Radiobiological aspects of dose summation and treatment planning

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Background

1. Biological effect is non-linear with physical dose
2. Physical dose is non-homogeneous
3. Other biology: cell migration, proliferation, hypoxia

Biologically Effective dose map
will be different from the
Physical dose map

How could this influence…

1. Treatment prescription, *e.g.* hypofractionation?
2. Ranking and choice of treatment plans?

Equieffective Dose

Effect of a single dose fraction of radiation d: $e = \alpha d + \beta d^2$

In cell-survival studies in vitro, e is: $e = -\log_e\left(SF_d\right)$

Total effect of n fractions is $E = ne$.
Total dose $D = nd$. Thus: $E = n\left(\alpha d + \beta d^2\right) = \alpha D + \beta dD$

Rearrange: $E/\alpha = D\left(1 + d/\left(\alpha/\beta\right)\right)$

Therefore for 2 isoeffective schedules $[d_1, D_1]$ and $[d_2, D_2]$: $\frac{D_2}{D_1} = \frac{d_1 + \left(\alpha/\beta\right)}{d_2 + \left(\alpha/\beta\right)}$

Equieffective Dose and *EQD2*

For 2 isoeffective schedules [d_1, D_1] and [d_2, D_2]: $\frac{D_2}{D_1} = \frac{d_1 + (\alpha/\beta)}{d_2 + (\alpha/\beta)}$

Make D_2 an Equieffective Dose:

$$\frac{EQD2}{D} = \frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)} \qquad \boxed{EQD2 = D\frac{d + (\alpha/\beta)}{2 + (\alpha/\beta)}}$$

Specify α/β using nomenclature: $EQD2_{\alpha/\beta}$ e.g. $EQD2_3$ **ICRU**

Note that: $BED = EQD0$ $\qquad EQD2 = \frac{BED}{1 + 2/(\alpha/\beta)}$

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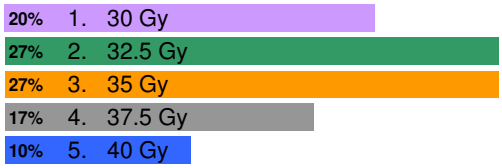
MCJ JM12 4

A regime of 10 × 3 Gy is prescribed to Brain. What is the $EQD2_2$?



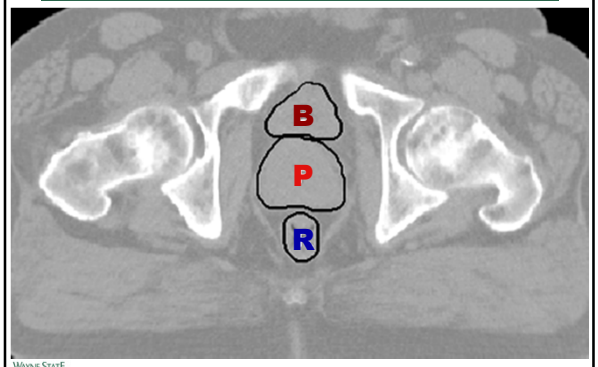
A regime of 10 × 3 Gy is prescribed to Brain. What is the $EQD2_2$?

1. 30 Gy
2. 32.5 Gy
3. 35 Gy
4. 37.5 Gy
5. 40 Gy

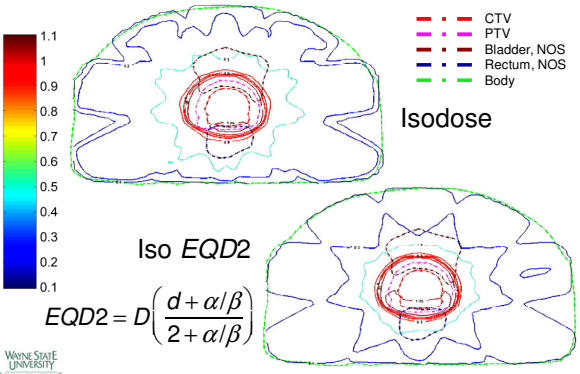
Answer 4

Ref: Joiner MC & Bentzen SB.
Basic Clincal Radiobiology 2009; Ch. 9

Tumor and OARs contoured



Analytic approach: Isodose → *EQD2*



$$EQD2 = D\left(\frac{d+\alpha/\beta}{2+\alpha/\beta}\right)$$

Analytic approach: *EQD2* → *gEUD2*

$$gEUD = \left(\frac{1}{N}\sum_{i=1}^{N}(D)_i^a\right)^{1/a} \qquad gEUD2 = \left(\frac{1}{N}\sum_{i=1}^{N}(EQD2)_i^a\right)^{1/a}$$

- *a* is volume parameter, indicating the relevance of a cold spot in the tumor or a hot spot in an Organ at Risk (OAR)
- For Tumor, $a < 0$; For OAR, $a > 0$
  Parallel behavior $|a| \approx 1$; serial → larger $|a|$

gEUD is the generalization of the Equivalent Uniform Dose concept of Niemierko, see:
Wu et al. *Int J Radiat Oncol Biol Phys* 2002;52:224-235

Analytic approach: NTCP and TCP

$$NTCP = \left[1 + \left(\frac{D_{50}}{gEUD2}\right)^{4\gamma}\right]^{-1} \qquad TCP = \exp(-N_0 S)$$

$$S = (SF2)^{\frac{gEUD2}{2}}$$

e.g. for Prostate:

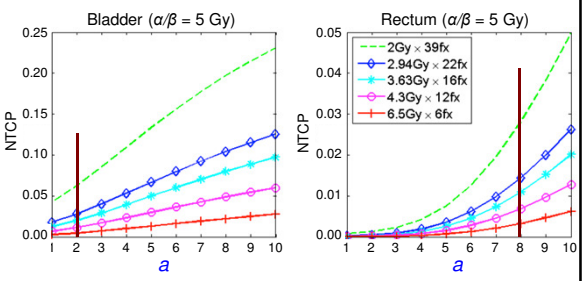
OAR	D_{50}	γ
Bladder	80 Gy	3.0
Rectum	75 Gy	2.5

$N_0 = 10^6, 5 \times 10^6, 10^7$

SF2 = 0.3 – 0.9

α/β = 5 Gy

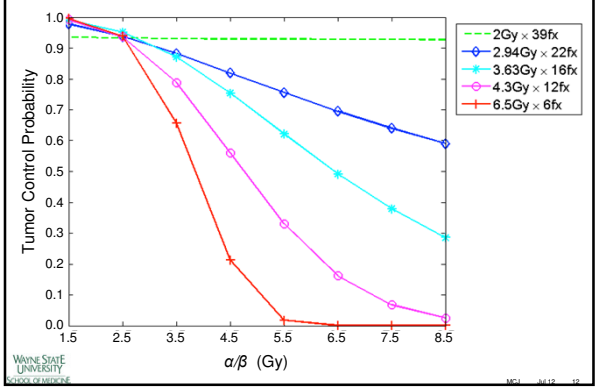
NTCP for organs at risk: volume effect



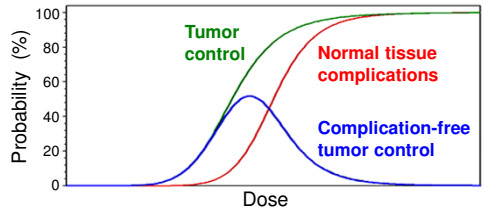
Parallel behavior |*a*| ≈ 1; serial → larger |*a*|

Song et al. *Med Phys* 2007;34:352-65

TCP: SF2 = 0.6, $N_0 = 5 \times 10^6$



Complication-free TCP: P+

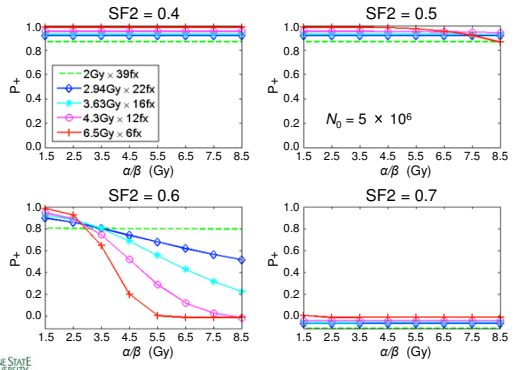


$$P+ = TCP - TCP \cap NTCP$$
$$= TCP - NTCP + \delta \times (1 - TCP) \times NTCP$$

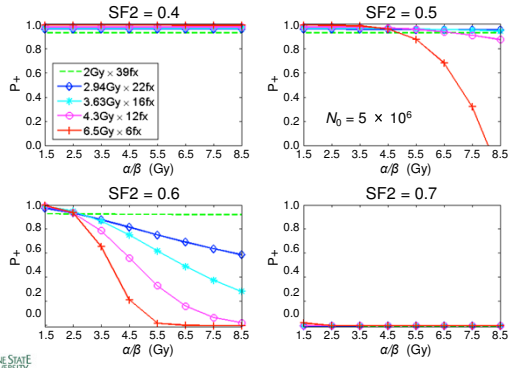
δ is fraction of patients with independent tumor and normal tissue response. Vary δ from 0 to 20%

Källman et al. *Int J Radiat Biol* 1992;62:249-262

P+ referenced to bladder NTCP



P+ referenced to rectal NTCP



Order of calculation is important

1. Physical dose distribution → *gEUD* → *gEUD2*
2. Physical dose distribution → *EQD2* distribution → *gEUD2*

Example:

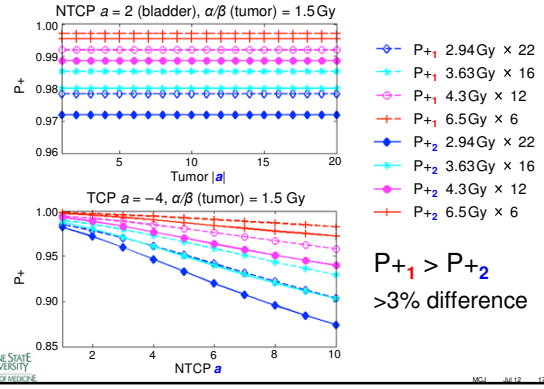
30 × 2 Gy = 60 Gy to target in 10 × 10 matrix.

4 × 4 cold spot in matrix gets 30 Gy.

Assume $a = -4$, $\alpha/\beta = 2$ Gy, representative prostate ca

gEUD2 (1) = 46 Gy, *gEUD2* (2) = 41 Gy, **11% difference**

Order of calculation is important



$P+_1 > P+_2$

>3% difference

If cold spots exist in a target volume, calculating *EQD2* at voxel level changes *gEUD2* how:

13% 1. Increases
20% 2. Decreases
17% 3. Unchanged
30% 4. Increase or decrease depending on dose
20% 5. Can't be calculated without more information

If cold spots exist in a target volume, calculating *EQD2* at voxel level changes *gEUD2* how:

1. Increases
2. Decreases
3. Unchanged
4. Increase or decrease depending on dose
5. Can't be calculated without more information

Answer 2

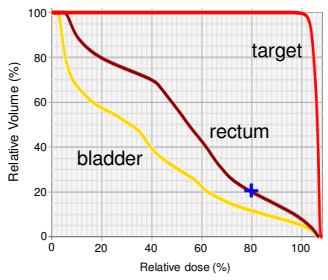
Ref: Liao Y et al. *Int J Radiat Oncol Biol Phys* 2010;76:260-8

Spatial Dose-Volume Histogram: sDVH

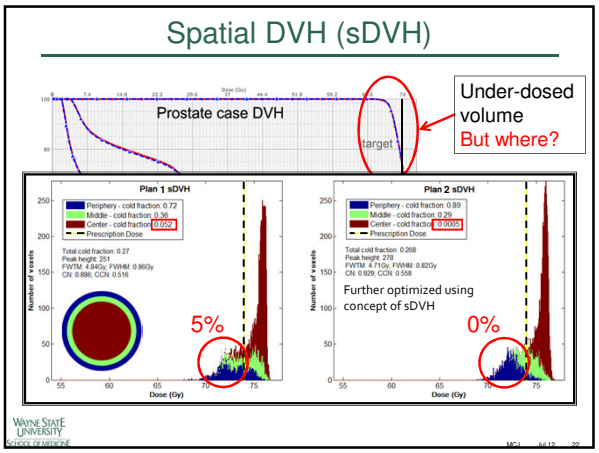
Treatment planning

3D → 2D Dose-Volume Histogram (DVH)

- used both to optimize and evaluate treatment plans
- physical absorbed dose… no spatial information!



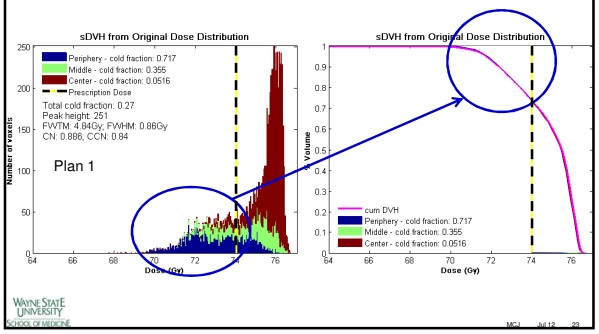
Spatial DVH (sDVH)



Spatial DVH (sDVH)

Differential sDVH

Cumulative sDVH



Spatial DVH (sDVH)

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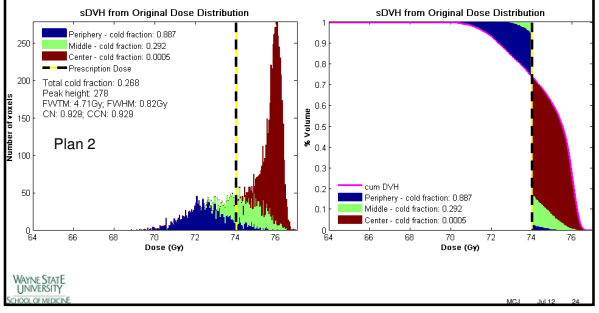

Now also add the radiobiology

1. voxel d_i → structure *gEUD* → $gEUD_2$

2. voxel d_i → voxel $EQD_{2,i}$ → $gEUD_2$

Could the choice of model change the plan ranking?

Models versus plan ranking

For **either** Model **1** **or** **2**

NTCP: logistic vs LKB
TCP: logistic vs Poisson

Two clinical cases, 10 plans

Rankings do NOT change

Models versus plan ranking

For Model **1** vs **2**

Two clinical cases, 10 plans

Rankings can change!

Challenge to biologically conformal planning:
which model is more appropriate clinically?

To distinguish plans using distribution of biologically effective dose, *absolutely* requires:

20% 1. Large voxel sizes
20% 2. Knowing expression of biological markers
20% 3. Knowing clonogen density
23% 4. Retention of spatial information within DVH
17% 5. Highly accurate knowledge of radioresponse

To distinguish plans using distribution of biologically effective dose, *absolutely* requires:

1. Large voxel sizes
2. Knowing expression of biological markers
3. Knowing clonogen density
4. Retention of spatial information within DVH
5. Highly accurate knowledge of radioresponse

Answer 4

Ref: Zhao B et al. *Med Phys* 2010;37:5586-92

Conclusions

- Including even basic biology (non-linear dose effect) can influence treatment prescription
- If considered in treatment planning, biological factors should be included at the voxel level
- Different calculation paths for Biologically Effective Dose, and inclusion of biological factors, can lead to different choices of treatment plan
- sDVH is a new tool for intercomparing plans with similar DVH but different dose distributions
- Whether these different plan choices are actually resolvable in clinical response, needs testing!