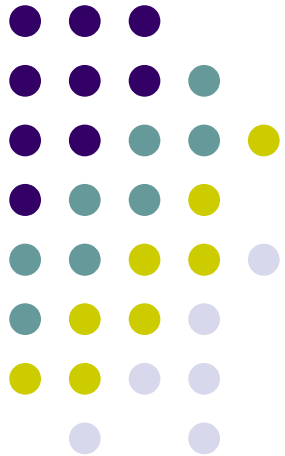
Curso de Radiobiología
UDELAR
Facultad de Ciencias
Unidad de Física Médica

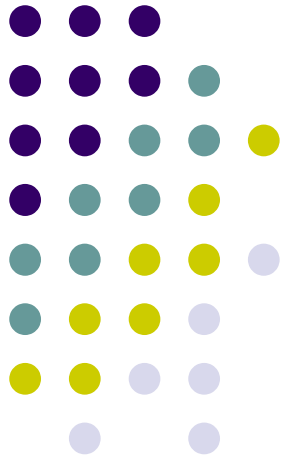
Dr. Eduardo Francisco Larrinaga Cortina



Radiobiología.
Aplicaciones en Radioterapia

Créditos:

Dr. Hatim Fakir



2011

Radiation Therapy Applications

Medical Biophysics 4467/9567B

Hatim Fakir,Ph.D

London Regional Cancer Program
University of Western Ontario

Slides courtesy of Jake Van Dyk, J. Battista and S. Karnas

Main Goal of Radiation Therapy

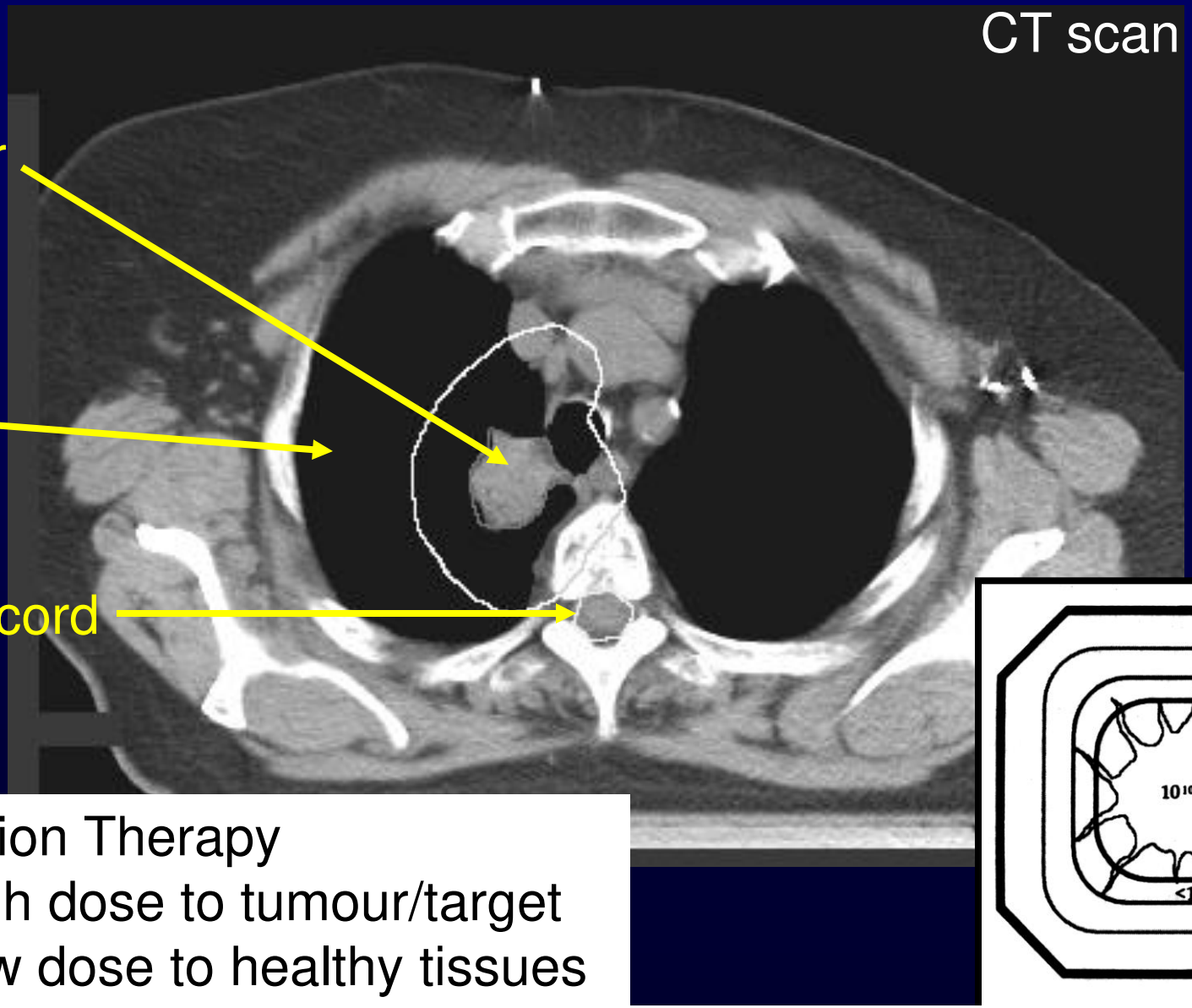
Maximize tumour control and minimize normal tissue effects

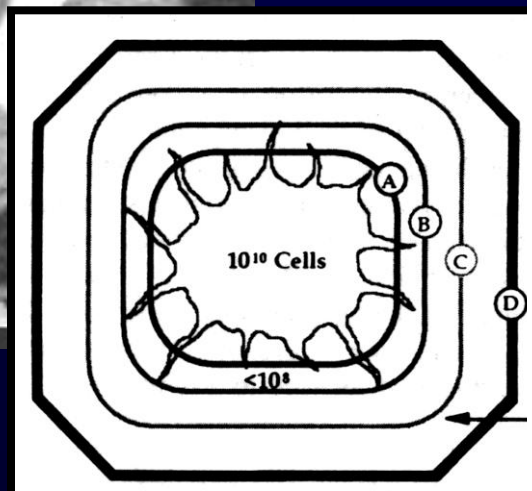
- ➔ Physics: dose distribution (gradients)
- ➔ Radiation biology: response of tissues to radiation
  Radiosensitizers/radioprotectors

Objectives/Outline

- To describe the biological principles of radiation therapy
- To describe endpoints for measuring tumour and normal tissue response
- To be able to use mathematical models relating to tissue response
- To consider rationale for fractionated treatments
- To describe the effects of radiation-stimulated proliferation
- To describe the rationale for alternative fractionation

Clinical Example - Lung Cancer





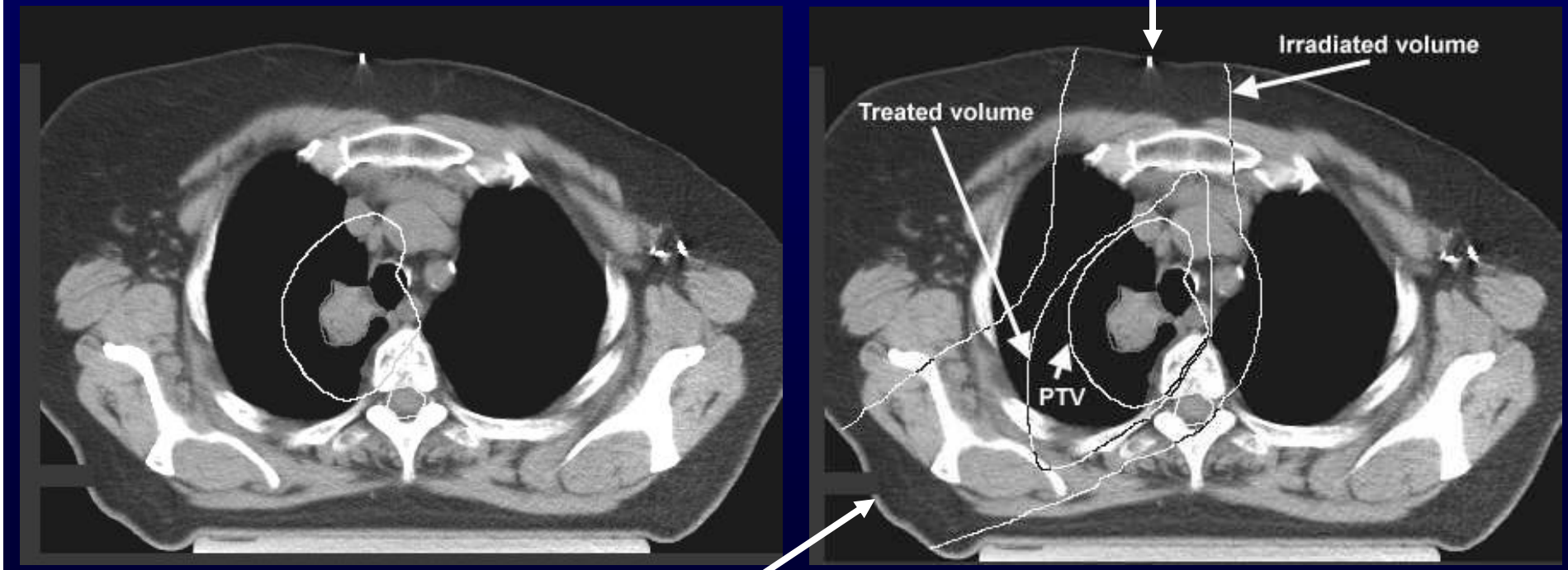
Radiation Therapy

- High dose to tumour/target
- Low dose to healthy tissues

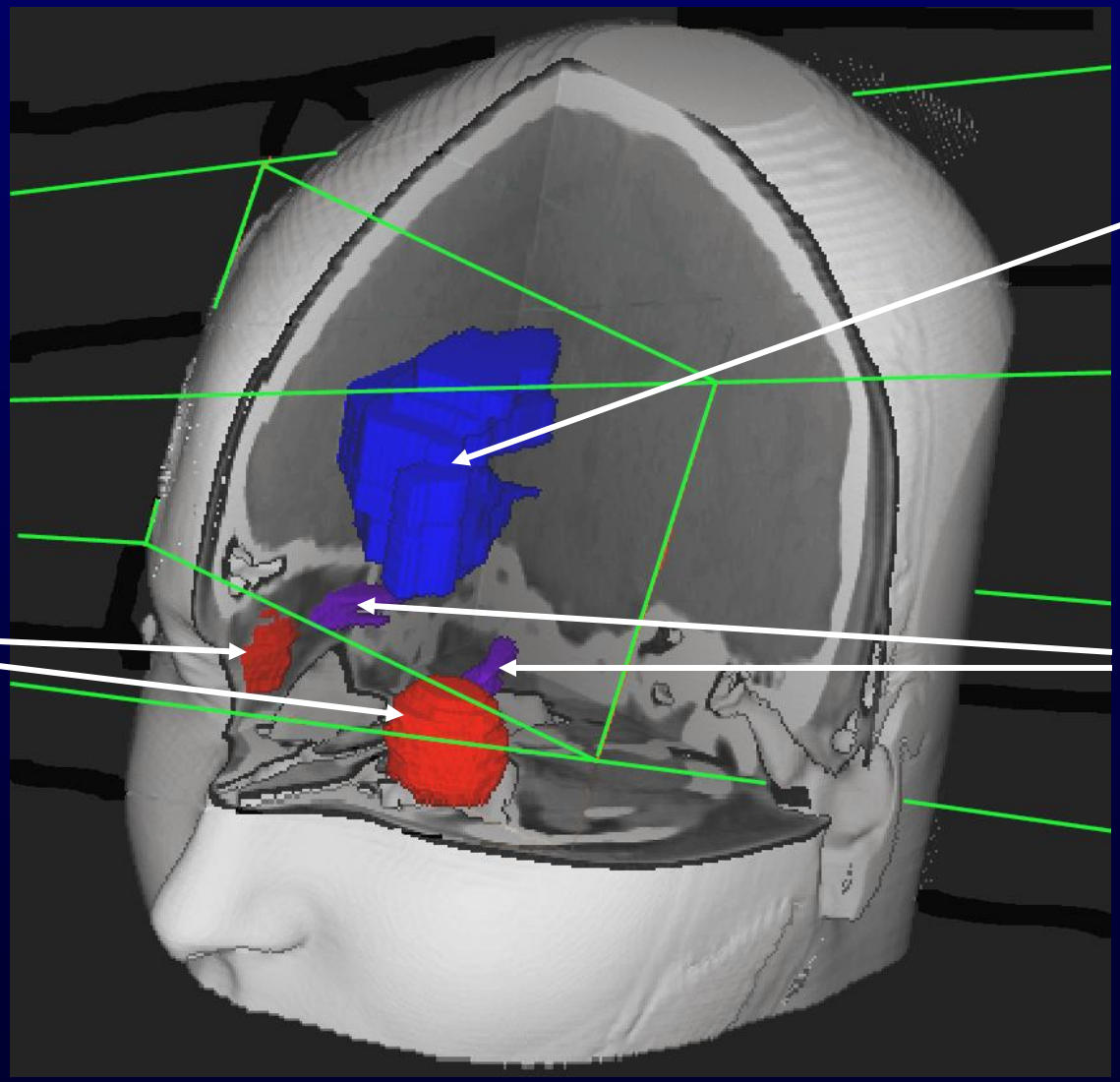
Radiation Therapy

Planning CT image

Isodose distribution



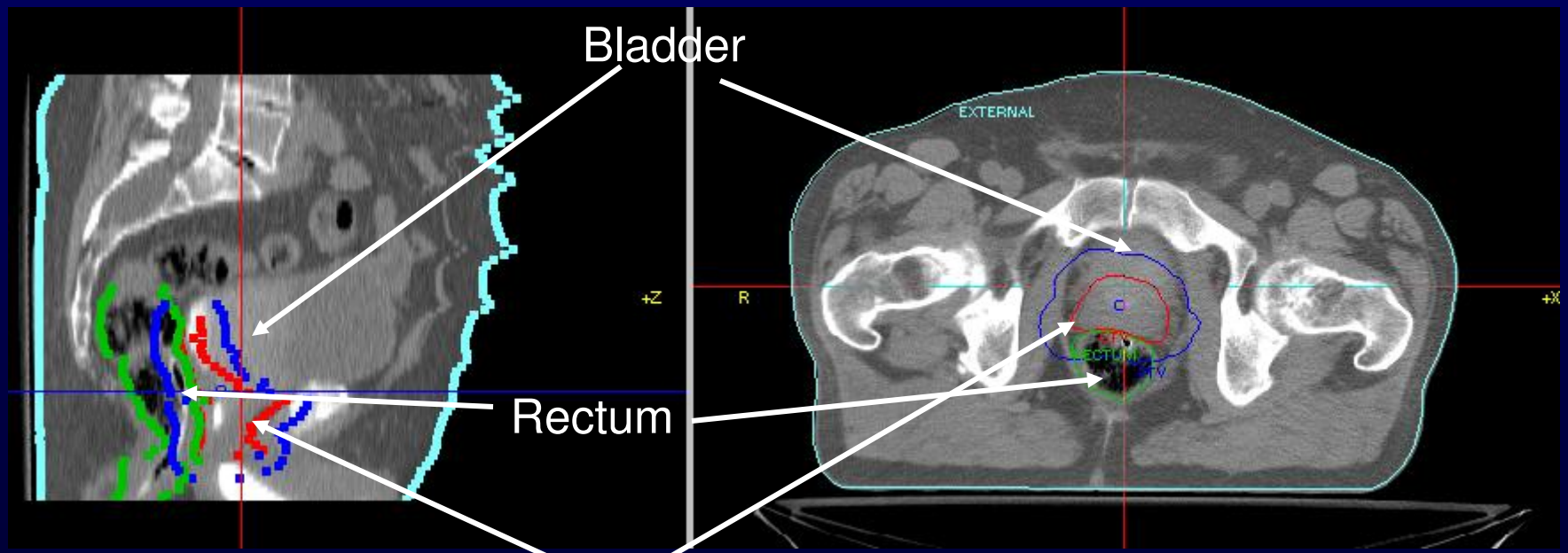
Clinical Example - Brain Tumour



Clinical Example - Prostate Cancer

Sagittal view

Transverse view



The Question

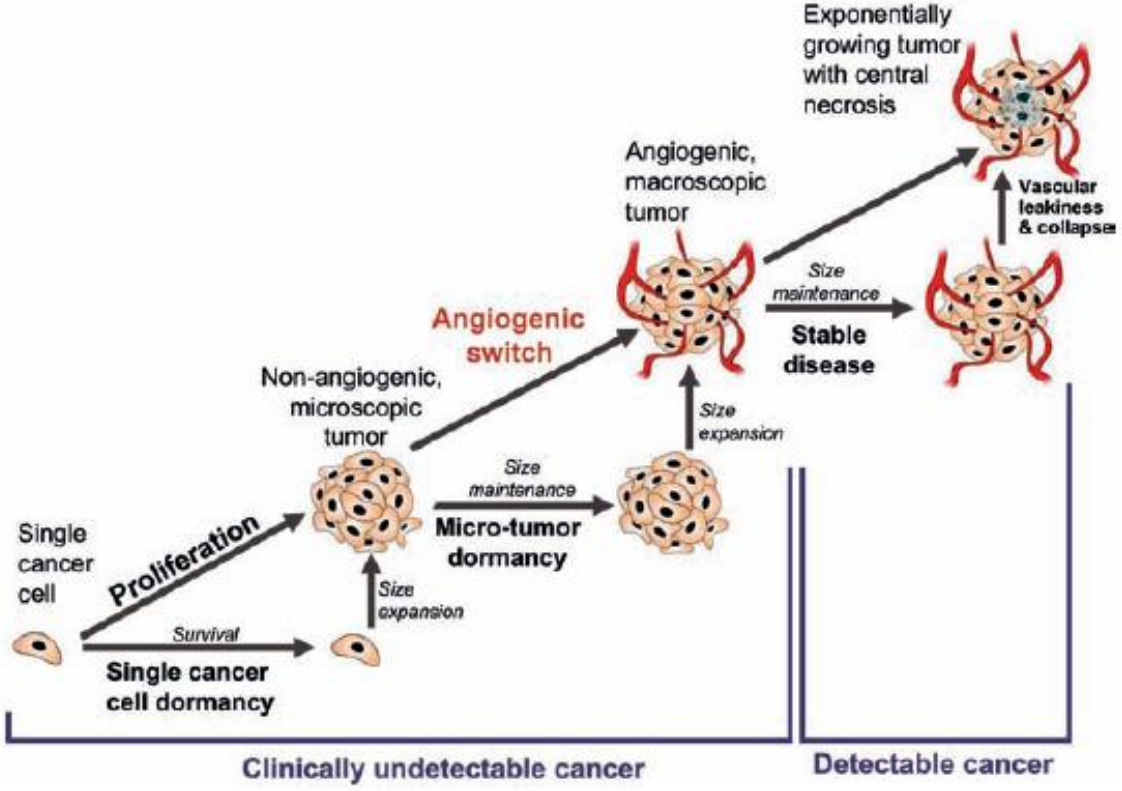
- How do we optimize radiation treatment to maximize tumour control and minimize normal tissue effects?

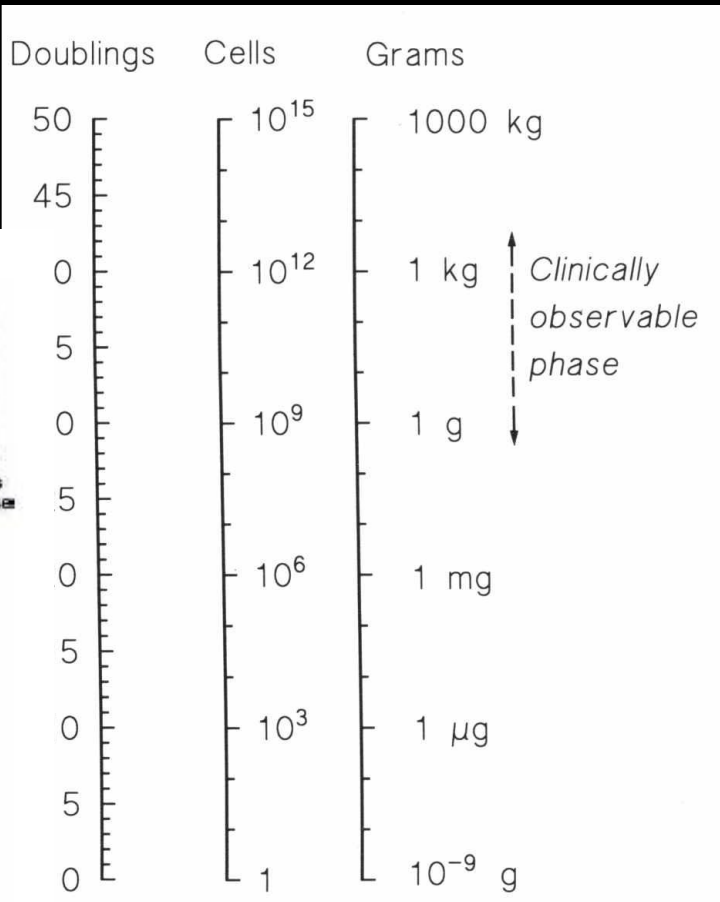
- Need to understand and quantify:
  - Dose-response of tumour and normal tissue response
  - Factors influencing biological response
    - e.g., effects of dose, number of fractions, volume irradiated, ...

Response of Tissues to Radiation

- Tumour response:
  - Regression
  - Cure or local control - no regrowth
  - Regrowth/recurrence
- Normal tissue response:
  - Range of responses
    - Non-clinical - e.g., observed on images
    - Mild symptoms - discomfort
    - Life threatening or death

Tumour Size Nomogram





ure 2.1 The relationship between the weight of a tumour, number of cells it contains (assuming 10^9 per gram), and number of doublings from a single cell.

Steel, 1997

Tumor Growth and factor affecting it

- Exponential growth: assuming constant growth rate

$$V = V_0 \, e^{\frac{\ln 2}{T_d} time}$$

- T_d : *tumour* doubling time (Lung: 2-6 months, colorectal carcinoma: 2 y)
- GF: growth fraction (proliferating cells) (measured in tumor biopsies)
- T_c : duration of cell cycle (~2 days for carcinoma)
- T_{pot}: potential doubling time. Cell doubling time without any cell loss.
- Φ: cell loss factor,

$\Phi = 1 - T_{pot}/T_d$

Steel, 1997

Table 3.1 Kinetic parameters of a typical human tumour

Cell cycle time (≈ 2 d)	Potential doubling time (≈5d)	Volume doubling time (≈ 70 d)
Growth fraction (≈40%)		
Cell loss (≈90%)		

Tumor growth in a real world

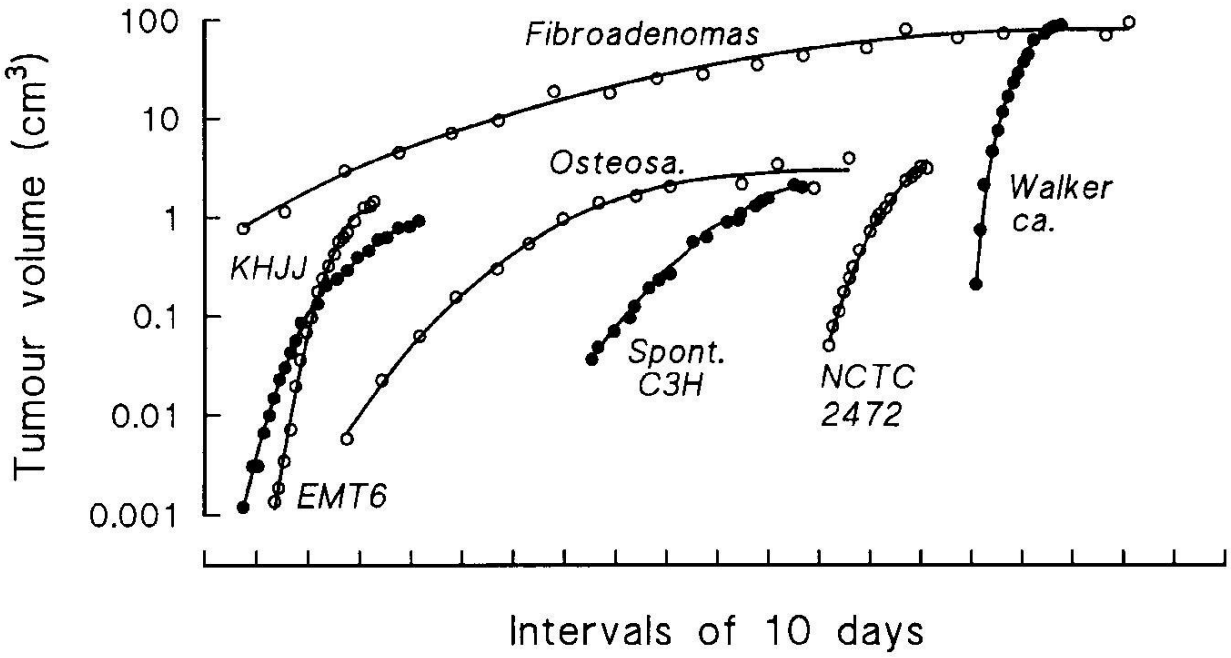
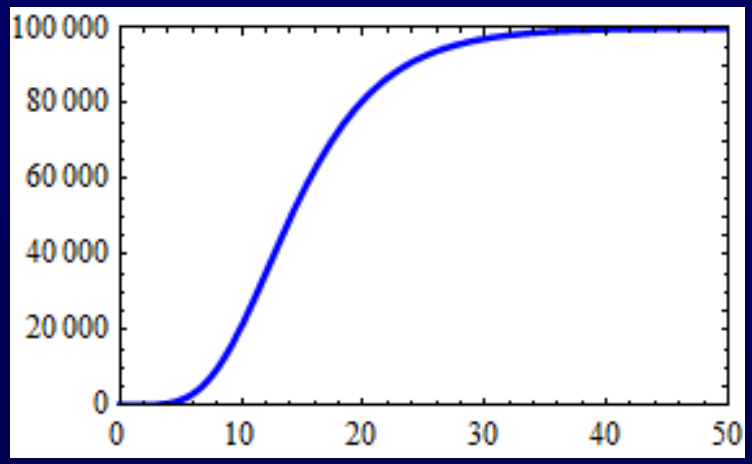


Figure 2.3 Growth curves for tumours in rats and mice. The primary breast fibroadenomas and the Walker tumours were in rats, the others in mice. The fitted curves are Gompertz equations. From Steel (1977), with permission.

More realistic models of tumor growth

Gompertzian growth:

$$V = V_0 \exp\left[\frac{A}{B}(1 - e^{-Bt})\right]$$



Where V_0 = volume at time 0

A & B are parameters determining growth rate

For small t, $V = V_0 \exp(At)$ ⟵ Exponential Growth

For large t, $V = V_0 \exp(A/B)$ ⟵ Maximum Value

Logistic growth:

$$\frac{dV}{dt} = r.N\left(1 - \frac{V}{K}\right)$$

K: carrying capacity

r: intrinsic rate of growth

Tumour Response to Radiation Treatment

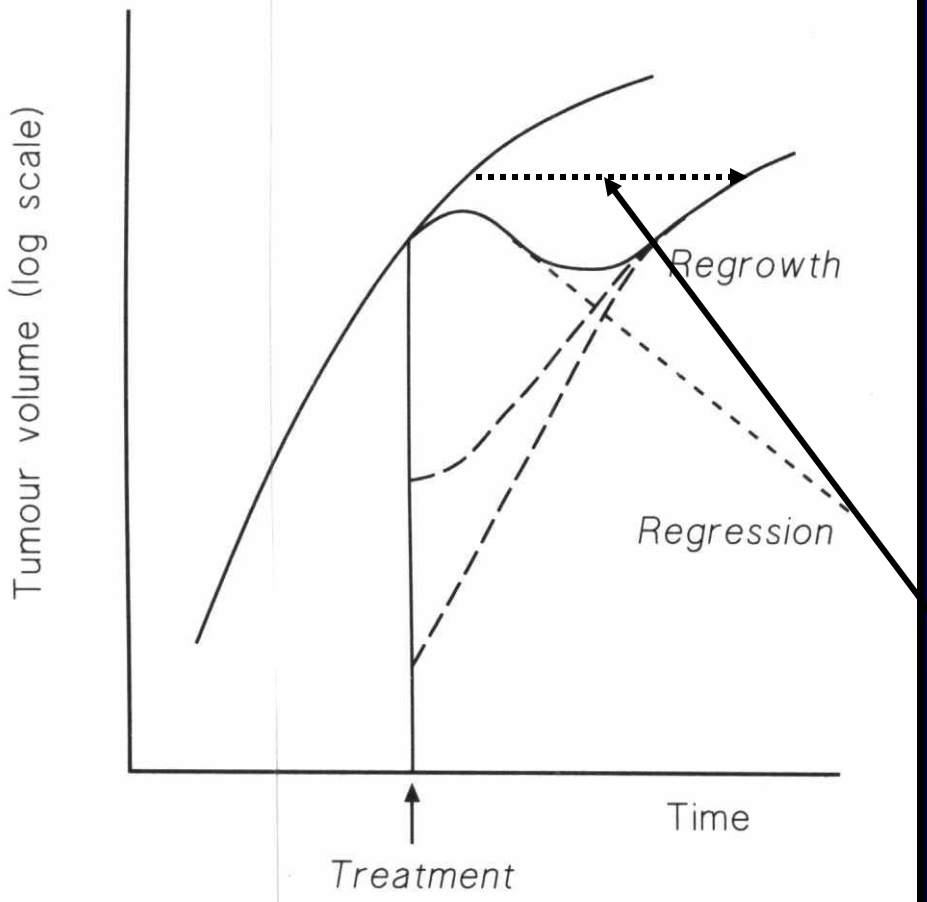


Figure 2.8. The volume response of an uncontrolled tumour is the resultant of two processes: regression and regrowth. Repopulation during the period of regression may take place at a rate that may differ from the growth rate of the untreated tumour.

Assays

- Partial remission
  - Not preferred
- Duration of disease free interval
  - Preferred
- Tumour growth delay (lab)
  - Preferred for measurable tumours

Steel, 1997

Tumor Control Probability (TCP)

- Mechanistic models:
- TCP is usually described statistically by a Poisson distribution (Discussed by J. Battista in earlier lecture)

$$TCP = e^{-N_0 \times SF}$$

- N_0: initial number of cells.
- SF: surviving fraction. Depends on: dose, fractionation, cell sensitivity, repopulation,….

Tumor Control Probability (TCP)

- Empirical models:
- Data analyses. No biological basis.
- Usually logistic regression is used.
- Typical example: TCP for NSCLC

$$TCP = \frac{1}{1+\left(\frac{D50}{D}\right)^{4\gamma}}$$ (Martel et al., Lung Cancer, 24, 1999)

D_{50}: dose to achieve 50% probability of control

γ : normalized slop of the sigmoid curve at D_{50}.

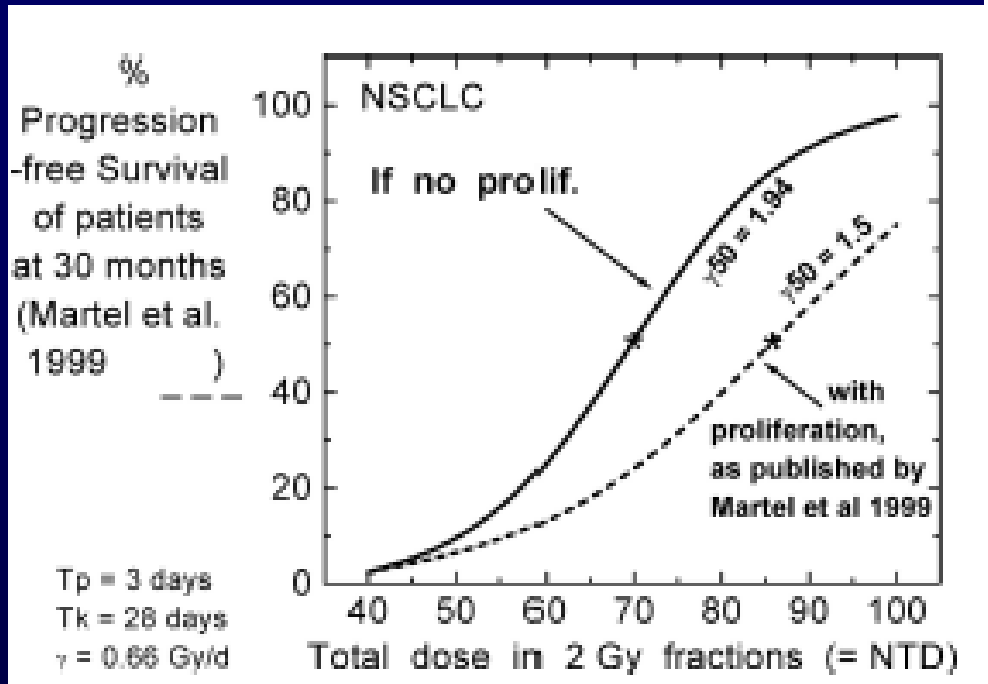


FIGURE 2. Recurrence-free survival percentage at 30 months. Lower (dashed) curve: as in Figure 1 including repopulation with 2Gy given 5 fractions per week. Upper (full) curve: the same data after subtracting the effect of proliferation from the x-axis at 0.66 Gy/d from the 28th day after starting irradiation of NSCLC, assuming Tk = 28 days, T_p = 3 days, radiosensitivity (α = 0.35 In/Gy and α/β = 10 Gy. (Reprinted with permission from Elsevier Inc. *Int J Radiat Oncol Biol Phys*[35]).

Normal Tissue Response

- Time of response:

Categories	Time	Caused by	Example	Repair
Early effects (tissues with rapid rate of turnover)	Few days or weeks	Death of large number of cells	Gastrointestinal epithelium, epidermal layer of the skin, hematopoietic system,	Rapid, usually reversible
Late effects	months or years	Damage to slowly proliferating tissues	Lung, kidney, heart, liver, CNS	Incomplete repair

Normal Tissue Complication Probability (NTCP)

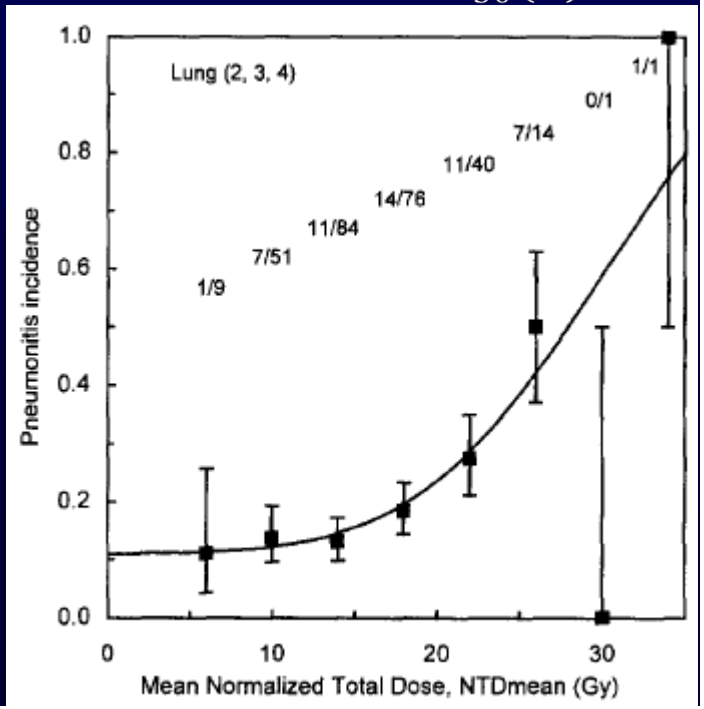
- Usually empirical with no mechanistic background
- Improving data sets is more problematic than deriving correct models.
- Lyman model: most widely used

$$NTCP(D,V) = \frac{1}{\sqrt{2\pi}} . \int_{-\infty}^{u(D,V)} \exp\left(-\frac{1}{2}x^2\right) dx$$

$$u(D,V) = \frac{D - TD_{50}(V)}{m.TD_{50}(V)}$$

$$TD_{50}(V) = \frac{TD_{50}(1)}{V^n}$$ Dose producing 50% incidence

- $TD_{50}(1)$: Uniform total dose to the whole which would lead to complication in 50 % of the population.
- $0 \leq n \leq 1$: Volume effect (more pronounced for larger n values)
- m: inversely related to the steepness of the curve.



Kwa, 1998

Normal Tissue Complication Probability (NTCP)

Volume effect

0 ⟷ n ⟷ 1

Small volume effect
NTCP correlates with the maximum dose

Large volume effect
NTCP correlates with the mean dose

Serial organs

Parallel organs

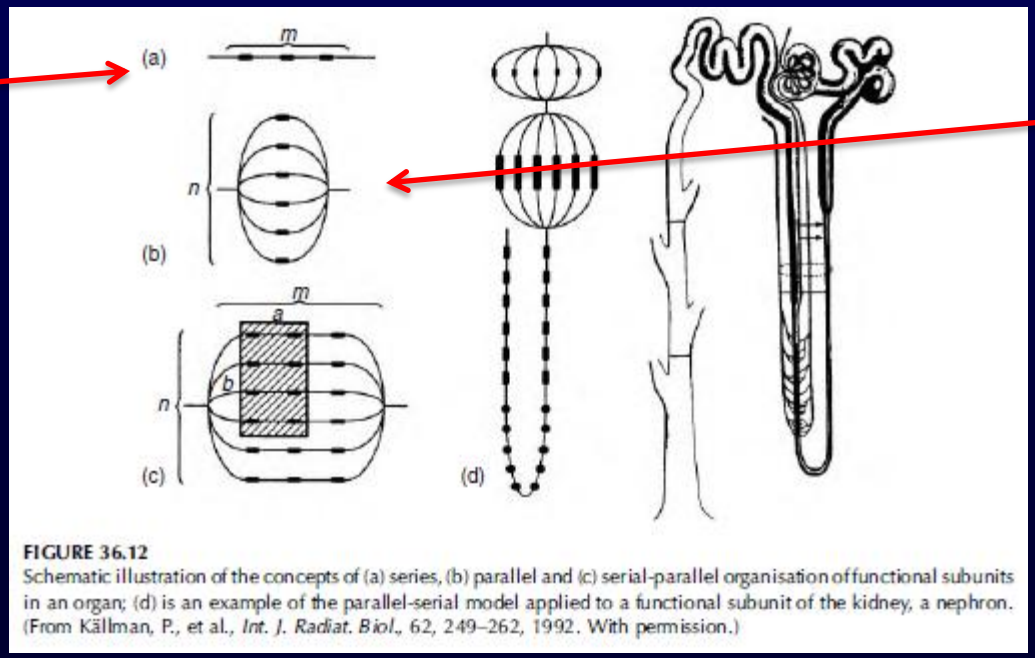
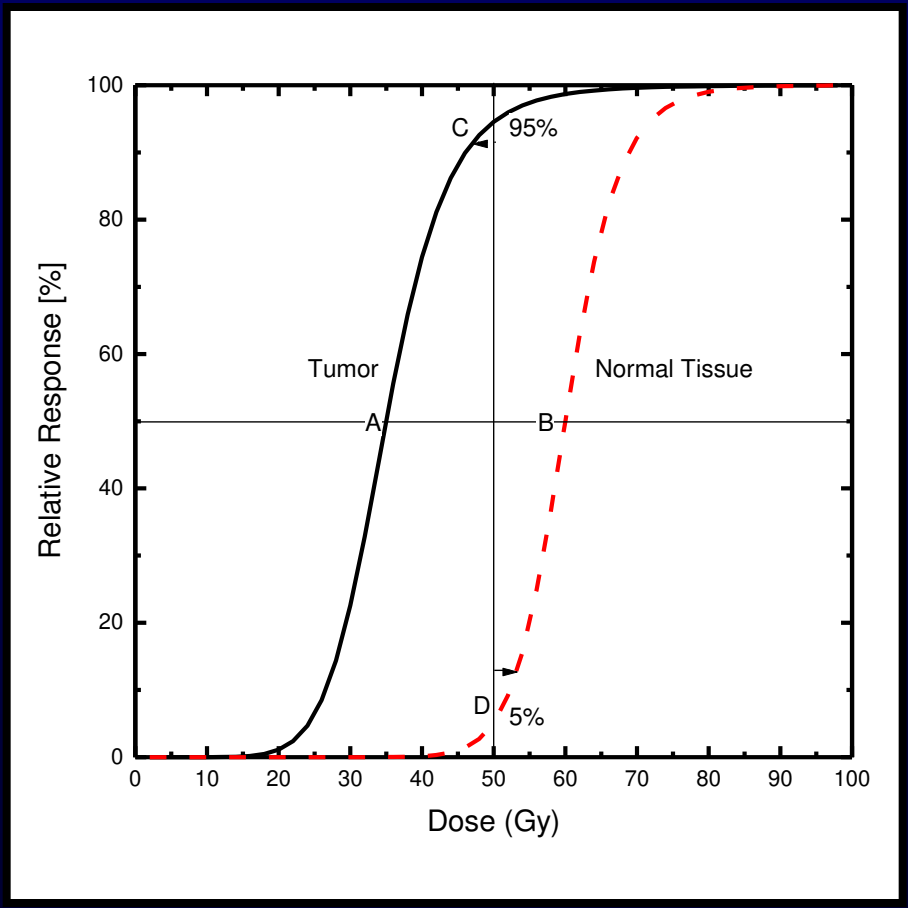


FIGURE 36.12
Schematic illustration of the concepts of (a) series, (b) parallel and (c) serial-parallel organisation of functional subunits in an organ; (d) is an example of the parallel-serial model applied to a functional subunit of the kidney, a nephron. (From Källman, P., et al., *Int. J. Radiat. Biol.*, 62, 249–262, 1992. With permission.)

Joiner, 2009

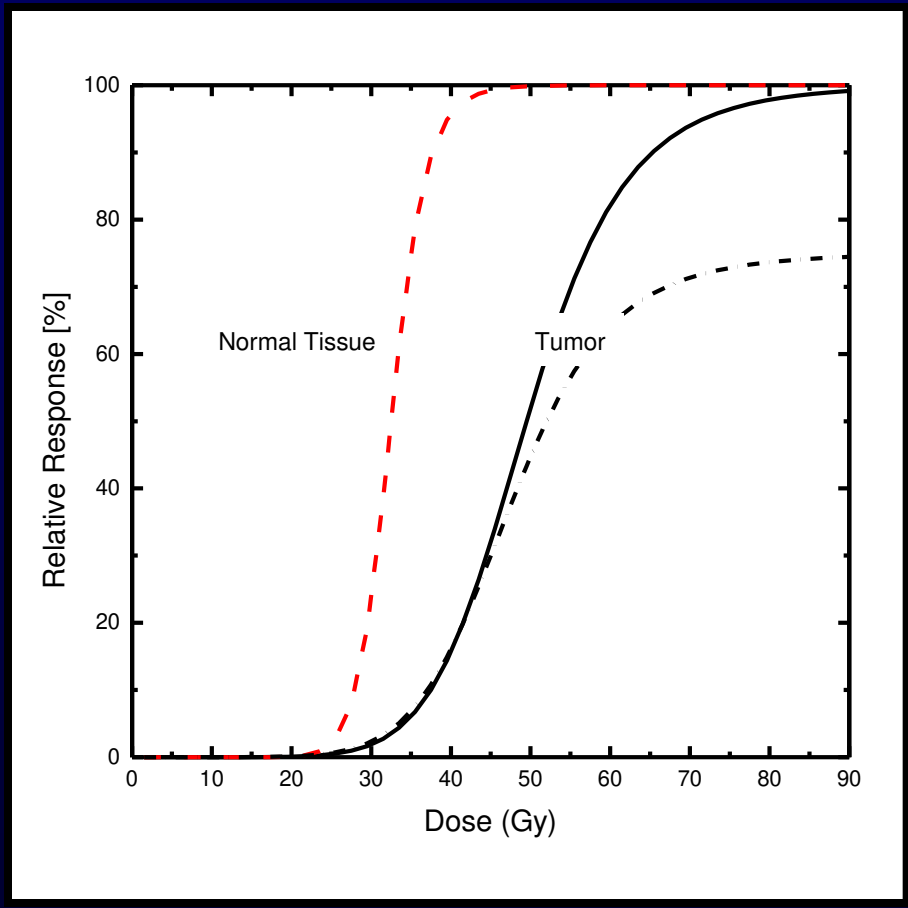
Basic Principles of Radiation Therapy

Favorable therapeutic ratio



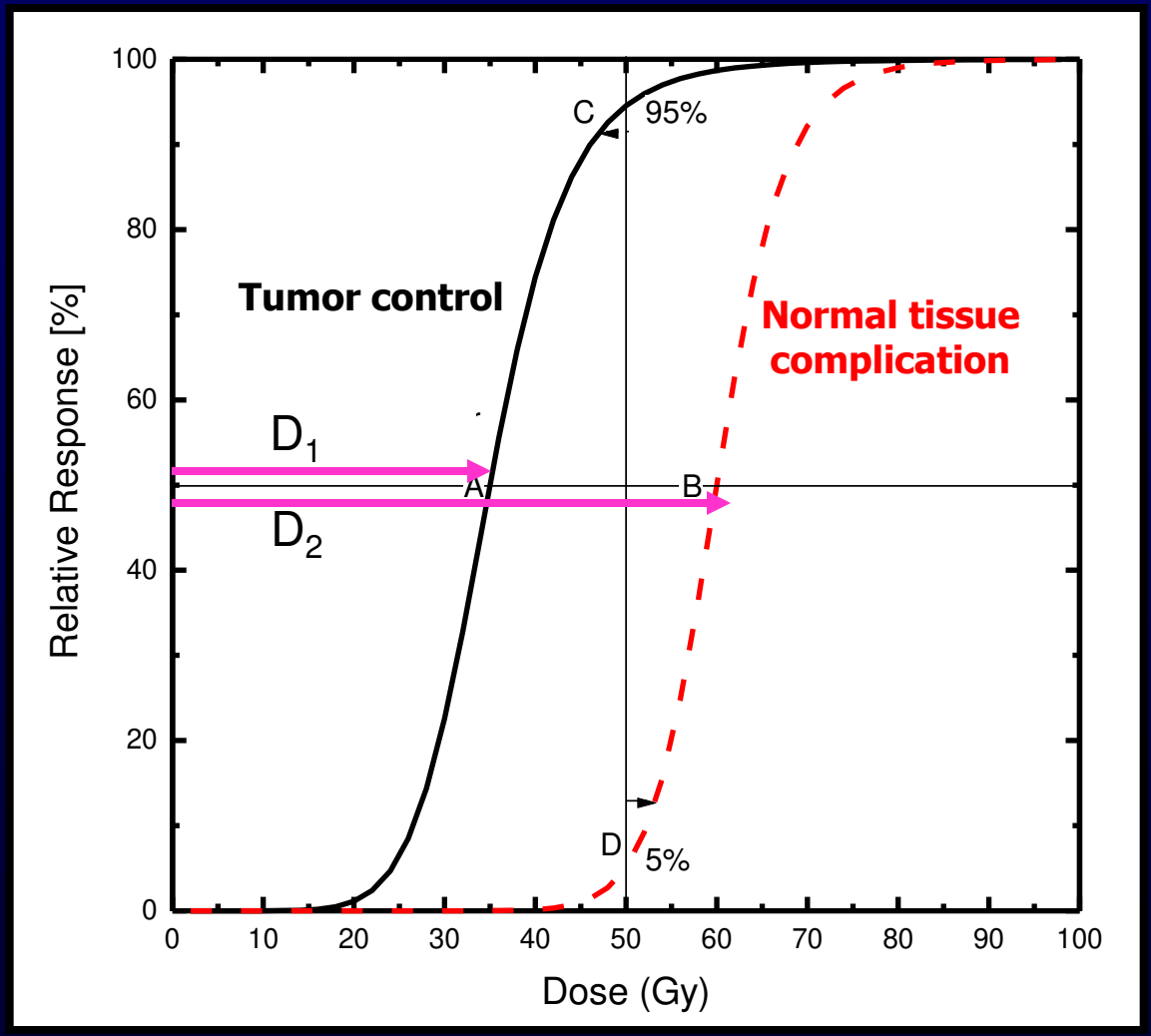
Ideal

Non Favorable therapeutic ratio



Realistic

Therapeutic Ratio



Therapeutic dose ratio = D_2/D_1

- Want to maximize therapeutic ratio
  - i.e., separate curves
  - Parameters used to maximize the therapeutic ratio:
  - Time, fractionation, hyper-fractionation (greater sparing of late-responding normal tissue, radio-sensitizers, cytotoxic agents,),

Therapeutic Index / Gain: with and without radiosensitizer

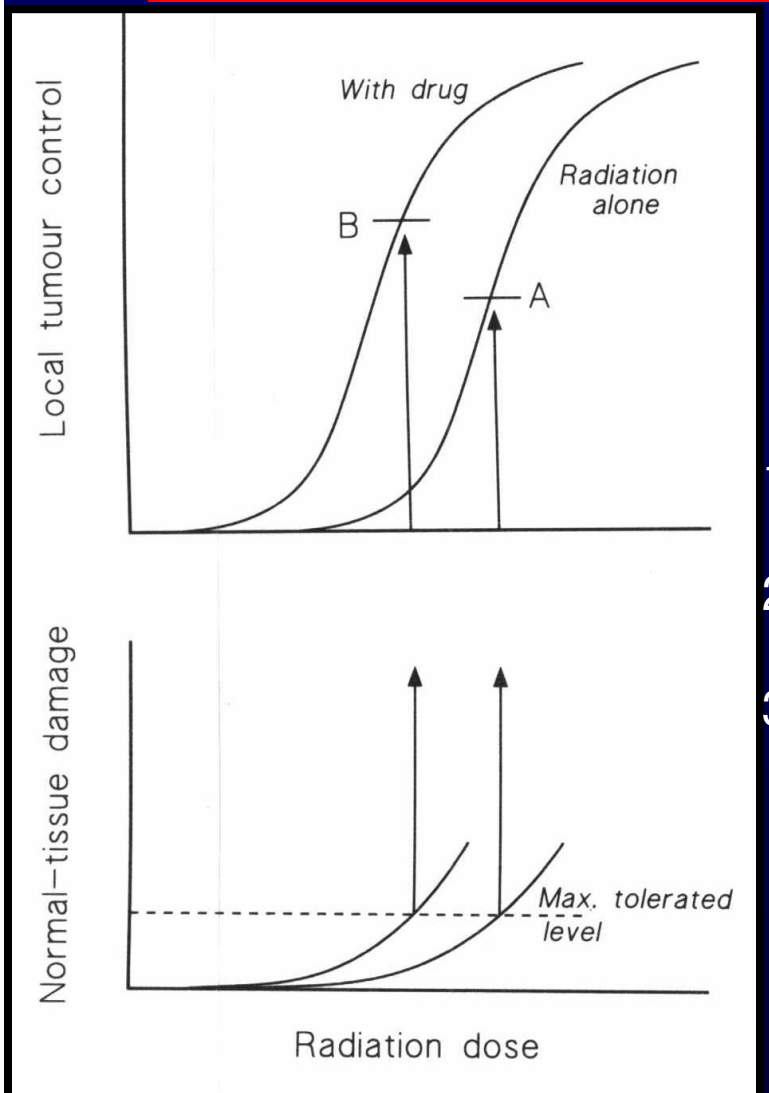


Figure 1.4 The procedure by which an improvement in *therapeutic index* might be identified, as a result of adding chemotherapy to radiotherapy. *See also* Figures 12.3, 18.1.

Note: chemotherapy drugs can cause radiosensitivity

1. Decide the tolerance level (max permitted level of complication)
2. Find the optimal protocol that satisfies the tolerance level (B).
3. A proven therapeutic gain is achieved if B is statistically higher than A

Steel, 1997

Dose Fractionation

- 4 R's radiobiology
  - Repair of sublethal damage
  - Reassortment
  - Repopulation
  - Reoxygenetion
- Dividing dose in no. fractions ***spares*** normal tissues
  - Repair normal tissue
  - Repopulation of normal tissue
- Dividing dose in no. fractions ***increases*** damage to tumour
  - Reoxygenation
  - Reassortment into radiosensitive phases

Late responding tissues are more sensitive to fractionation

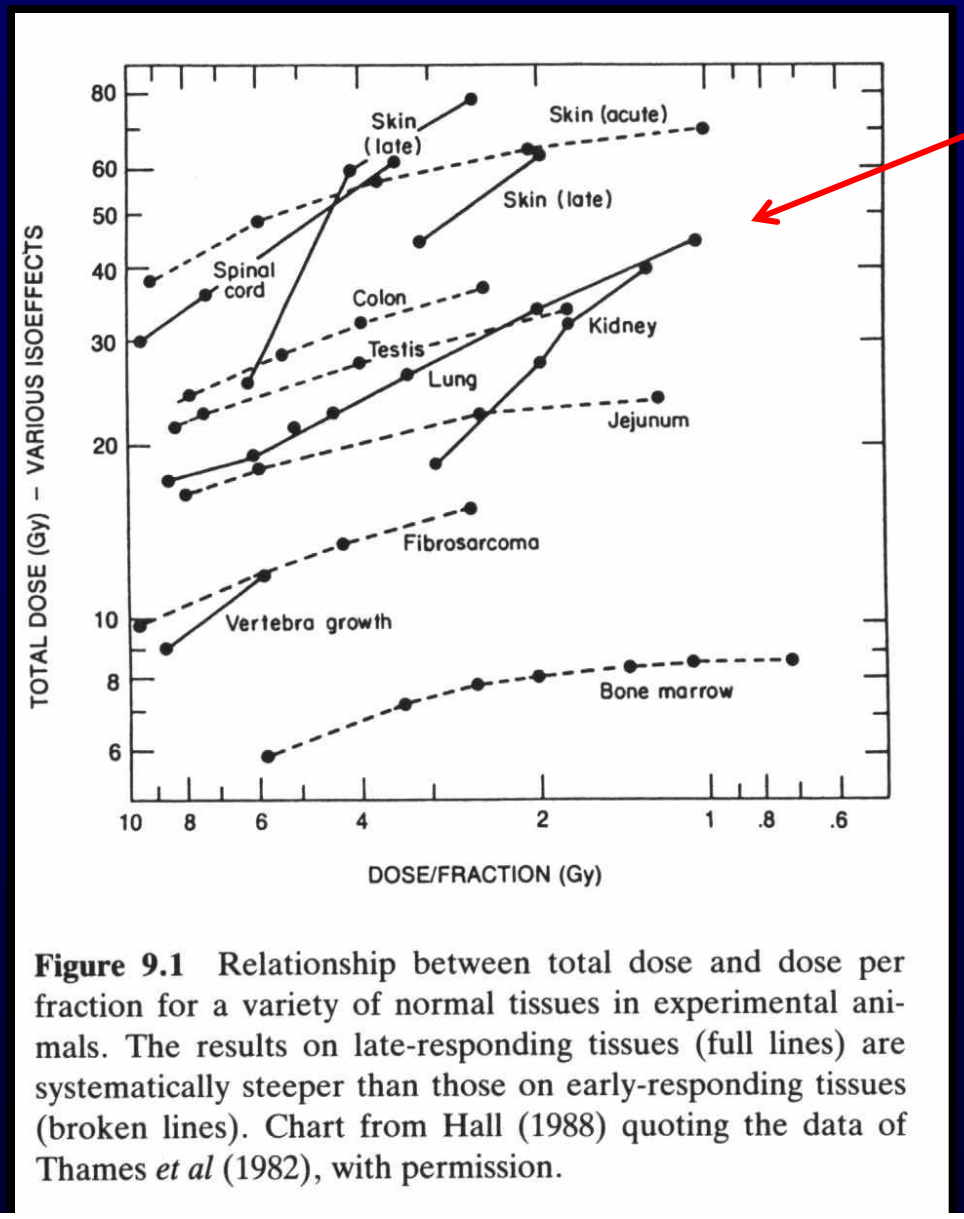
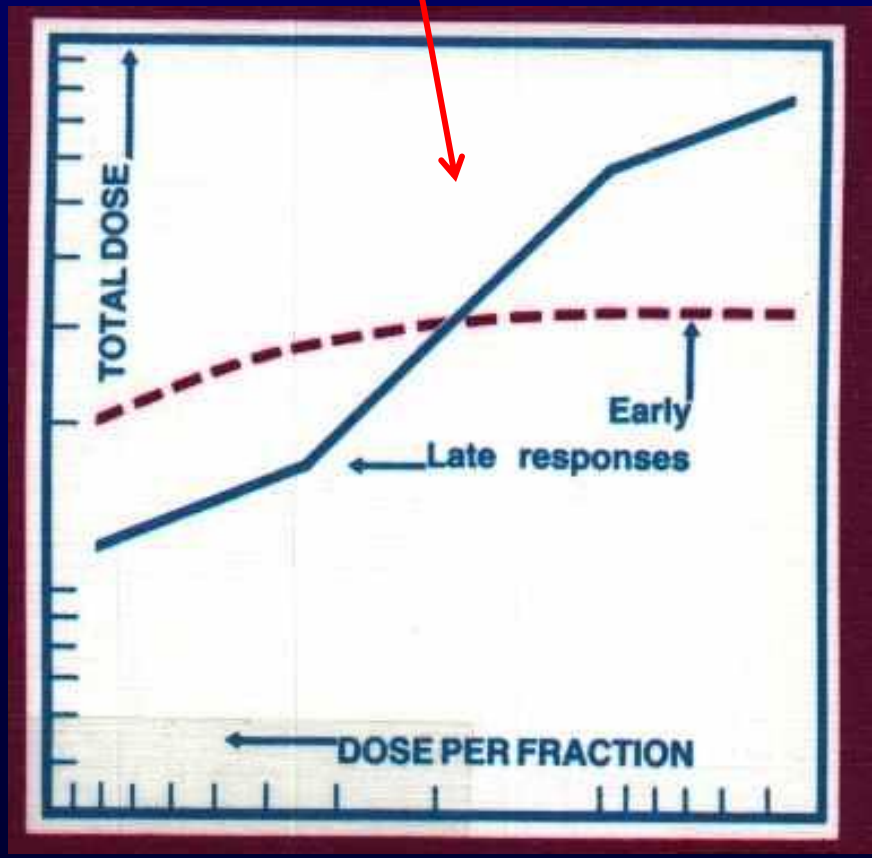
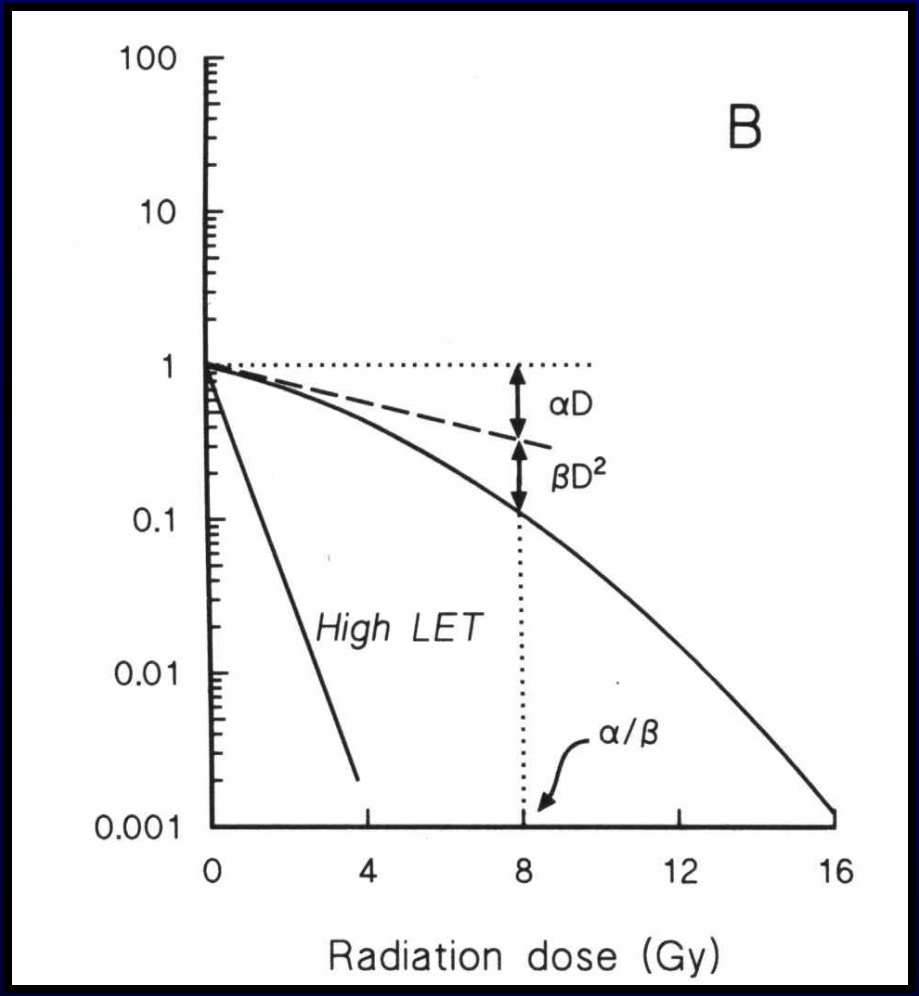


Figure 9.1 Relationship between total dose and dose per fraction for a variety of normal tissues in experimental animals. The results on late-responding tissues (full lines) are systematically steeper than those on early-responding tissues (broken lines). Chart from Hall (1988) quoting the data of Thames *et al* (1982), with permission.

Isoeffect curves



Recall LQ Model For Cell Survival



$$S = e^{-(\alpha D + \beta D^2)}$$

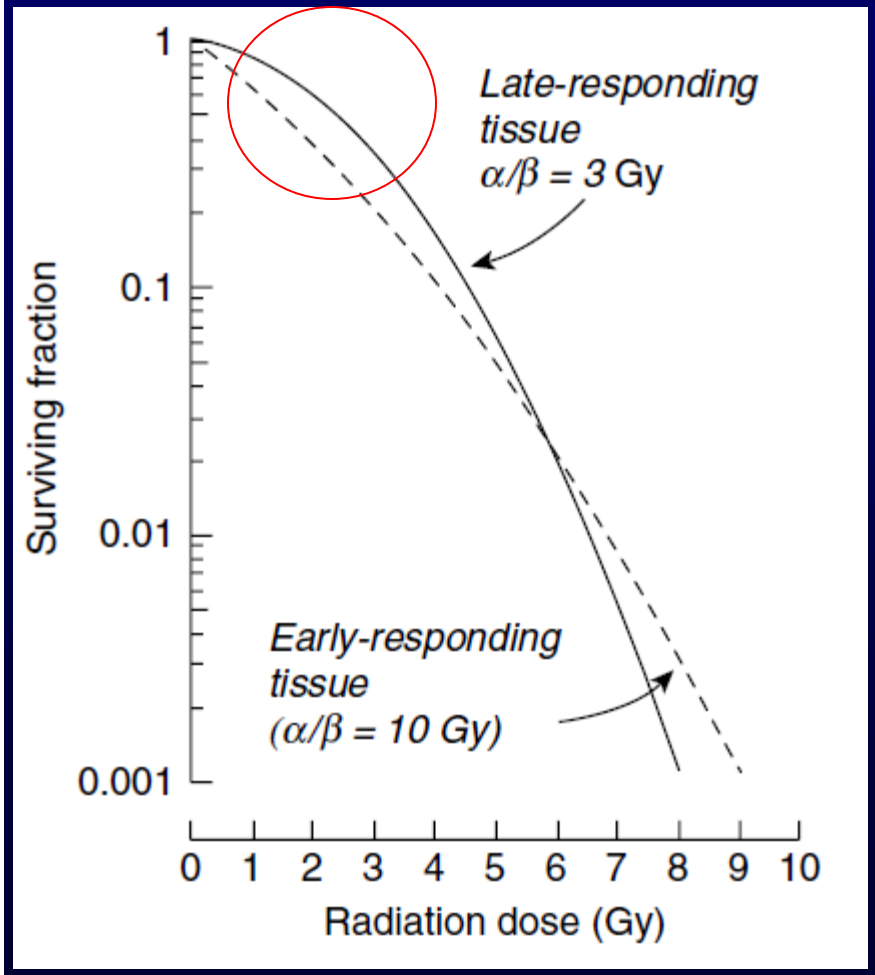
Where D = dose

α, β are parameters defining curvature

α defines initial slope

α/β [Gy]

Late *versus* Early reacting tissues in terms of the LQ Model



- Late responding tissues show higher fractionation sensitivity.

P. Mayles, 2007

Fractionation: early vs late responding tissues

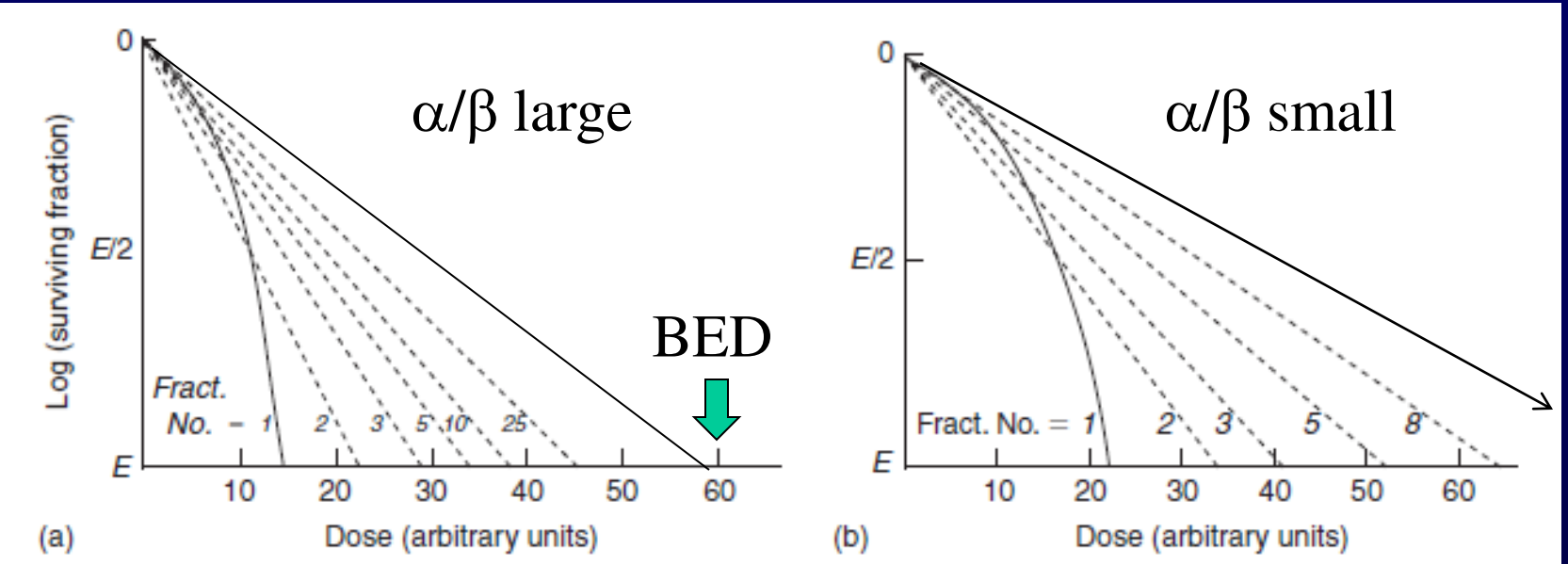


Figure 8.3 Schematic survival curves for target cells in (a) acutely responding and (b) late-responding normal tissues. The abscissa is radiation dose on an arbitrary scale. From Thames and Hendry (1987), with permission. Joiner, 2009

- Effect E: reduction in cell survival that is equivalent to tissue tolerance.
- Because the survival curve for late responding tissues is more curvy, the isoeffective total dose increases more rapidly with increasing number of fractions.
- BED is the dose that produces E for an infinite # of very small doses

Fractionation

- The difference in steepness of isoeffect curves between early and late responding tissues can be described by a single parameter: α/β.
- Late responding tissues are more sensitive to changes in fraction size. α/β is small.
- Early responding tissues (including tumour) are less sensitive to changes in fraction size. α/β is large.
- Some tissues are more sensitive than others for any chosen dose per fraction. **α and β varies with tissue type.**

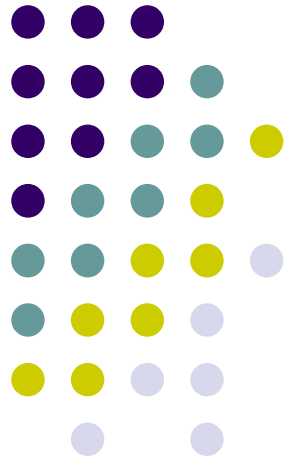
α/β ratios from lab data
(From Thames and Hendry)

Early Reactions	**High α/β: ~10***	α/β
skin		9.4 - 21.0
hair follicles		5.5 - 7.7
lip mucosa		7.9
jejunum		7.1
colon		8.4
testis		13.9
spleen		8.9
*prostate exception		3.0
Late Reactions	**Low α/β: mostly ~3**	
spinal cord		2.1 - 5.2
brain		2.1
eye		1.2
kidney		0.4 - 4.1
bladder		7.2 - 7.8
lung		2.1 - 4.3
bowel		3.0 - 5.0

Table 9.1 Fractionation sensitivity of human normal tissues and tumours

Tissue/organ	Endpoint	α/β (Gy)	95% CL (Gy)	Source
Early reactions				
Skin	Erythema	8.8	6.9; 11.6	Turesson and Thames (1989)
	Erythema	12.3	1.8; 22.8	Bentzen *et al.* (1988)
	Dry desquamation	~8	N/A	Chogule and Supe (1993)
	Desquamation	11.2	8.5; 17.6	Turesson and Thames (1989)
Oral mucosa	Mucositis	9.3	5.8; 17.9	Denham *et al.* (1995)
	Mucositis	15	−15; 45	Rezvani *et al.* (1991)
	Mucositis	~8	N/A	Chogule and Supe (1993)
Late reactions				
Skin/vasculature	Telangiectasia	2.8	1.7; 3.8	Turesson and Thames (1989)
	Telangiectasia	2.6	2.2; 3.3	Bentzen *et al.* (1990)
	Telangiectasia	2.8	−0.1; 8.1	Bentzen and Overgaard (1991)
Subcutis	Fibrosis	1.7	0.6; 2.6	Bentzen and Overgaard (1991)
Breast	Cosmetic change in appearance	3.4	2.3; 4.5	START Trialists Group (2008)
	Induration (fibrosis)	3.1	1.8; 4.4	Yarnold *et al.* (2005)
Muscle/vasculature/ cartilage	Impaired shoulder movement	3.5	0.7; 6.2	Bentzen *et al.* (1989)
Nerve	Brachial plexopathy	<3.5*	N/A	Olsen *et al.* (1990)
	Brachial plexopathy	~2	N/A	Powell *et al.* (1990)
	Optic neuropathy	1.6	−7; 10	Jiang *et al.* (1994)
Spinal cord	Myelopathy	<3.3	N/A	Dische *et al.* (1981)
Eye	Corneal injury	2.9	−4; 10	Jiang *et al.* (1994)
Bowel	Stricture/perforation	3.9	2.5; 5.3	Deore *et al.* (1993)
Bowel	Various late effects	4.3	2.2; 9.6	Dische *et al.* (1999)
Lung	Pneumonitis	4.0	2.2; 5.8	Bentzen *et al.* (2000)
	Lung fibrosis (radiological)	3.1	−0.2; 8.5	Dubray *et al.* (1995)
Head and neck	Various late effects	3.5	1.1; 5.9	Rezvani *et al.* (1991)
Head and neck	Various late effects	4.0	3.3; 5.0	Stuschke and Thames (1999)
Supraglottic larynx	Various late effects	3.8	0.8; 14	Maciejewski *et al.* (1986)
Oral cavity + oropharynx	Various late effects	0.8	−0.6; 2.5	Maciejewski *et al.* (1990)
Tumours				
Head and neck				
Various		10.5	6.5; 29	Stuschke and Thames (1999)
Larynx		14.5*	4.9; 24	Rezvani *et al.* (1993)
Vocal cord		~13	'wide'	Robertson *et al.* (1993)
Buccal mucosa		6.6	2.9; ∞	Maciejewski *et al.* (1989)
Tonsil		7.2	3.6; ∞	Maciejewski *et al.* (1989)
Nasopharynx		16	−11; 43	Lee *et al.* (1995)
Skin		8.5*	4.5; 11.3	Trott *et al.* (1984)
Prostate†		1.1	−3.3; 5.6	Bentzen and Ritter (2005)
Breast		4.6	1.1; 8.1	START Trialists Group (2008)
Oesophagus		4.9	1.5; 17	Geh *et al.* (2006)
Melanoma		0.6	−1.1; 2.5	Bentzen *et al.* (1989)
Liposarcoma		0.4	−1.4; 5.4	Thames and Suit (1986)

CL, confidence limit.
*Re-analysis of original published data.
†Several more estimates are available from comparisons of outcome after brachytherapy versus external-beam therapy.
Reference details are available from Søren Bentzen. See also Thames *et al.* (1990) and Table 13.2.



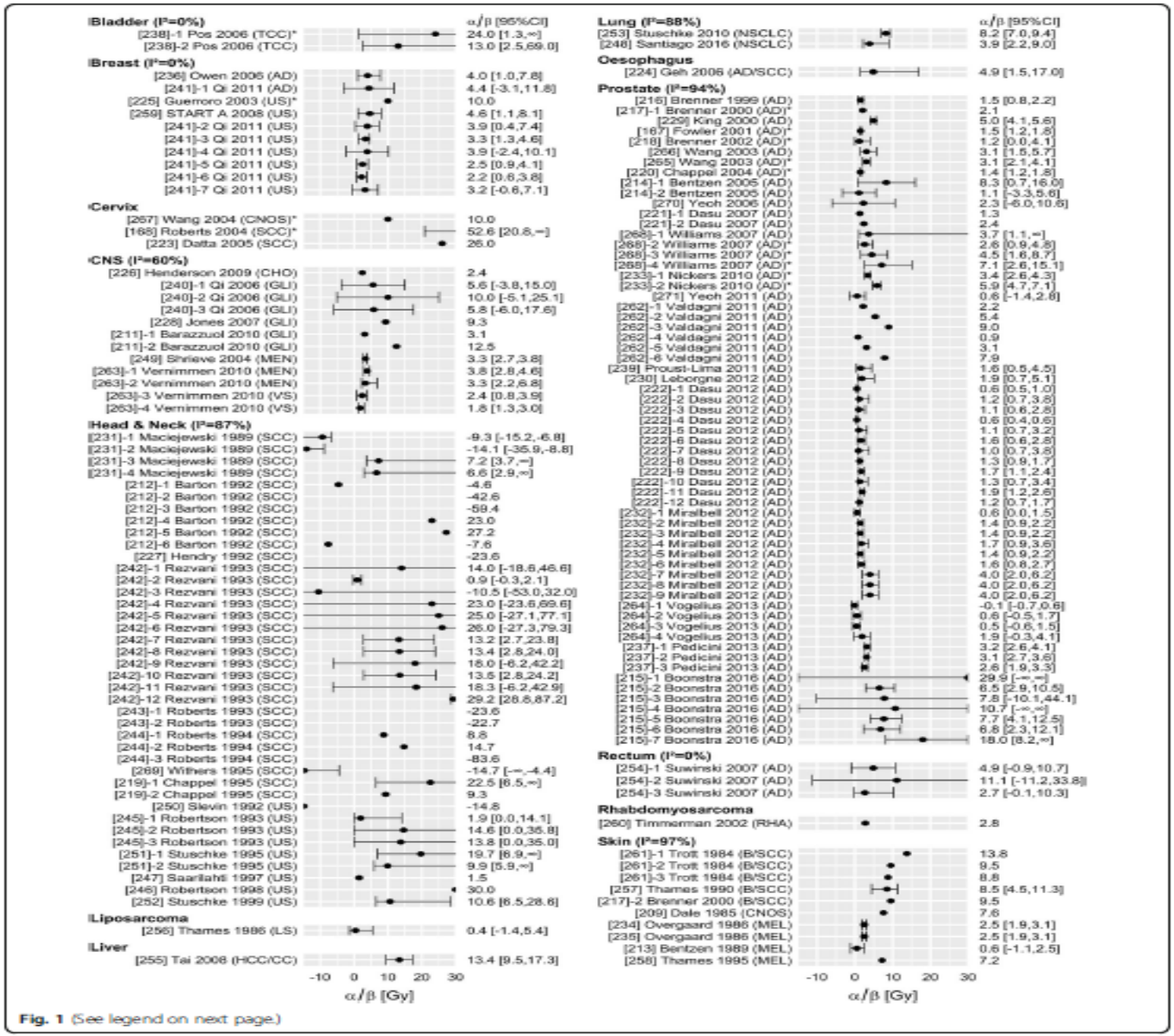


Fig. 1 (See legend on next page.)

The alfa and beta of tumours: a review of parameters of the linear-quadratic model, derived from clinical radiotherapy studies. van Leeuwen et al. Radiation Oncology (2018) 13:96

The LQ isoeffect equation

What change in total radiation dose is required when we change the dose per fraction?

- Isoeffective fractionations:

$$E = (\alpha . d_1 + \beta . {d_1}^2) . n_1 = (\alpha . d_2 + \beta . {d_2}^2) . n_2 \Rightarrow \frac{D_1}{D_2} = \frac{d_1 + \frac{\alpha}{\beta}}{d_2 + \frac{\alpha}{\beta}}$$

- Equivalent dose in 2 Gy fractions (EQD_2):

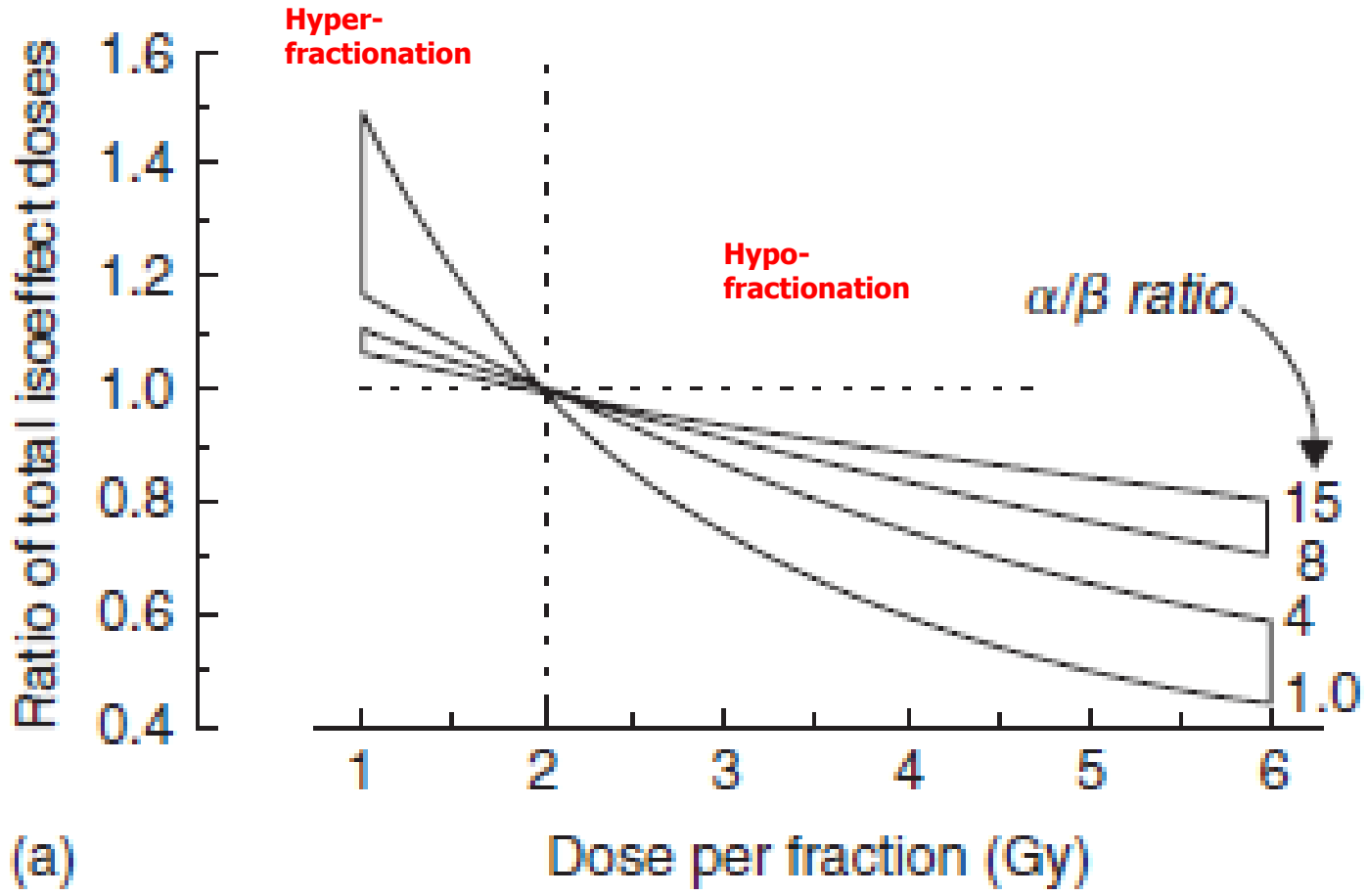
$$EQD_2 = D \frac{d + \frac{\alpha}{\beta}}{2 + \frac{\alpha}{\beta}}$$

The dose in 2Gy fraction that is biologically equivalent to a total dose D given with a fraction size of d.

EQD_2 allows comparing the effectiveness of different treatment regimens with total doses and doses per fraction. It is used to normalize TCP and NTCP as well as DVHs.

Iso-Effect Curves

D/EQD_2



Biologically Effective Dose (BED)

$$S = e^{-(\alpha D + \beta D^2)}$$

$$S = e^{-n(\alpha d + \beta d^2)}$$

Effect, *E = -ln(S)*

$$E = \alpha d + \beta d^2 \quad \text{for 1 fraction}$$

$$E = nd(\alpha + \beta d) \quad \text{for } n \text{ fractions}$$

$$BED = \frac{E}{\alpha} = nd\left(1 + \frac{d}{\alpha / \beta}\right) \quad [\mathrm{Gy}_{\alpha/\beta}]$$

! BED is not a real dose

As d → 0, n → ∞,
Then BED = n×d = D on x-axis

BED is the total dose which if given in infinitely small fractions is equivalent to the actual fractionated regimen with dose per fraction d and total dose D.

- BED is regarded as a measure of the true biological dose delivered by particular combination of dose per fraction and total dose to a given tissue characterized by a specific α/β ratio.
- Even if D is kept constant, the BED will increase if d increases.
- The BED for each tissue (α/β ratio) is a measure of the extent to which the dose can be escalated if treating with very small d.

Biologically Effective Dose (BED)

Assume a standard dose fractionation: 30 fraction X 2 Gy = 60Gy.
what is the permitted dose per fraction in case n = 20?

$$BED = 100\ Gy_3 = 20d\left(1 + \frac{d}{3}\right)$$

$\alpha/\beta=3$

d = 2.65 Gy; D = 53 Gy

What is the effect of a hot spot of 110% in the normal tissue?
The resultant BED=138.6 Gy_3

Biological doses are enhanced proportionally more than the physical doses at hot spots due to the quadratic term in the LQM ("double trouble" effect).

For large volumes with inhomogeneous dose distributions, BED calculations should not be based on one single reference point.

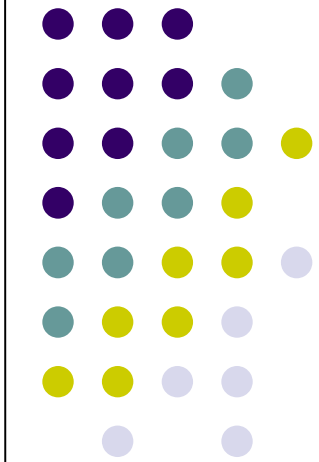
BED Explained Further

- BED allows “normalization” of bio-effects to a common reference quantity (infinite number of small doses).
- BED’s for different exposures can be added biologically
- Useful quantity when radiation treatments are interrupted or intentionally split
- See the additional explanations and illustrations in DropBox Folder “Reference _Material”

So far, we have ignored Repair and Repopulation..

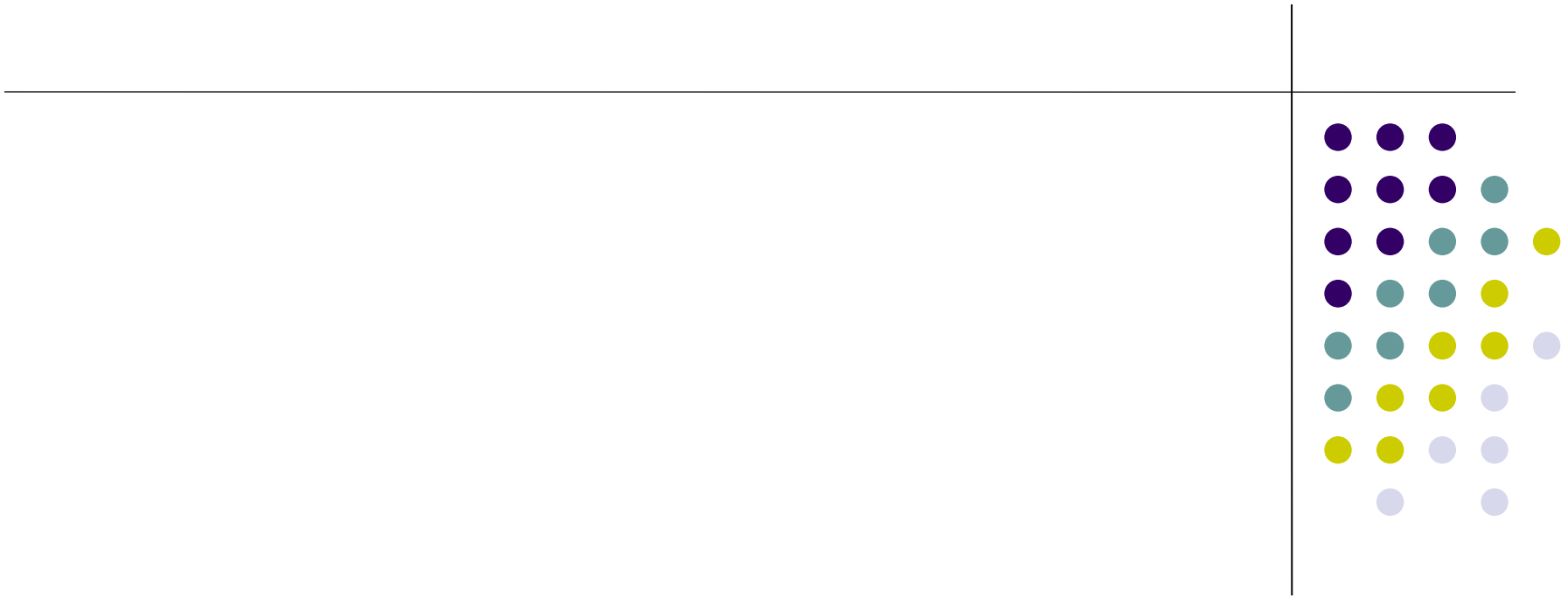
Ejemplo 1

¿Cuál será el número de fracciones que es necesario impartir en un esquema de tratamiento dado a 3 Gy por fracción, 1 fracción al día, 5 días a la semana para que sea equivalente a un tratamiento en el que se imparten 50 Gy a 2 Gy por fracción, 1 fracción al día, 5 días a la semana? Consideraremos un valor de $\alpha/\beta = 10$ Gy para efectos de respuesta precoz y tejidos tumorales y un valor de $\alpha/\beta = 3$ Gy para efectos de respuesta tardía de los tejidos sanos.



Ejemplo 2

En un tratamiento se administran 54 Gy en 16 fracciones, 1 fracción al día, 5 días a la semana. ¿Cuál será la dosis equivalente administrada en 2 Gy por fracción, 1 fracción al día, 5 días a la semana con respecto a los efectos tardíos de los tejidos sanos?



Ejemplo 3

Sobre un tumor de cabeza y cuello se planifica un tratamiento de 60 Gy en 30 fracciones a 2 Gy por fracción, una fracción al día, 5 días a la semana. En este tratamiento original la médula recibe 48 Gy y la piel 60 Gy durante el tratamiento. Por un error dosimétrico, durante las 10 primeras fracciones del tratamiento tanto el tumor, como la médula y la piel reciben 2,5 Gy por fracción. Una vez detectado el error se decide continuar el tratamiento conforme a la planificación inicial. ¿Cuántas fracciones de 2 Gy según la planificación original habrá que administrar para conseguir un tratamiento equivalente al previsto? Consideraremos la fibrosis subcutánea como efecto tardío en la piel ($\alpha/\beta = 2$ Gy), la mielopatía de la médula espinal ($\alpha/\beta = 3$ Gy) y un valor de $\alpha/\beta = 10$ Gy para el tumor. No se tendrá en cuenta el efecto de la proliferación.