP* (*Marsden* model)

ii. *NTCP* (L-K-B and Relative-Seriality Models)

with user-choosable parameters, given the *differential* DVHs

EMAIL ME: alan.nahum@ccotrust.nhs.uk

Fees, Booking and Registration

The cost for the full 4-day course is £550. For those wishing to attend either the first two days only (Basic Radiobiology) or the final two days (Radiobiological Modelling) the cost is £300. **Please note that the full course runs from Tuesday until Friday.**

The fee includes full notes on each lecture (including a comprehensive reference list), a CD of the presentations (as pdf files), lunches (buffet), coffee/tea and light refreshments, and the course dinner. Accommodation is available in local hotels from around £45 per night.

REGISTRATION FORM

Name: .....

Organisation: .....

Address: .....

.....

.....

Postcode (or equivalent): .....

Telephone/Fax ...../.....

Mobile .....

Email : .....@.....

I should like to enrol for the **Full Four Days*** / **First Two Days*** / **Final Two Days***

(*Delete as appropriate)

I enclose a cheque for the full amount of £..... payable to:

"Clatterbridge Centre for Oncology (8-11 May 2007)"

Or

If you wish to pay by direct bank transfer, please send an email to Sue Nixon (see below) and she will send back the necessary details by return email.

Please mail the completed form, and forward payment (if cheque) to:

Sue Nixon, Radiobiology Course Secretary, Physics Department, Clatterbridge Centre for Oncology, Clatterbridge Road, Bebington, Wirral CH63 4JY, UK
Tel/Fax: +44 (0)151 482 7960; Email: Sue.Nixon@ccotrust.nhs.uk

Information also at: www.ccotrust.nhs.uk
http://www.wirral.nhs... FLYERMay07 Version2April.pdf

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