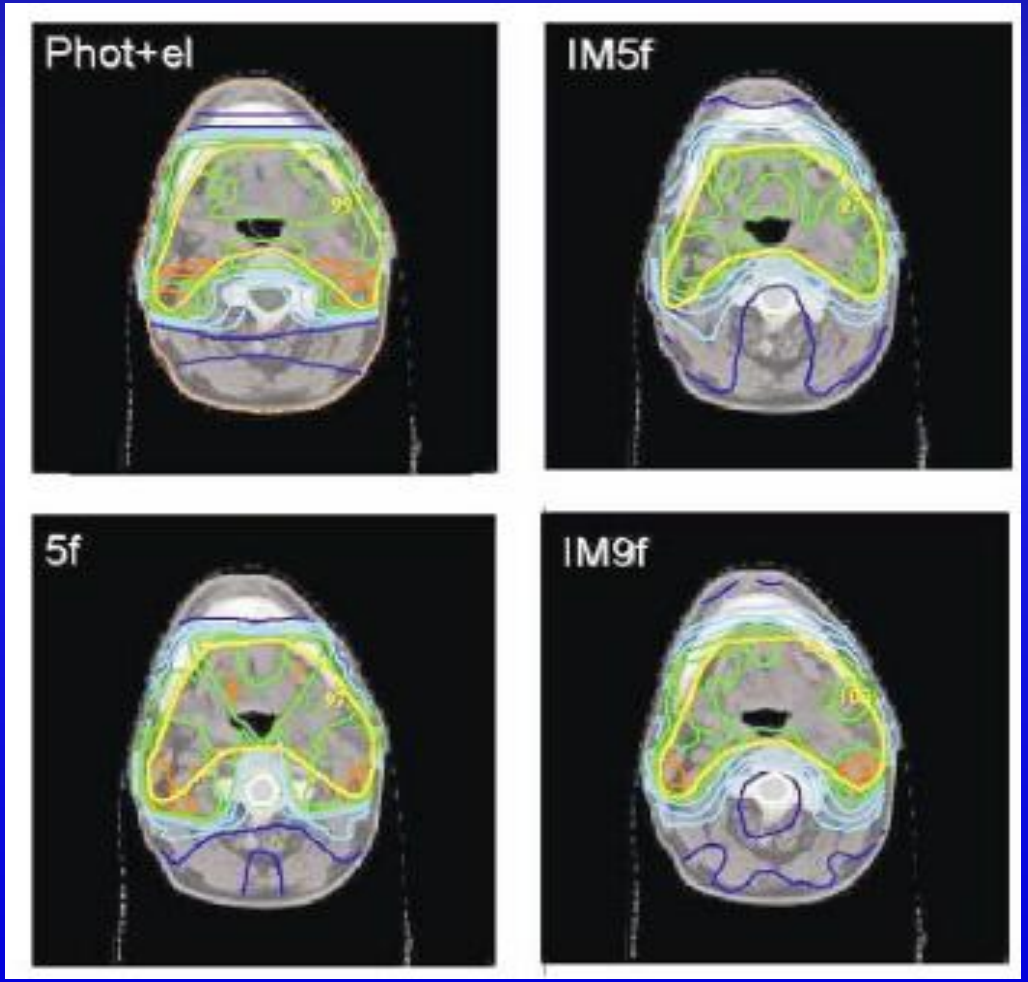
Radiobiological comparison of treatment plans

- 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: very subjective

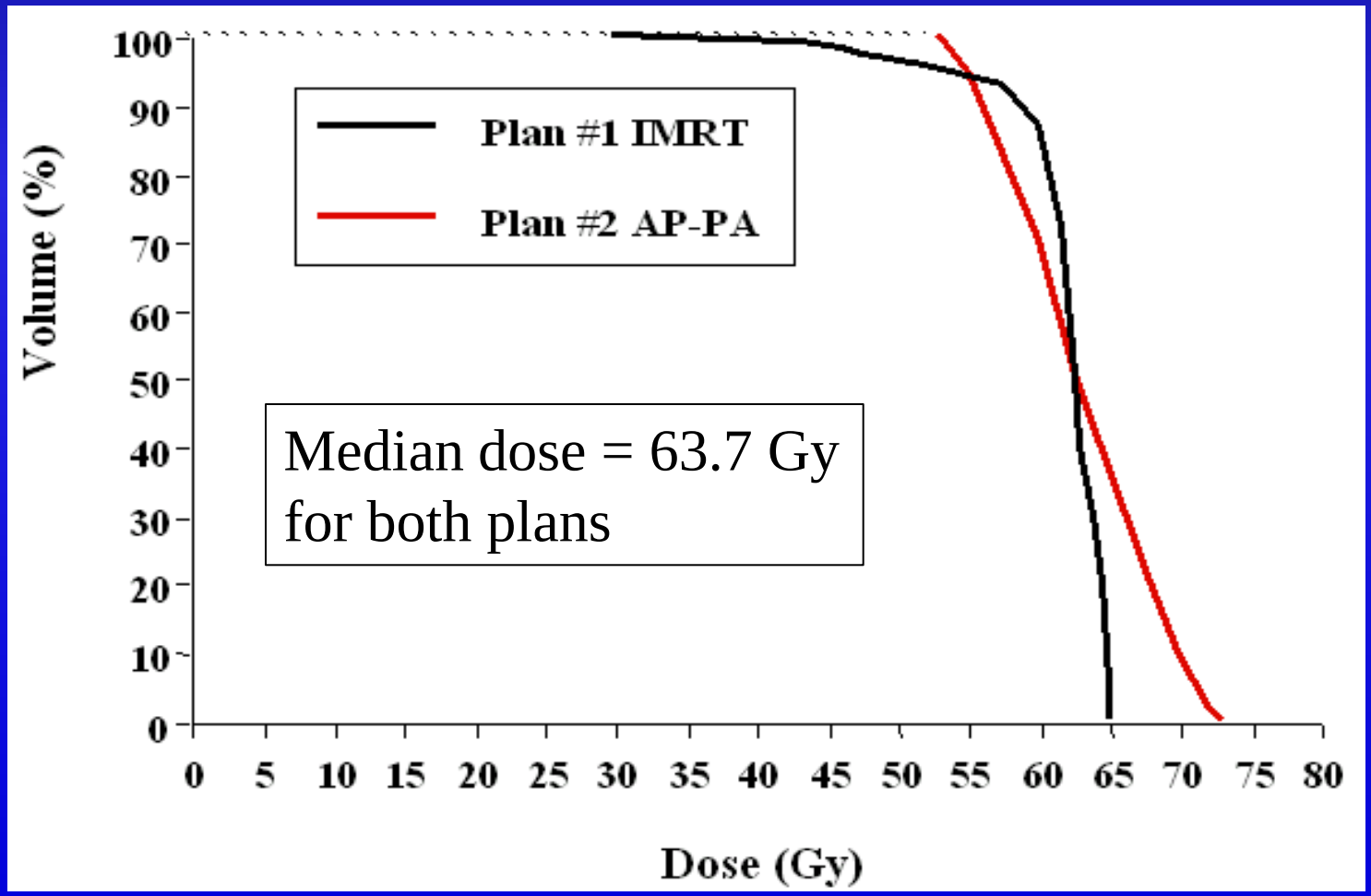
Four plans for comparison:

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



Comparison of tumor DVHs

(from Andrzej Niemierko, ASTRO, 2001)



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?

- Need a volume-effect model of dose response
  - *most common is the power-law model*

Power-law volume-effect models (*they've 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

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

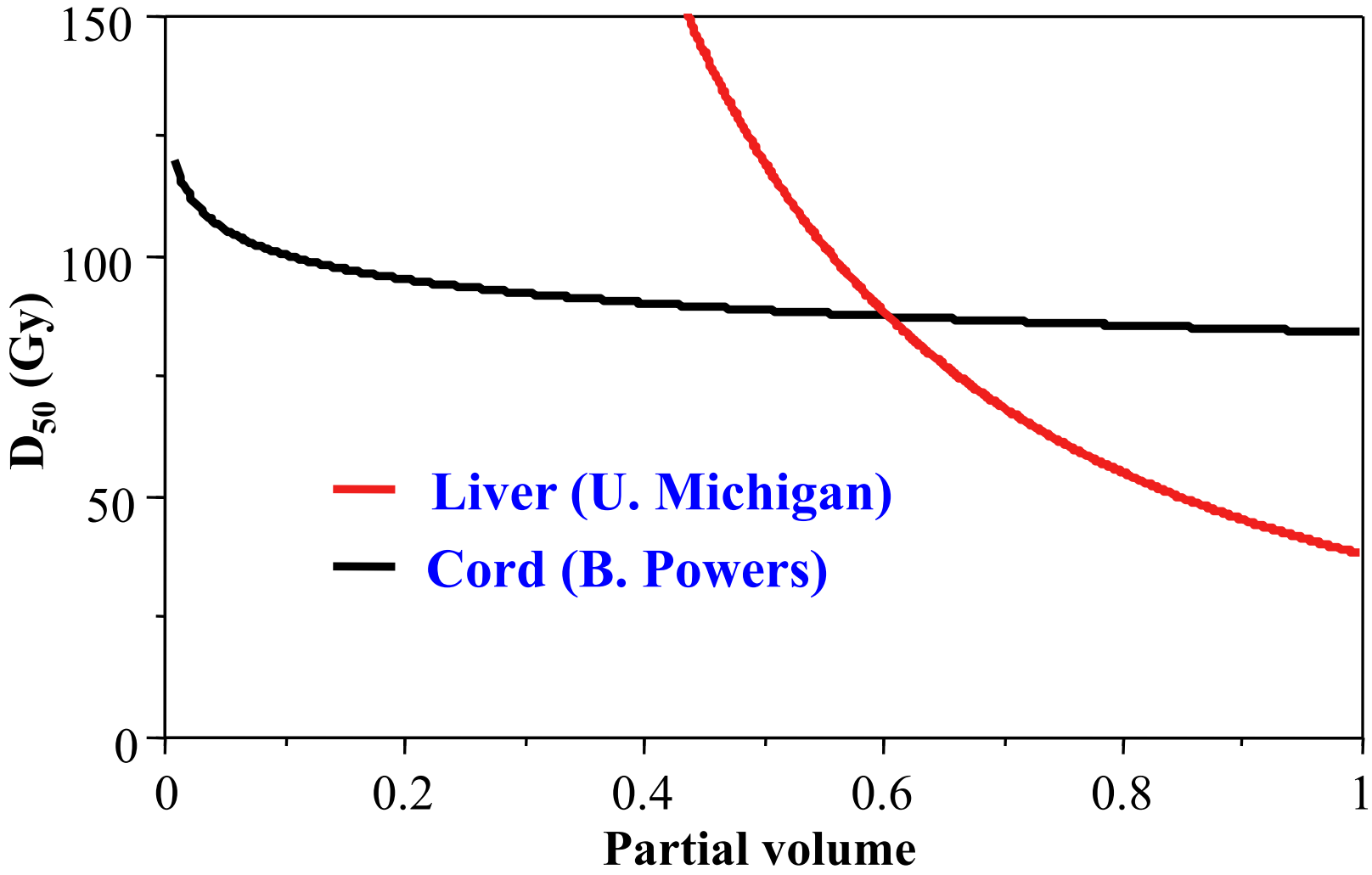
where D_v is the dose which, if delivered to fractional volume, v, of an organ, will produce the same biological effect as dose D_1 given to the whole organ

This is the basis of most dose-volume histogram reduction 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)



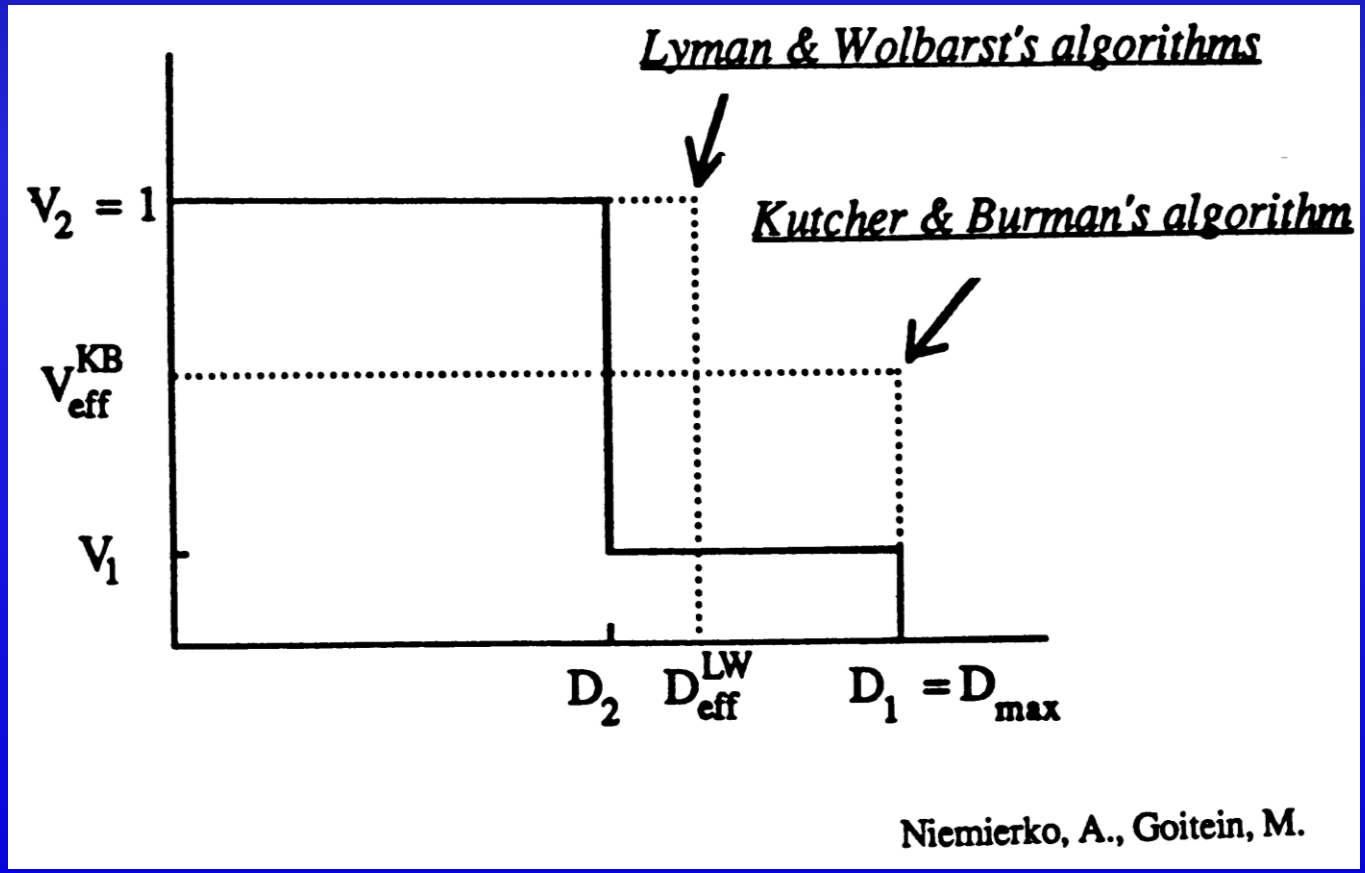
(from Andrzej Niemierko, ASTRO, 2001)

Dose-volume histogram reduction methods

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}



Determination of D_{eff}

Need to sum the effects for the subvolumes of tissue represented by each step of the DVH

Mohan et al (1992) expression for D_{eff} (derived from the Kutcher and Burman method)

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

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"

Equivalent Uniform Dose (*EUD*)

(Niermierko, 1999)

For any dose distribution, the *EUD* is the dose which, if distributed uniformly across the entire target volume or organ at risk, causes the same biological effect as the actual inhomogeneous dose distribution

(*originally defined for tumors only in 1997 but extended to normal tissues in 1999*)

The generalized *EUD* equation (Niemierko, 1999)

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

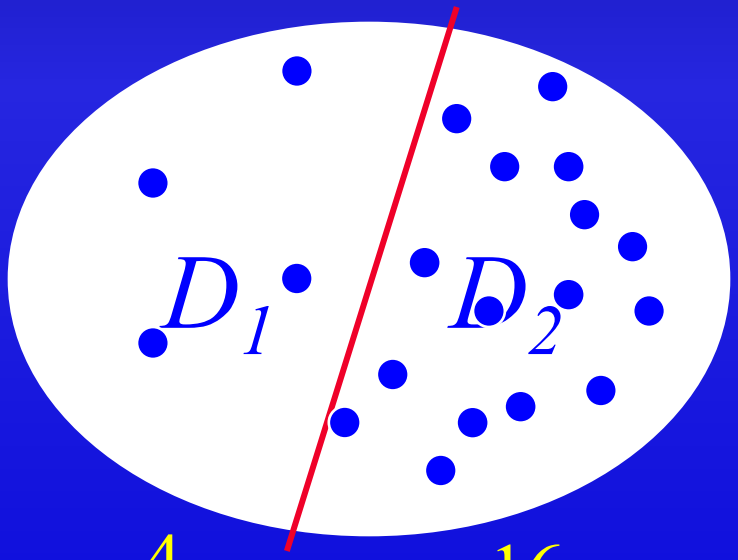
where v_i is the volume of the tissue in dose bin D_i as a fraction of the volume of the total organ or tumor i.e.

$v_i = V_i/V_{tot}$

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

Generalized Equivalent Uniform Dose (g*EUD*)

$D_1 < D_2$

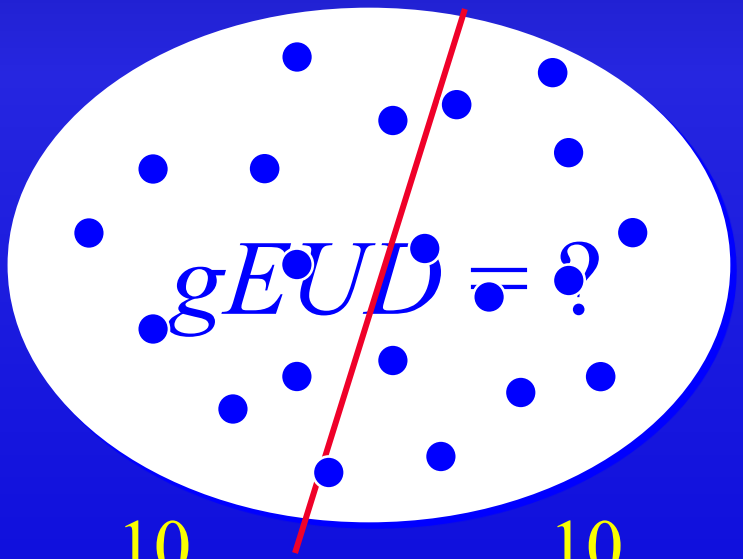


4 16

Total effect = 4 + 16 = 20

=

$D_1 < gEUD < D_2$



10 10

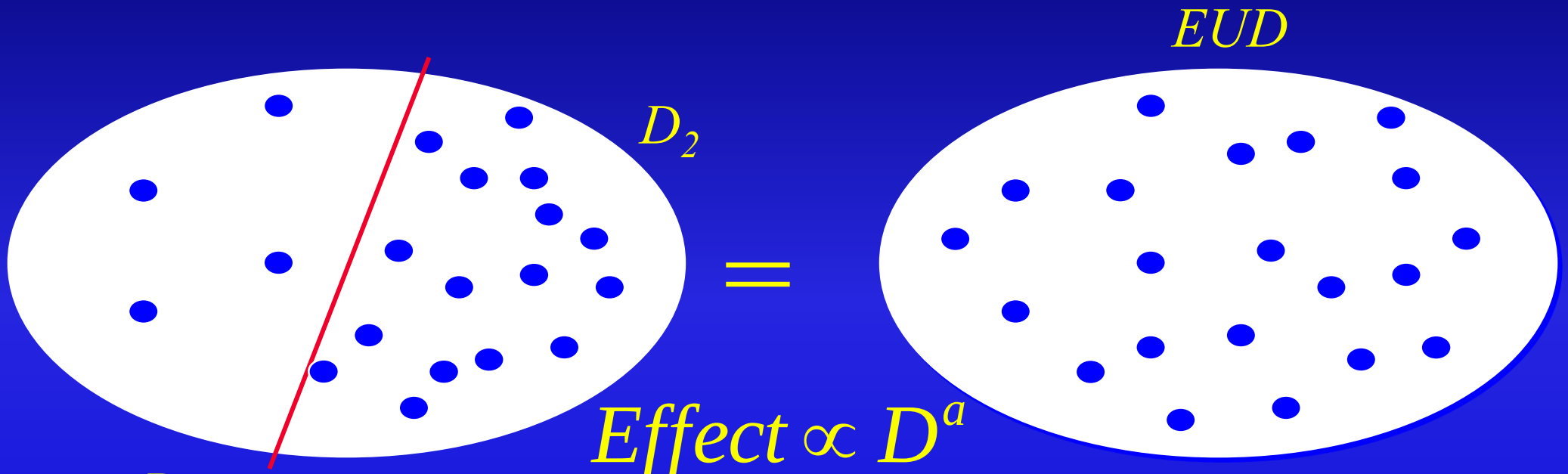
Total effect = 20

Often gEUD is simply referred to as EUD

(from Andrzej Niemierko, ASTRO, 2001)

Generalized Equivalent Uniform Dose (g*EUD or EUD*)

(from Andrzej Niemierko, ASTRO, 2001)



$$Effect \propto D^a$$

$$0.5D_1^a + 0.5D_2^a = EUD^a$$

$$EUD = \left(0.5D_1^a + 0.5D_2^a\right)^{1/a}$$

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

Tumors

Normal tissues

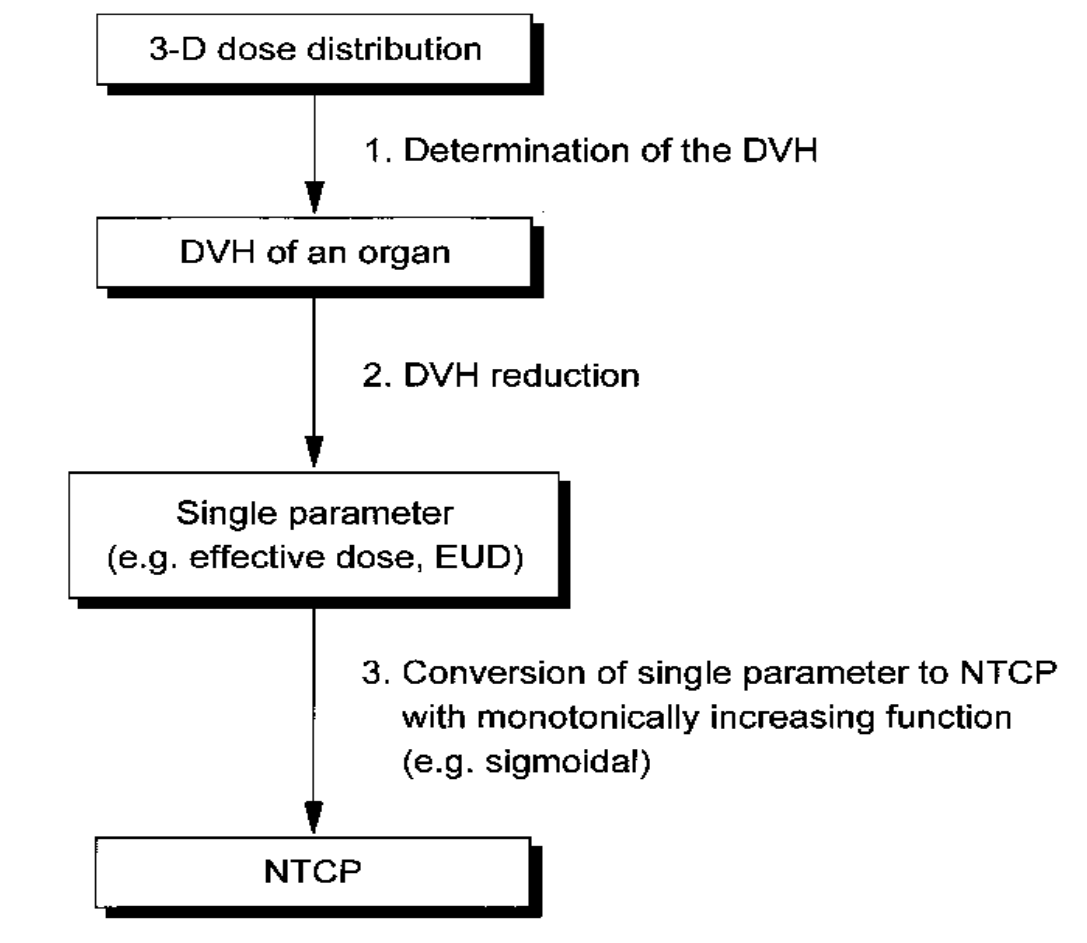
Structure (Source)	End-point	a
Chordoma base of skull (MGH)	Local control	-13
Squamous cc (Brenner)	Local control	-13
Melanoma (Brenner)	Local control	-10
Breast (Brenner)	Local control	-7.2
Parotids (Eisbruch)	Salivary function (<25%)	<0.5
Parotids (Chao)	Salivary function (<25%)	0.5
Liver (Lawrence)	Liver failure	0.6
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)

Can complication and tumor control probabilities be calculated?

Physicians want to minimize normal tissue complication probability (NTCP) and maximize tumor control probability (TCP)

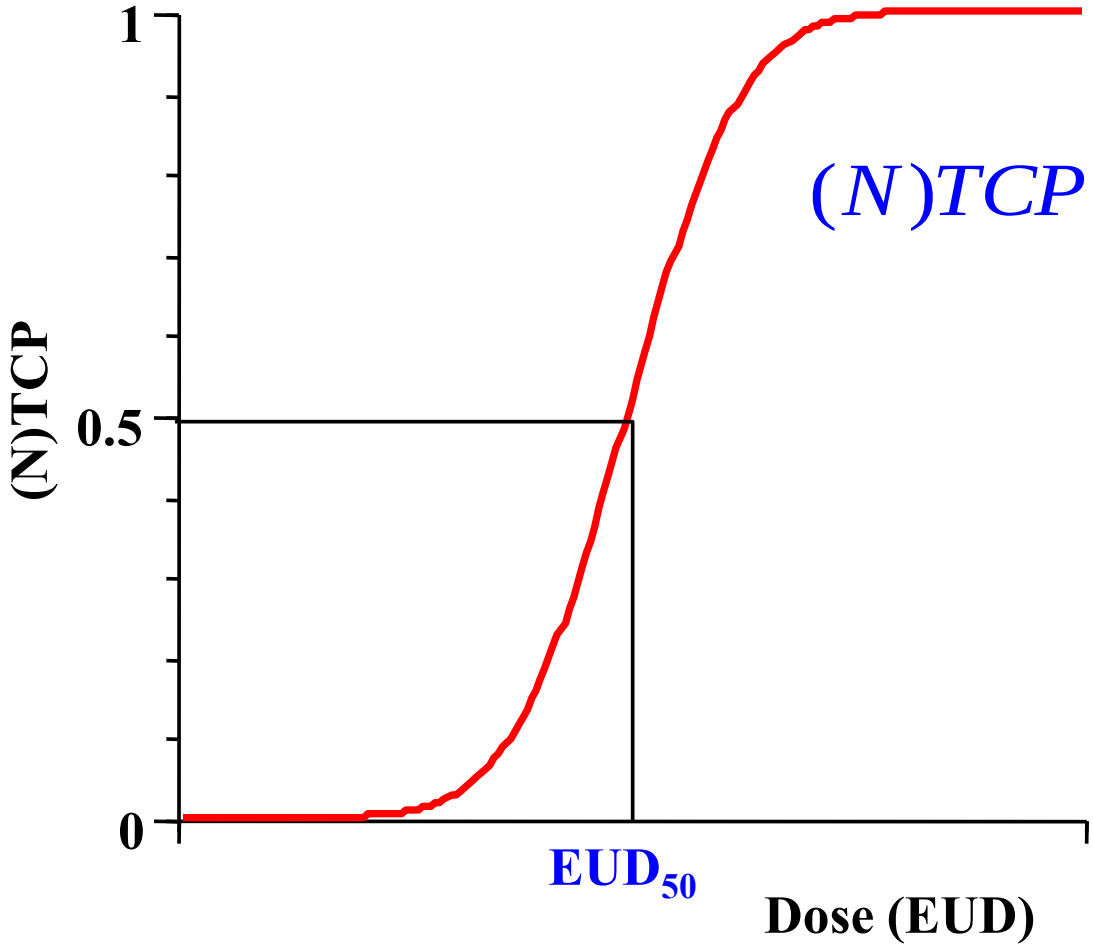
NTCP (or similarly TCP) determination from a DVH



Kwa, et al, Radiotherapy and Oncology 48, 61, 1998

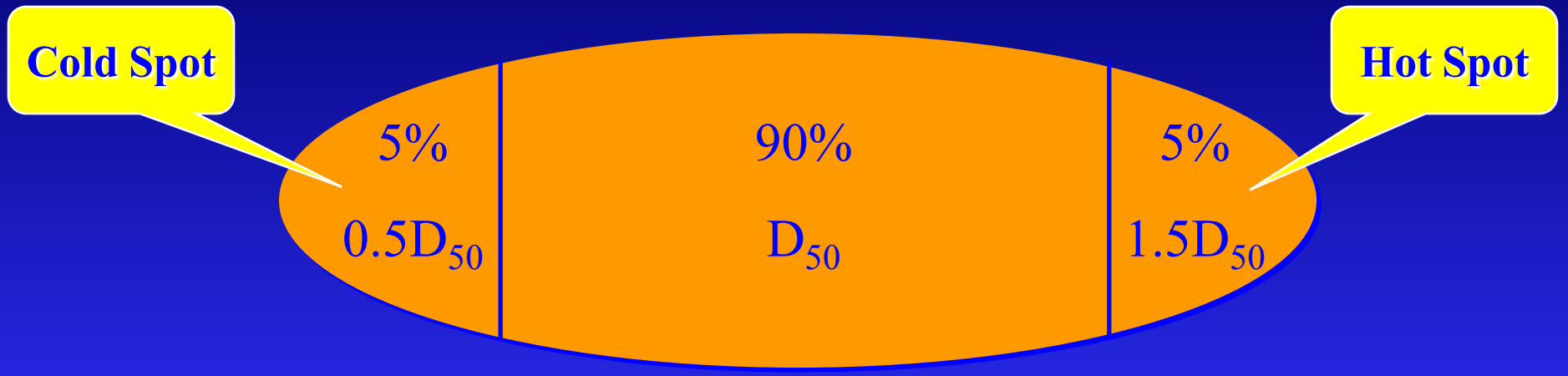
TCP & NTCP: logistic model

(from Andrzej Niemierko, ASTRO, 2001)



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

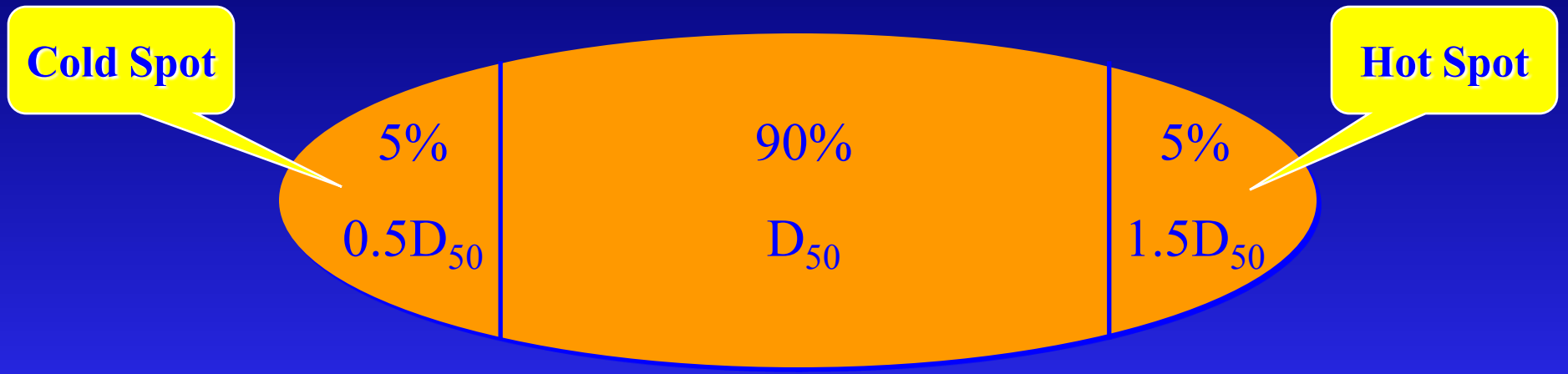
EUD – Tumors (from Andrzej Niemierko, ASTRO, 2001)



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

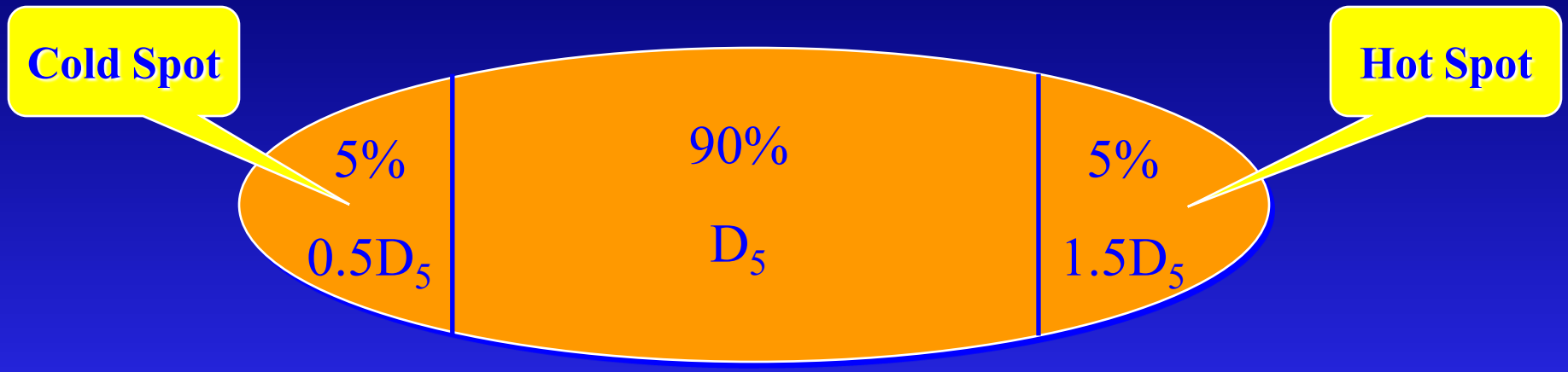
Tumor	a	EUD/D_{50} %	TCP(%) (γ_{50}=2)
Breast	-7.2	74	8

EUD – Tumors (from Andrzej Niemierko, ASTRO, 2001)



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

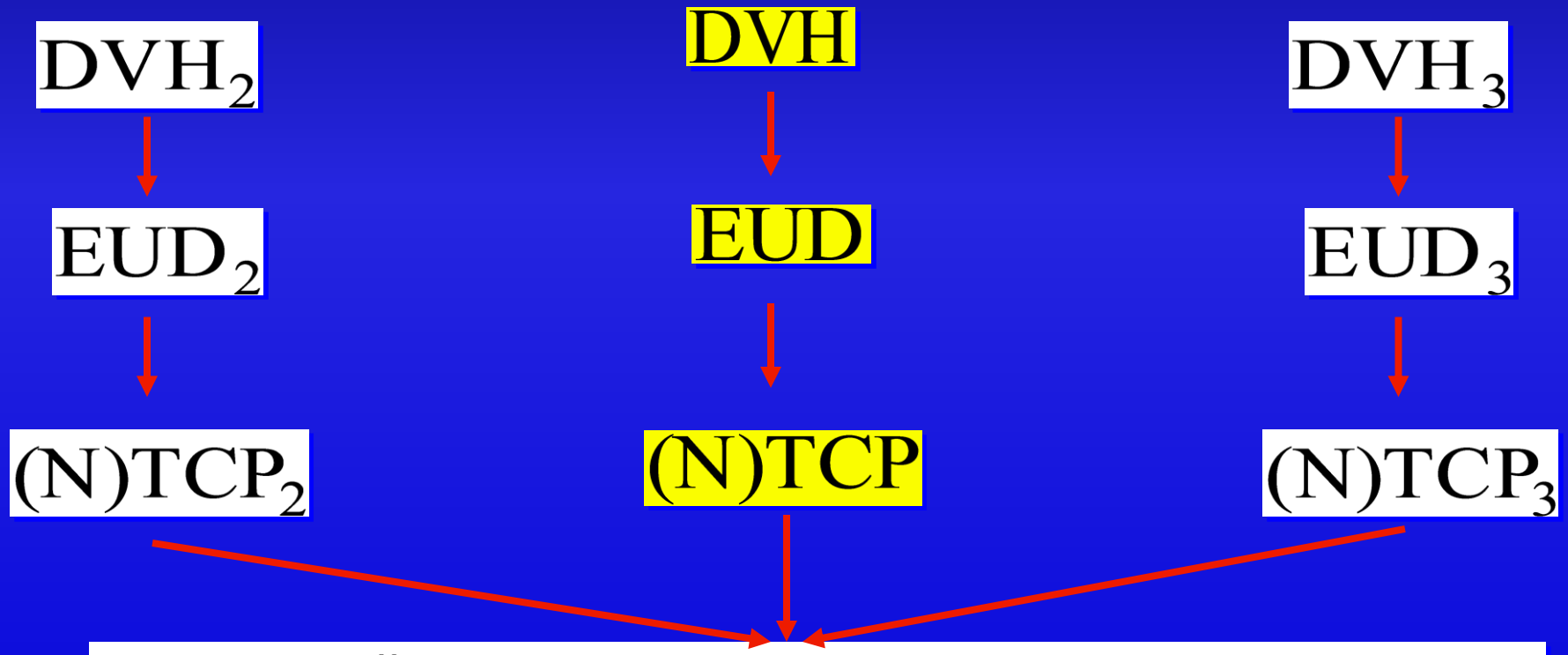
EUD - Normal Structures (from Andrzej Niemierko, ASTRO, 2001)



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

Creating a Score function for plan optimization or plan evaluation

(from Andrzej Niemierko, ASTRO, 2001)



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

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

The NTCP equation 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,

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

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

Another example: the relative seriality model

According to the relative seriality model, the NTCP for each organ at risk due to inhomogeneous dose distribution is:

$$NTCP = \left[1 - \prod_i \left[1 - P(D_i)^s \right]^{\Delta v_i} \right]^{1/s}$$

where D_i is the dose in ith subvolume of fractional volume ΔV_i

$P(D_i)$ is the probability of complication if the entire organ were to be irradiated to dose D_i

s is a volume effect power law exponent (restricted to the range 0 – 1)

$P(D_i)$ values are calculated using a dose-response model such as logistic, probit, or Poisson

Yet 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 :

$$TCP = e^{-N_0 S_m}$$

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

The 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: PLC 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:

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

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

Comparison of treatment plans: Summary

- Treatment plans can be compared quantitatively by converting the dose distributions in tumors and normal tissues to a single number, such as the EUD and then calculating the TCPs and NTCPs
- Warning: this is still under development
  - *the models and the parameters used need to be "proven" effective*