Radiobiological Optimization of Treatment Plans

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Biological models discussed

- Effective volume, effective dose, and generalized equivalent uniform dose (gEUD) models
  - *to account for volume effects on radiobiological response*
- Tumor control probability (TCP) and normal tissue complication probability (NTCP) models
- The linear-quadratic (L-Q) model
  - *to account for fractionation and dose-rate effects*
- The use of these models in commercial treatment planning systems

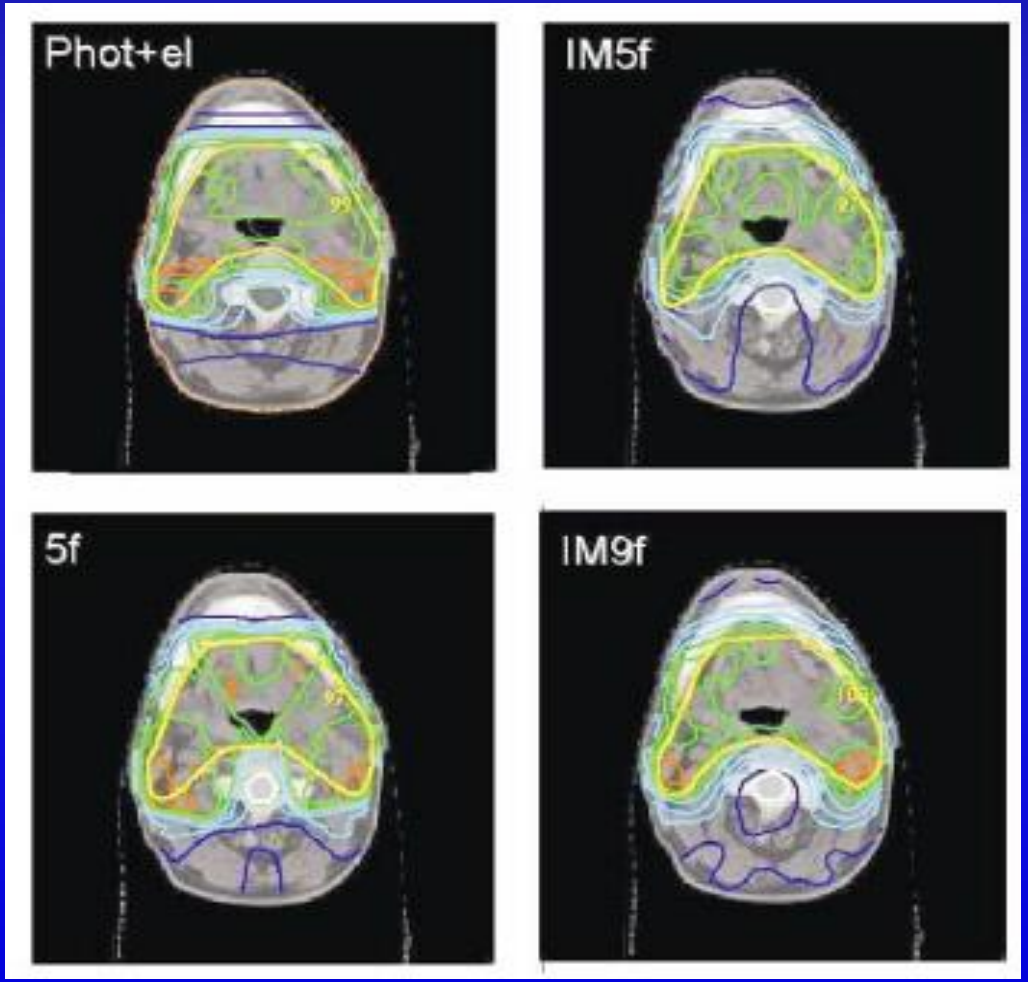
How can an optimal treatment plan be selected?

- Visual inspection of isodose distributions (2D, 3D)
  - *highly subjective*
- Visual comparison of DVHs
  - *fairly subjective*
- Quantitative measures of plan “quality” from DVH
  - D_{min}, D_{max}, *D90, D100, V90, V100, etc.*
  - V_{eff}, D_{eff}, *EUD*
  - *TCPs, NTCPs*

Visual inspection of isodose plans

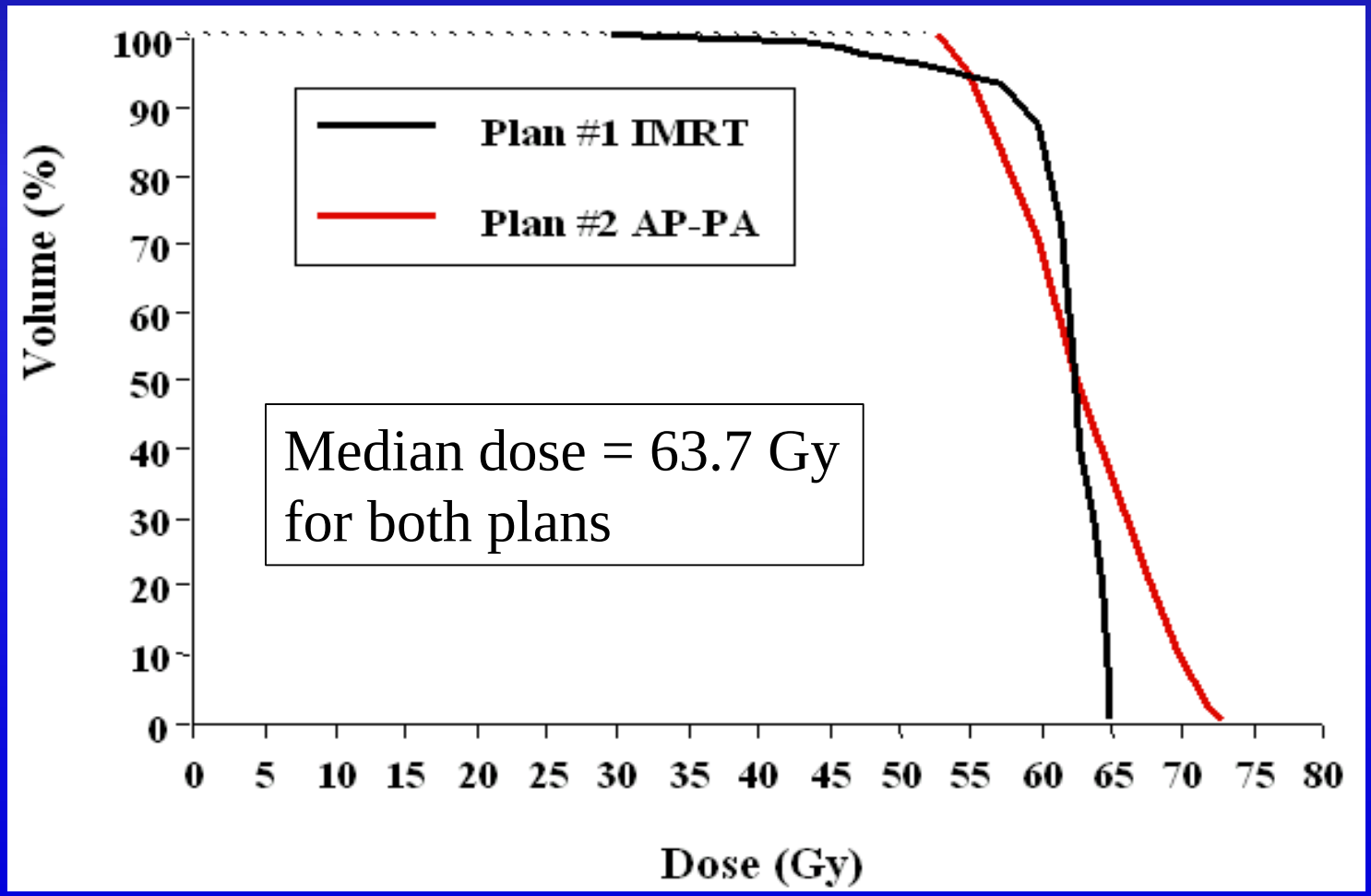
Four plans for comparison:

- photons + electrons
- 5-field photons
- 5-field IMRT
- 9-field IMRT



Comparison of tumor DVHs

(from Andrzej Niemierko, ASTRO presentation)



Some quantitative measures to go by

Plan	D90	D100	V90	V100	Range (Gy)	Std. dev. (Gy)
IMRT	59Gy	30Gy	94%	50%	30 - 65	2.5
AP-PA	57Gy	55Gy	83%	50%	55 - 73	3.5

IMRT: most uniform (lower standard deviation), higher V90, but lower D100

AP-PA: higher D100, but lower V90 and also higher D_{max}

But which is the better plan?

- Need to consider both tumor and normal tissue DVHs
- Want good coverage of the target, low D_{max} to normal tissues, and low volume of normal tissues receiving doses close to "tolerance"

Can the DVH be reduced to a single "biologically relevant" number?

- Yes, if we have a volume-effect model of dose response
  - *most common is the power-law model*

Power-law volume-effect models (*they have been around for a long time and we still use them today*)

$$\text{Skin tolerance dose} \propto A^{-0.33}$$

Cube - root rule, Meyer, 1939

$$\text{Tissue tolerance dose} \propto V^{-0.11}$$

Jolles, 1946

General power-law model

$$D_v = D_1.v^{-n}$$

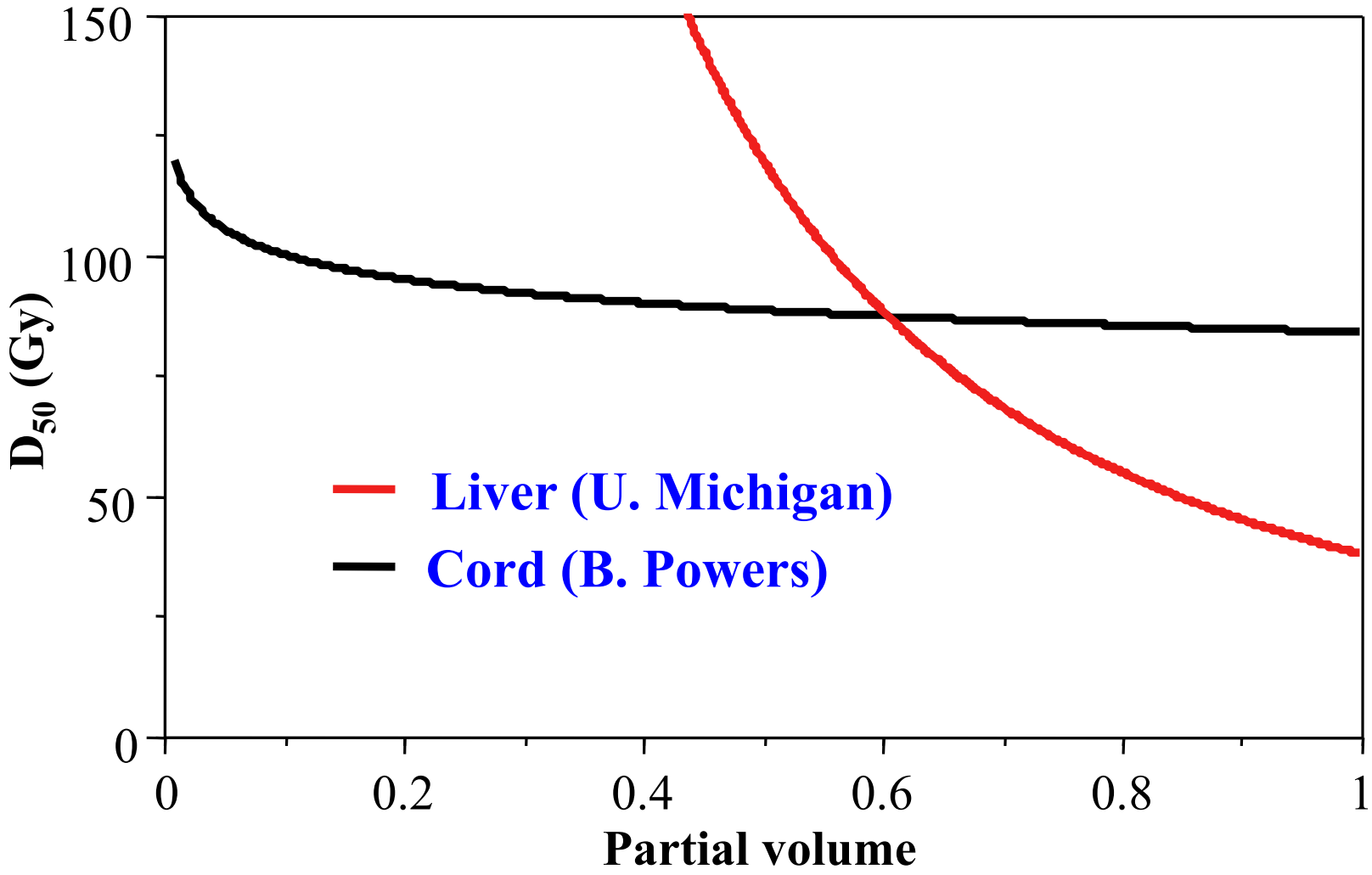
where D_v is the dose which, if delivered to fractional volume, v, of an organ, will produce the same biological effect as dose D_1 given to the whole organ

This is the basis of many present-day biological treatment planning methods

What does the volume effect exponent "*n*" mean?

- *n* is negative for tumors
- *n* is positive for normal tissues
- *n* = 0 means that cold spots in tumors or hot spots in normal tissues are *not* tolerated
- *n* = 1 means that isoeffect doses change linearly with volume
- *n* large means that cold spots in tumors or hot spots in normal tissues are *well* tolerated

Hot-spots not tolerated - spinal cord (*n* small)
Hot-spots well tolerated – liver (*n* large)



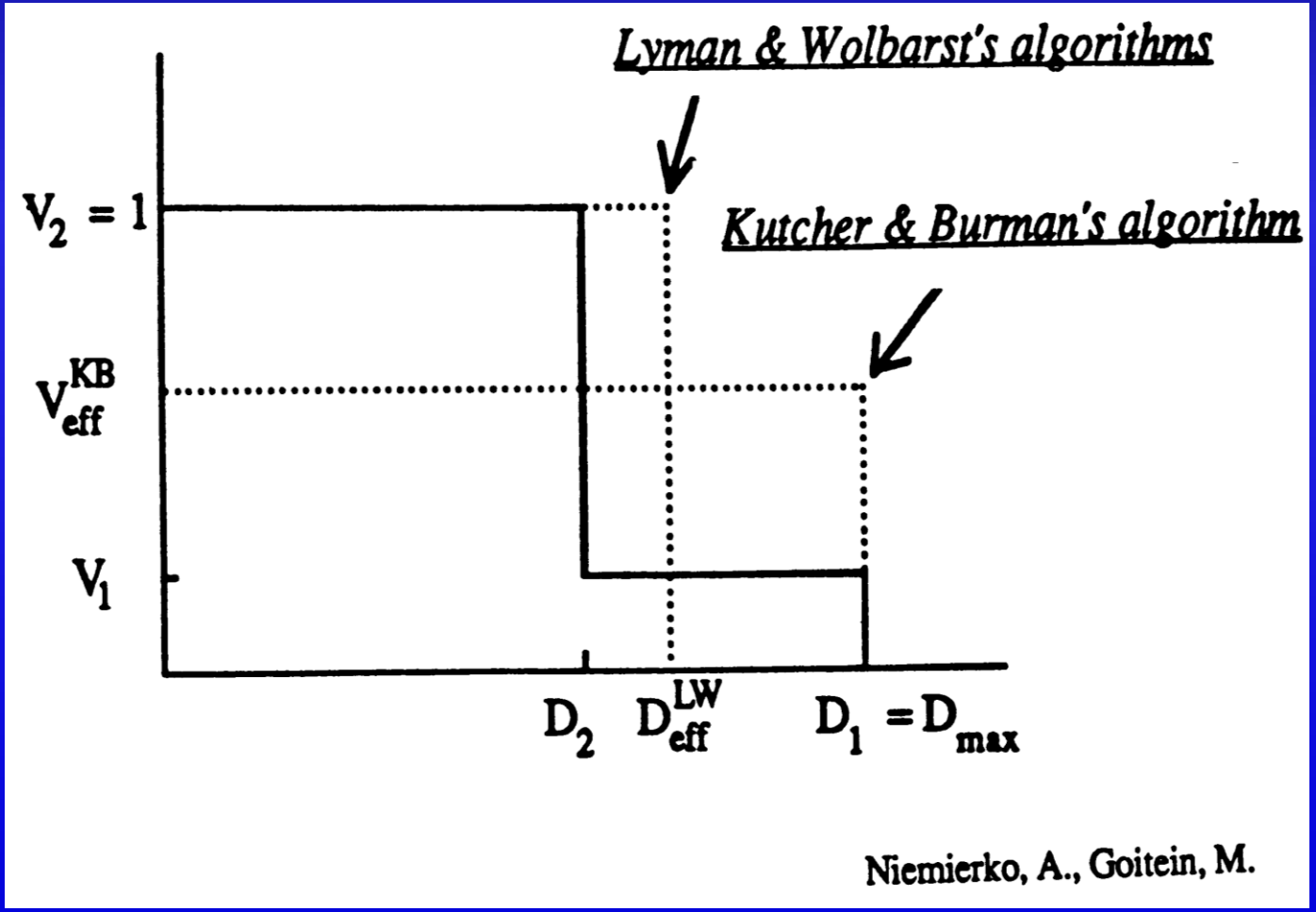
(from Andrzej Niemierko, ASTRO, 2001)

Two methods to get a single number to represent a DVH

As a very simple demonstration, a two-step DVH is reduced to one step:

Kutcher & Berman: *effective volume at maximum dose, V_{eff}*

Lyman & Wolbarst: *effective dose to whole (or reference) volume, D_{eff}*



Mohan et al expression for D_{eff} (1992)

$$D_{eff} = \left[\sum_i D_i^{1/n} \cdot (V_i / V_{tot}) \right]^n$$

where V_i is the subvolume irradiated to dose D_i, V_{tot} is the total volume of the organ or tissue, and n is the tissue-specific volume-effect parameter in the power-law model

Mohan et al called this the "effective uniform dose"

The *EUD* equation (Niemierko, 1999)

Niermierko renamed D_{eff} the Equivalent Uniform Dose *EUD* (originally defined only for tumors in 1997 but extended to all tissues in 1999 and initially called it the generalized EUD, or gEUD)

$$EUD = \left[\sum_i v_i D_i^{\,a} \right]^{1/a}$$

where v_i is the volume of the tissue in dose bin D_i as a fraction of the volume of the total organ or tumor i.e. $v_i = V_i/V_{tot}$

Note that *EUD* is identical to D_{eff}, of Mohan et al with $a = 1/n$

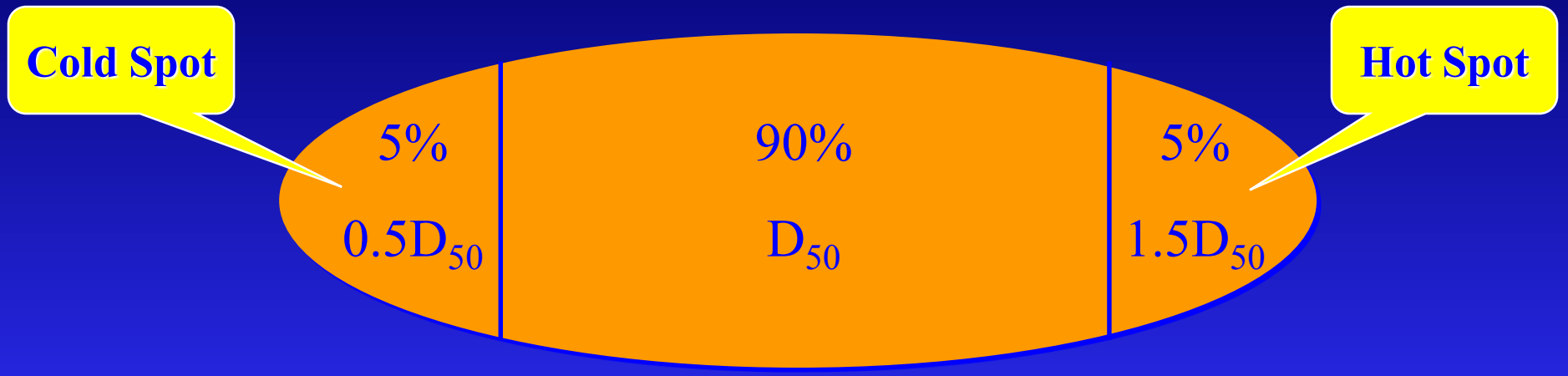
Tumors →

Normal tissues →

Structure (Source)	End-point	a
Chordoma base of skull (MGH)	Local control	-13
Squamous cc (Brenner)	Local control	-13
Melanoma (Brenner)	Local control	-10
Breast (Brenner)	Local control	-7.2
Parotids (Eisbruch)	Salivary function (<25%)	<0.5
Parotids (Chao)	Salivary function (<25%)	0.5
Liver (Lawrence)	Liver failure	0.6
Liver (Dawson)	Liver failure	0.9
Lung (Kwa)	Pneumonitis	1.0
Lung (Emami)	Pneumonitis	1.2
Kidney (Emami)	Nephritis	1.3
Liver (Emami)	Liver failure	2.9
Heart (Emami)	Pericarditis	3.1
Bladder (Emami)	Symptomatic contracture	3.8
Brain (Emami)	Necrosis	4.6
Colon (Emami)	Obstruction/perforation	6.3
Spinal cord (Powers)	White matter necrosis	13
Esophagus (Emami)	Perforation	18
Spinal cord (Schultheiss)	Paralysis	20

(from Andrzej Niemierko, ASTRO, 2001)

EUD – Tumors (modified from Andrzej Niemierko, ASTRO presentation)

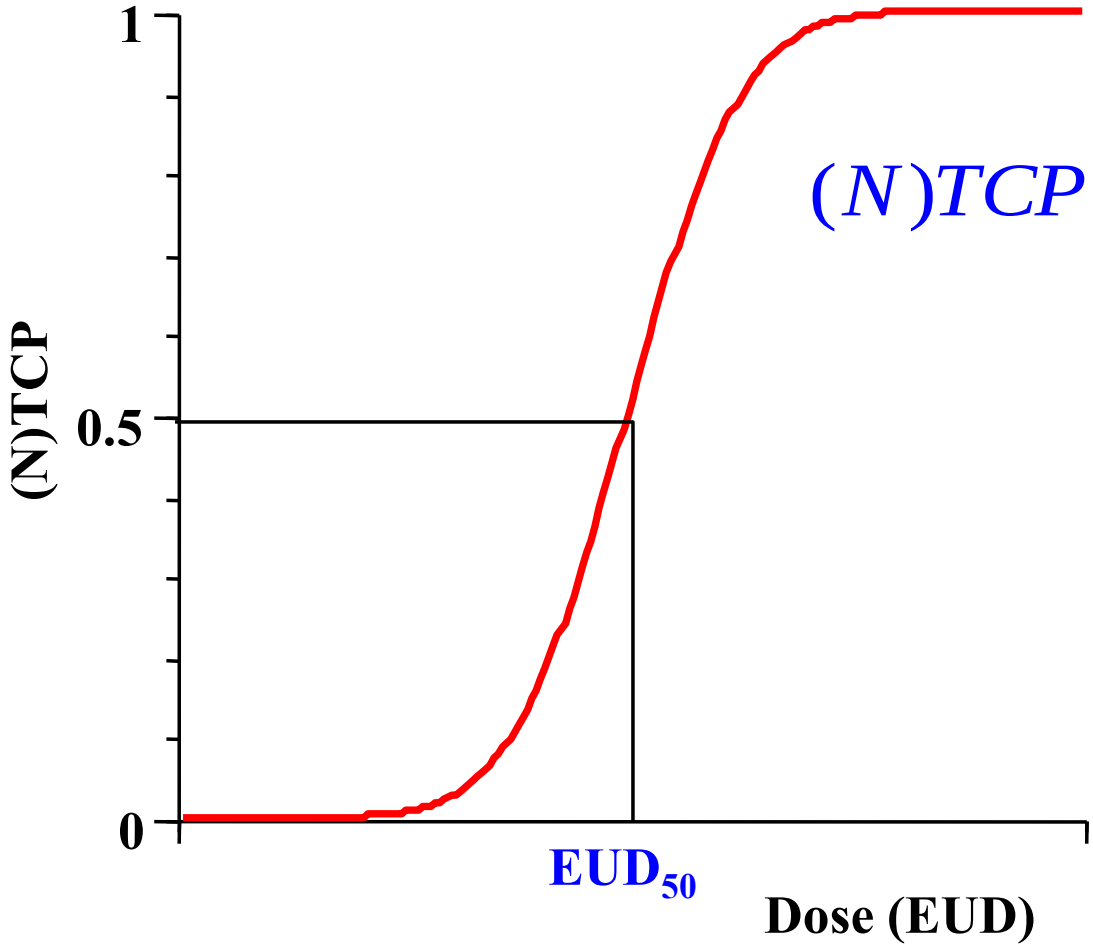


$$EUD = \left[0.05(0.5D_{50})^{a} + 0.9(D_{50})^{a} + 0.05(1.5D_{50})^{a}\right]^{1/a}$$

Tumor	a	EUD/D_{50} %	TCP(%) (γ_{50}=2)
Breast	-7.2	74	8

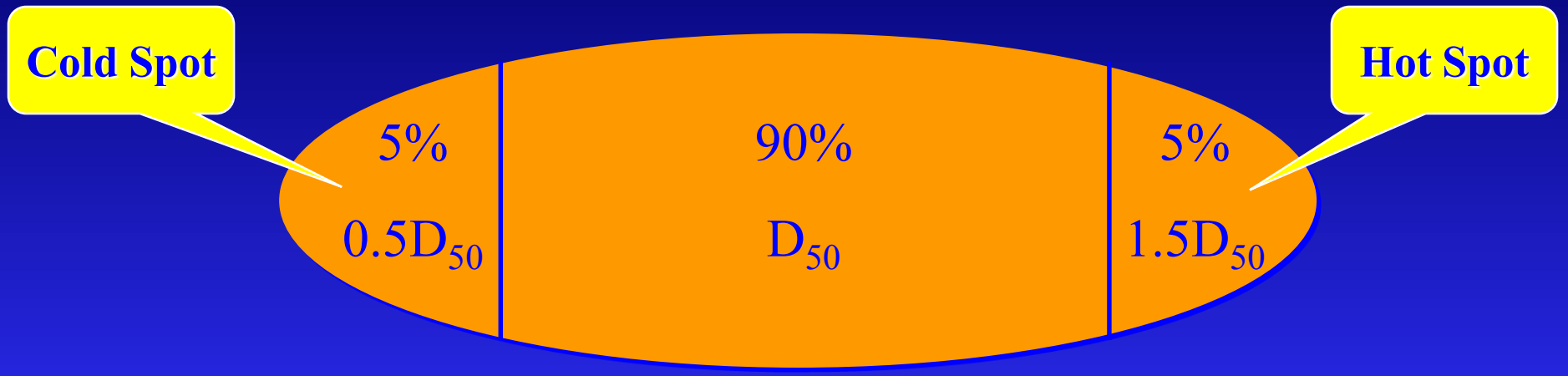
TCP & NTCP: logistic model

(from Andrzej Niemierko, ASTRO presentation)



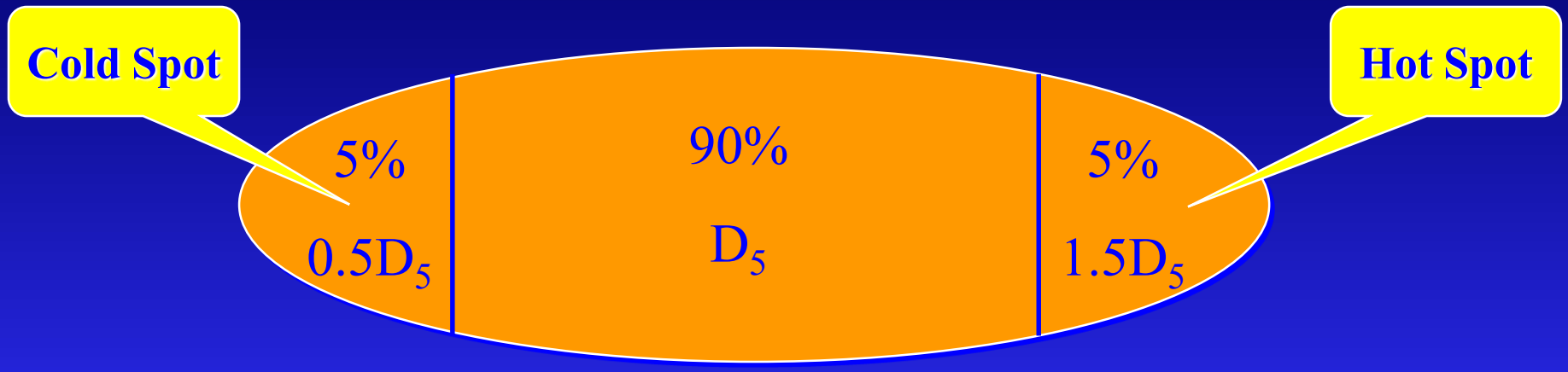
$$(N)TCP = \frac{1}{1 + \left[\frac{EUD_{50}}{EUD}\right]^{4\gamma_{50}}}$$

EUD – Tumors (modified from Andrzej Niemierko, ASTRO presentation)



Tumor	a	EUD/D_{50} (%)	TCP(%) (γ_{50}=2)
Breast	-7.2	74	8
Melanoma	-10	67	4
Chordoma	-13	63	2
	$-\infty$	50	<1

EUD - Normal Structures (modified from Andrzej Niemierko, ASTRO presentation)



Structure	a	EUD/D_5 (%)	NTCP(%) (γ_{50}=4)
Liver	0.6	99	4.6
Lung	1	100	5
Heart	3.1	103	7
Brain	4.6	105	10
Spinal cord	14	122	55
	+∞	150	>95

Optimization

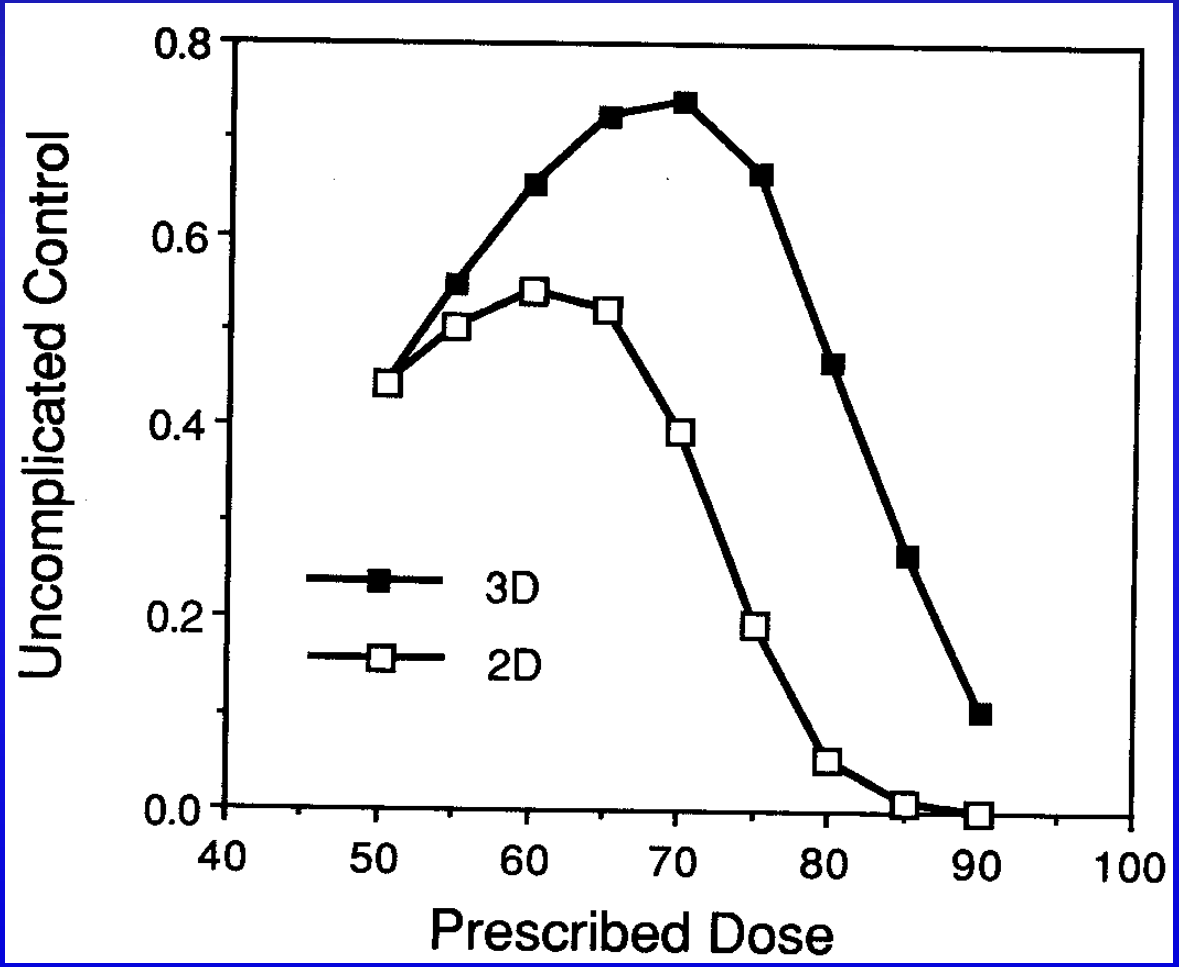
- The objective is to develop the treatment plan which will deliver a dose distribution that will ensure the highest TCP that meets the NTCP constraints imposed by the radiation oncologist
- This will usually be close to the peak of the probability of uncomplicated local control (PULC) curve

Nasopharynx: comparison of conventional (2-D) with non-coplanar (3-D) techniques

Kutcher, 1998

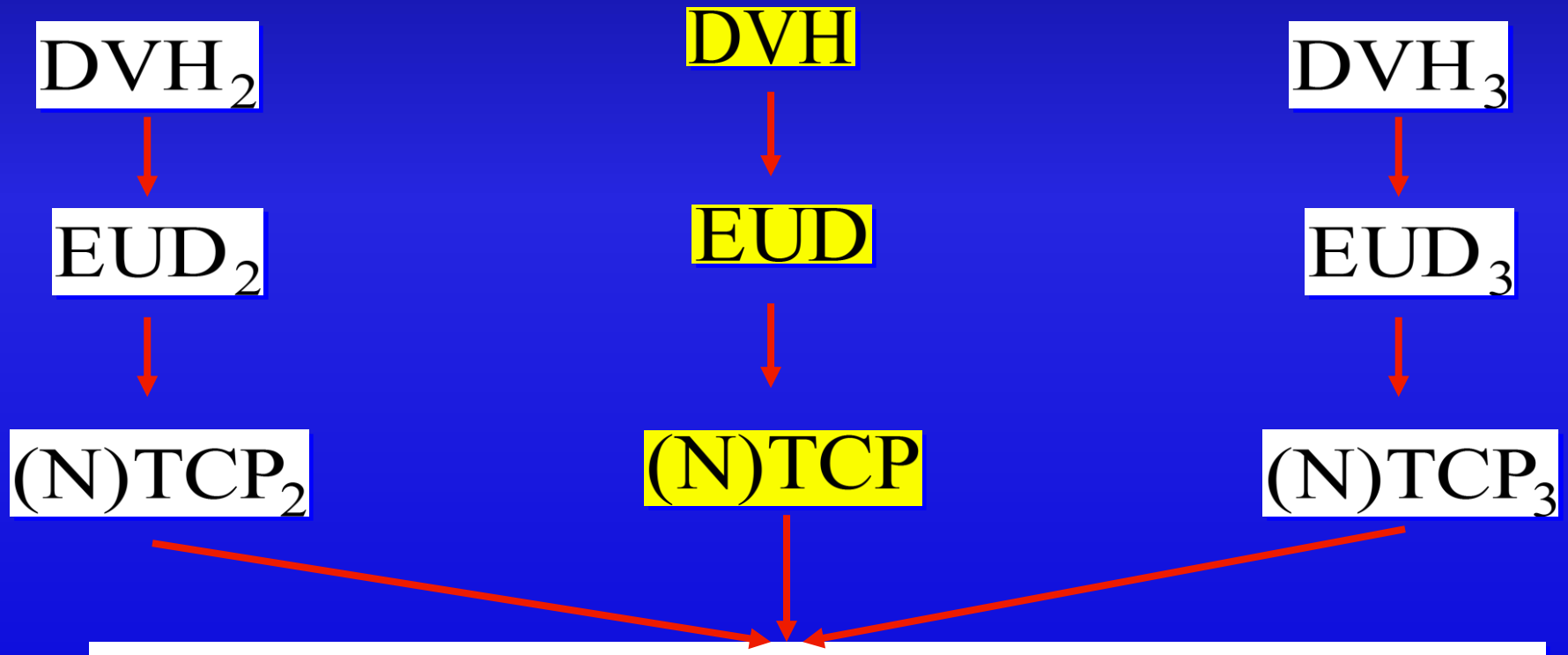
Probability of uncomplicated local control (PULC) given by:

PULC =TCP(1-NTCP)



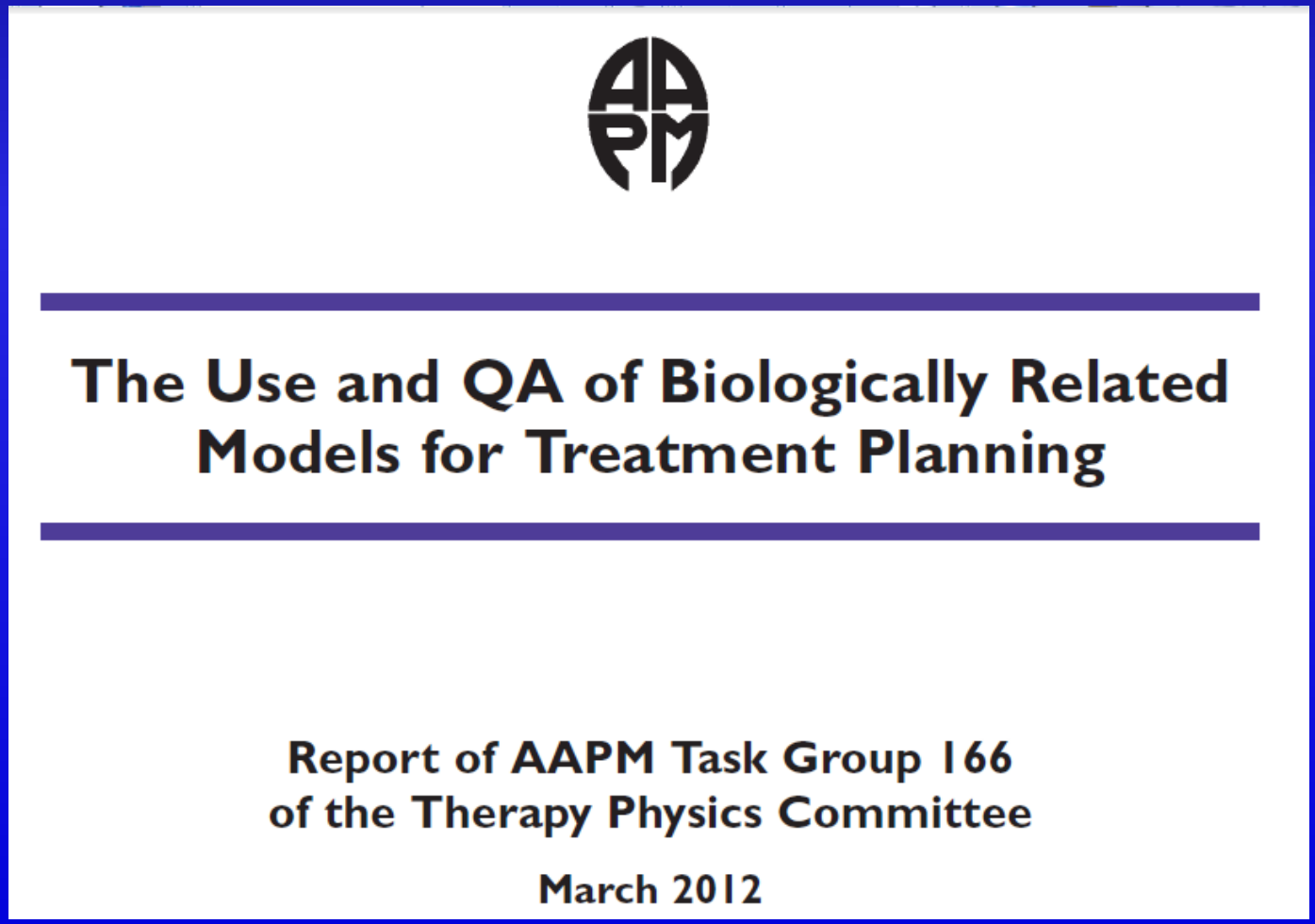
Creating a Score function for plan optimization or plan evaluation

(modified from Andrzej Niemierko, ASTRO presentation)



$$\text{Score} = \prod_{i}^{\#\text{targets}} \left(\text{TCP}_i\right)^{w_i} \prod_{k}^{\#\text{normal}} \left(1 - \text{NTCP}_k\right)^{w_k}$$

Excellent review



The Use and QA of Biologically Related Models for Treatment Planning

Report of AAPM Task Group 166
of the Therapy Physics Committee

March 2012

EUD used to optimize treatment plans

According to AAPM TG Report 166:

"*incorporating EUD-based cost functions into inverse planning algorithms for the optimization of IMRT plans may result in improved sparing of OARs without sacrificing target coverage*"

DVH data can be used directly without calculation of EUDs: the NTCP probit-based model

The Pinnacle TP system uses the Kutcher and Burman DVH reduction method to calculate the effective volume υ_{eff}

$$\mathrm{NTCP}_{(\mathrm{dose,volume})} = \frac{1}{2}\left[1 + \mathrm{erf}\left(\frac{t}{\sqrt{2}}\right)\right].$$

The parameter t is determined by the effective volume method,

$$t = \frac{D_{\max} - D_{50}(\nu_{\mathrm{eff}})}{\mathbf{m}D_{50}(\nu_{\mathrm{eff}})} : D_{50}(\nu_{\mathrm{eff}}) = D_{50}\nu_{\mathrm{eff}}^{-N},$$

$$\mathbf{m} = \frac{1}{\sqrt{2\pi} \times \gamma_{50}} \quad \text{and} \quad \nu_{\mathrm{eff}} = \frac{1}{\nu_{\mathrm{ref}}} \sum_i \nu_i \left(\frac{D_i}{D_{\max}}\right)^{1/N},$$

Another example: TCPs calculated using the Poisson statistics model

According to Poisson statistics, if a number of patients with similar tumors are treated with a certain regimen, the probability of local control, which is the probability that no cancer cells will survive, is given by:

$$TCP = e^{-N_m}$$

where N_m is the mean number of cancer cells surviving in any patient

Poisson statistics model (cont'd.)

Then, if the average number of cancer cells in each patient's tumor before treatment is N_0, and the mean surviving fraction of cells after treatment is S_m:

$$N_m = N_0 S_m$$

$$Hence: \quad TCP = e^{-N_0 S_m}$$

Which is better for optimization, EUD or TCP/NTCP?

"*Although both concepts can be used interchangeably for plan optimization, the EUD has the advantage of fewer model parameters, as compared to TCP/NTCP models, and allows more clinical flexibility*"

(AAPM TG 166 Report)

TG 166 conclusion

"A properly calibrated EUD model has the potential to provide a reliable ranking of rival treatment plans and is most useful when a clinician needs to select the best plan from two or more alternatives"

NTCP and TCP calculations: effect of dose/fraction

- Since biological effects are a function of dose/fraction, EUD, NTCP and TCP calculations need to take this into account
- One way to do this is to transform all doses within the irradiated volume to “effective” doses at some standard dose/fraction e.g. 2 Gy, before calculation of the TCP or NTCP
- This may be done using the linear-quadratic model

Conversion to 2 Gy/fraction equivalent dose

$$D_i\left(1+\frac{d_i}{\alpha/\beta}\right) = D_2\left(1+\frac{2}{\alpha/\beta}\right)$$

$$\therefore\ D_2 = D_i\left[\frac{\left(1+\frac{d_i}{\alpha/\beta}\right)}{\left(1+\frac{2}{\alpha/\beta}\right)}\right]$$

Alternatively could use the LQ model directly: TCP calculations using Poisson statistics

According to the Poisson statistics model:

$$TCP_i = e^{-N_{0,i}S_{m,i}} \text{ and } TCP = \prod_i TCP_i$$

where, using the L-Q model:

$$S_{m,i} = e^{-\left(\alpha d_i + \beta d_i^2\right)N}$$

$$\text{so } TCP_i = e^{-N_{0,i}e^{-\left(\alpha d_i + \beta d_i^2\right)N}}$$

Want more on calculation of TCPs?

Try reading:

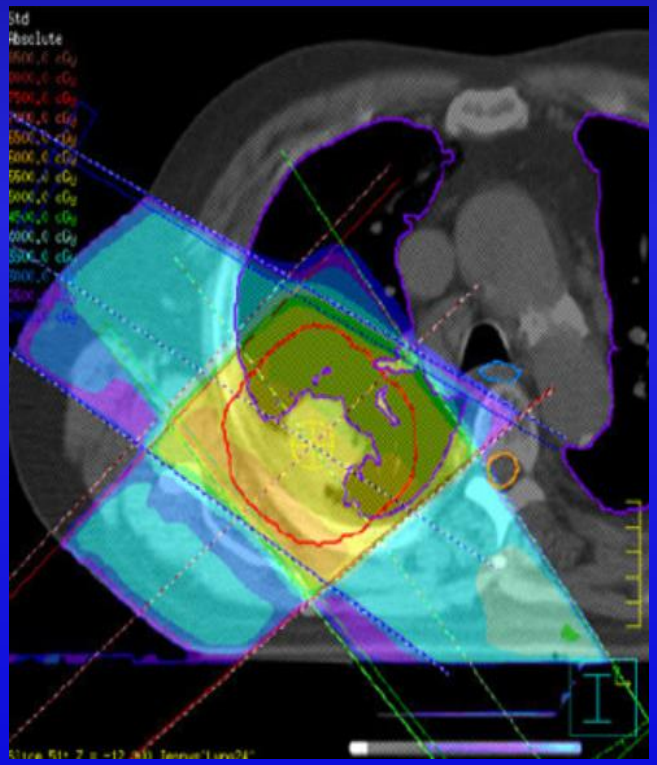
"*Tumor control probability in radiation treatment*"

by Marco Zaider and Leonid Hanin, Med. Phys. **38**, 574 (2011)

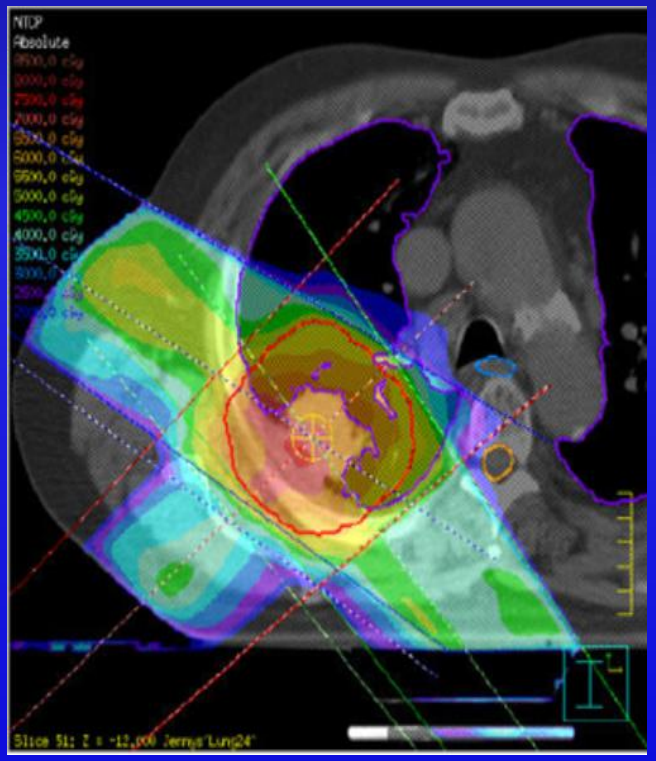
Biological models used in treatment planning systems

- Monaco
  - *Tumor: Poisson statistics cell kill model*
  - *Normal tissues: EUD*
- Pinnacle
  - *Tumor: LQ-based Poisson TCP model; EUD*
  - *Normal tissues: Lyman-Kutcher NTCP model; EUD*
- Eclipse
  - *Tumor: LQ-based Poisson TCP model; EUD*
  - *Normal tissues: LQ-based Poisson NTCP model; Lyman-Kutcher NTCP model*

Pinnacle example of a biologically optimized lung tumor plan



Physically optimized plan resulting in TCP of 40%



Biologically optimized plan resulting in TCP of 60% with the same NTCP

Nahum, Clatterbridge course on Radiobiology and Radiobiological Modelling in Radiotherapy, 2013

Alan Nahum: five levels of biological treatment planning

- Level I: treatment plan derived from dose-based criteria and then adjusting it until NTCP reaches the required level for a prescribed tumor dose
- Level II: individualization of both the dose and the number of fractions on an isotoxic basis
- Level III: expressions for TCP and NTCP and/or EUD are used in the objective function of the inverse planning process
- Level IV: patient-specific functional imaging data are added to radiobiological inverse planning
- Level V: individual patient biological data are also incorporated

Nahum, Clatterbridge course on Radiobiology and Radiobiological Modelling in Radiotherapy, 2013

Do we know what parameters to use?

- Yes, well, kind of!
- At least we are close for normal tissues due to the QUANTEC initiative stimulated by the AAPM
- QUANTEC: Quantitative Analyses of Normal Tissue Effects in the Clinic
  - *development of large data bases*
  - *model evaluation and data analysis*
  - *publication of best-fit models and parameters*

Summary

- Biological models can be used for treatment planning, optimization, and evaluation
- Power-law volume effect models are used extensively
- Inhomogeneous dose distributions, possibly corrected for the effect of fractionation, can be reduced to a single number, the EUD, TCP, NTCP, or PULC