Basic Clinical Radiobiology

Dose-response relationships in radiotherapy

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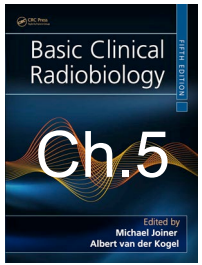
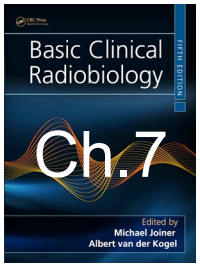
Toronto 2023



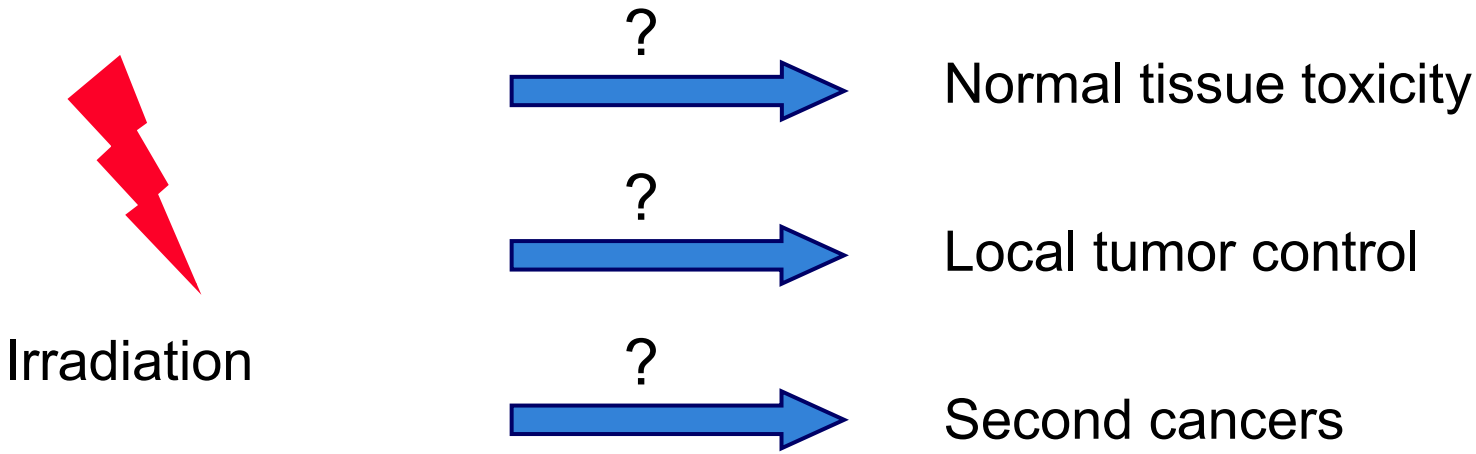


Definitions

Dose Response: Relationship between a given physical absorbed dose and the resulting biological response

Endpoint: A specific event that may or may not have occurred at a given time after irradiation

Dose responses – always document!

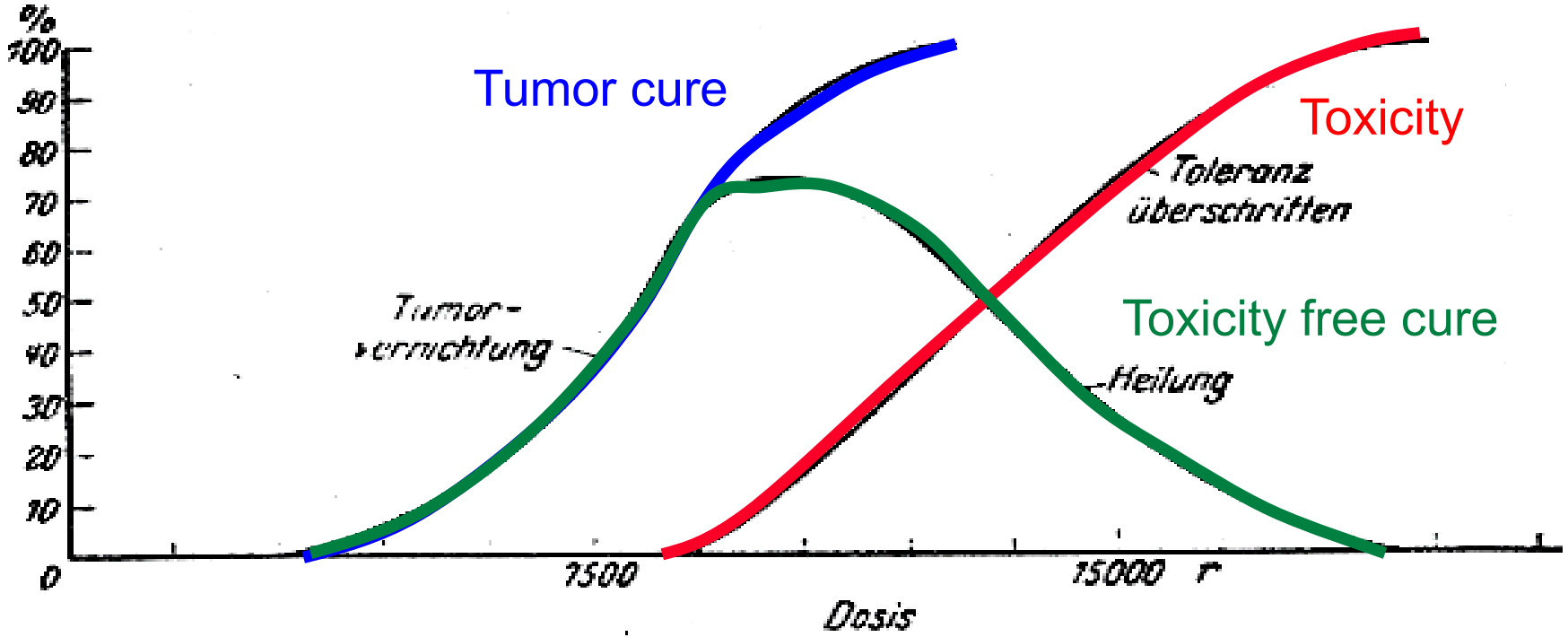


Relationship between given dose and each clinically relevant outcome needs to be defined

i.e. Define the incidence or probability of a certain outcome after a defined dose

Dose response: Empirical data

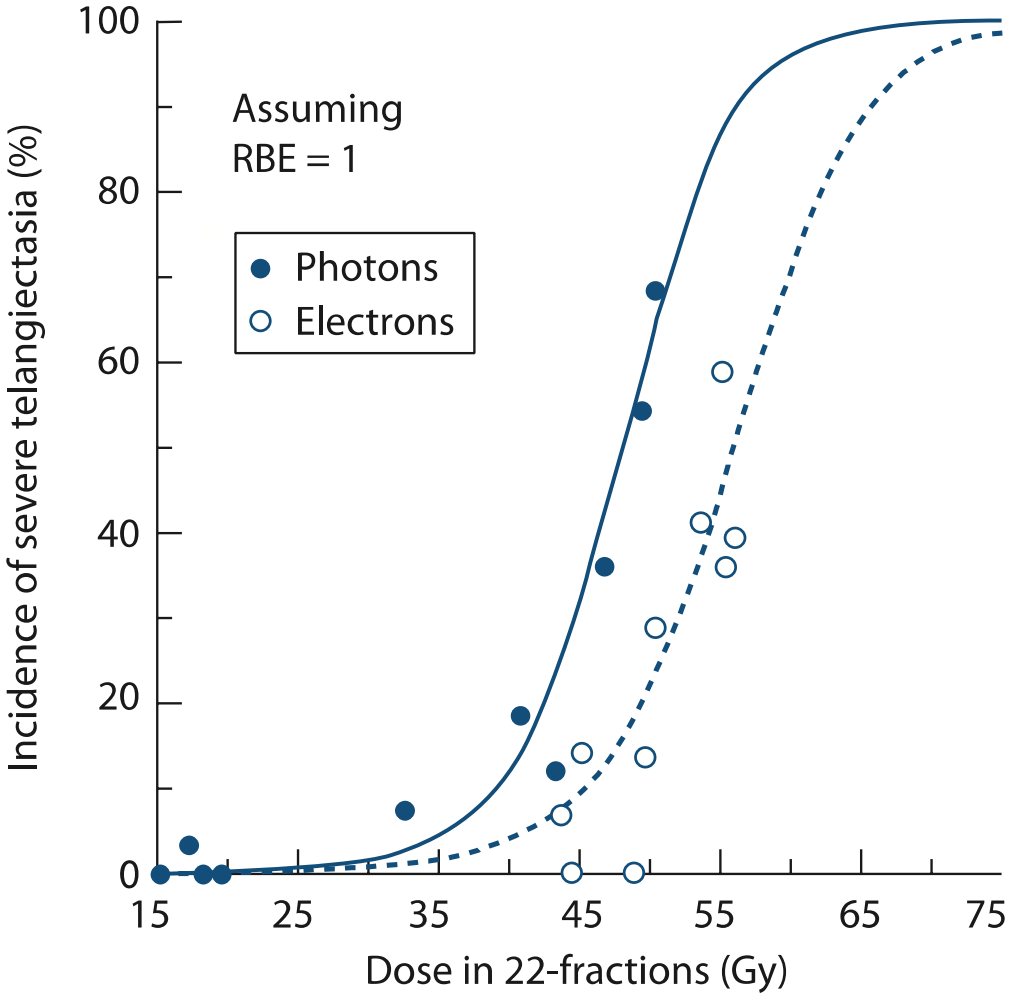
Sigmoid curves indicate variability of clinical radioresponse



Holthusen. *Strahlentherapie* 1936;57:254-68

Examples of dose response relationships

Sigmoid curves



Bentzen and Overgaard (1991)

Dose response models

Most frequently used models to fit sigmoid dose-response curves:

- Poisson model …tumor
- Logistic model …normal

Dose response model: Tumor control

The target cell hypothesis: Munro & Gilbert 1961

- Relevant is the number of tumor stem cells (clonogenic cells) left at the end of treatment
- This is reduced with dose in a manner which accounts for randomness in radiation effects, described by Poisson statistics
- The probability of tumor cure depends on the average number of clonogens surviving per tumor

Simulation of a Poisson distribution of surviving cells

0	0	0	2	1	1	1	0	0	0
0	0	0	0	0	0	0	0	1	0
0	0	0	2	1	2	1	2	0	1
1	0	0	0	0	2	1	0	1	2
1	2	0	0	0	0	0	0	0	3
0	0	0	0	0	0	0	1	1	0
1	0	2	0	0	0	0	0	0	1
0	0	0	0	0	3	0	0	1	0
0	3	1	1	1	1	0	0	0	1
0	1	2	1	1	0	0	1	1	0

100 tumors.
Average number of
surviving clonogens per tumor
= 0.5

Each box indicates
the number of surviving clonogens
actually in that tumor

Poisson Statistics – a reminder

In the **Poisson** statistical distribution,
the probability $P(x)$ of obtaining x surviving cells per tumor
when the mean number of surviving cells per tumor is λ, is:

$$P(x) = \frac{e^{-\lambda}\lambda^{x}}{x!}$$

Condition: a very, very **large** number of cells in each tumor, but the probability that *any given cell* survives is very, very **small**

Poisson Statistics: local tumor control ("cure")

Tumor Control Probability, *TCP*, is the probability of **no** surviving cells in the tumor (*i.e.* $x = 0$).

TCP is therefore given by:

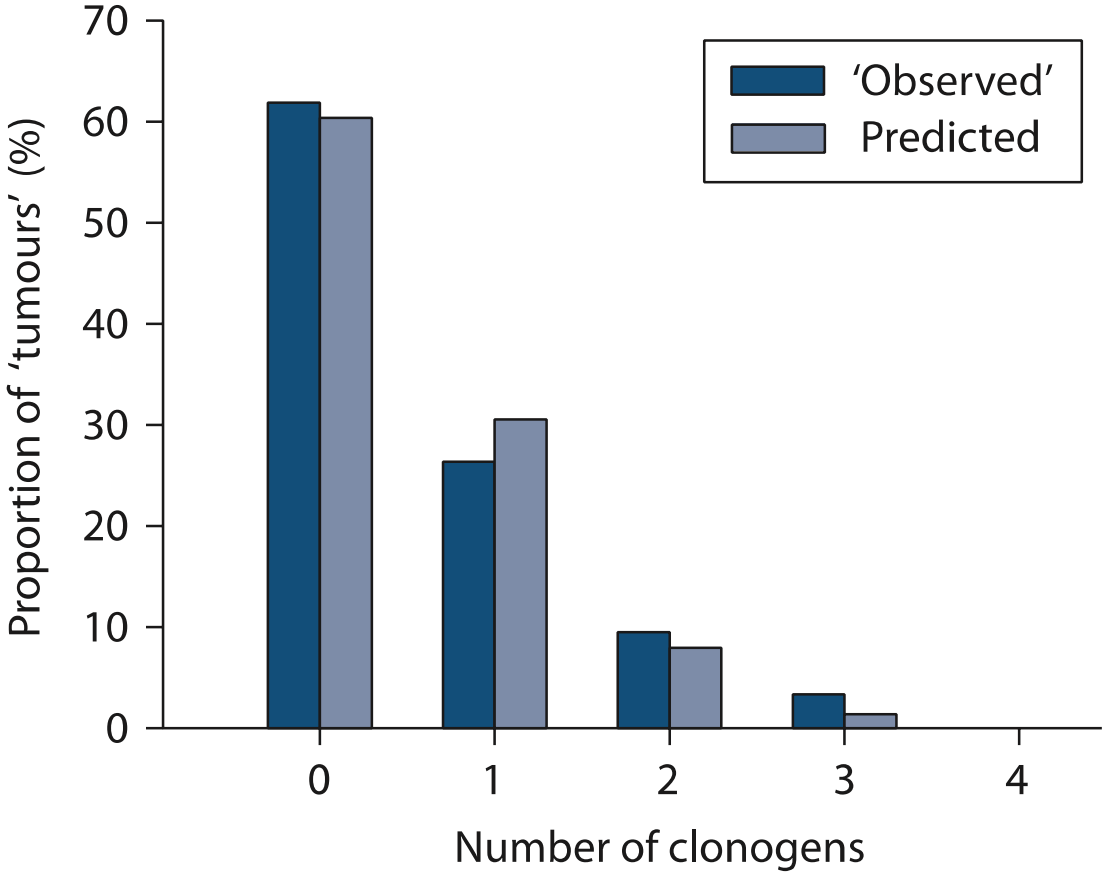
$$TCP = P(0) = \frac{e^{-\lambda}\lambda^{0}}{0!} = e^{-\lambda} = \exp\left(-\lambda\right)$$

λ is the mean number of surviving cells per tumor

Poisson “predicted” versus Monte Carlo “observed”

Average number of surviving clonogens = 0.5

Poisson distribution is confirmed by “observation”



But λ is a function of dose per fraction, d, and number of fractions, n. Total dose $D = nd$.

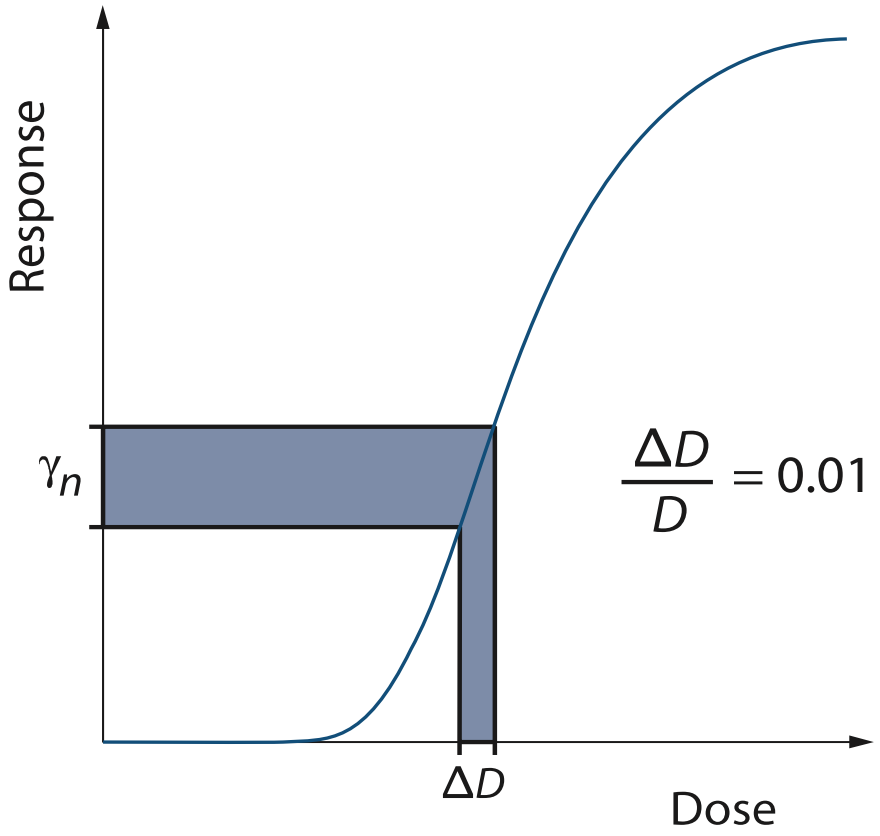
Remember that:

$$S = \lambda / N_0 = e^{-n\left(\alpha d + \beta d^2\right)} = \exp\left(-\alpha D - \beta d D\right)$$

Therefore:

$$TCP = \exp\left[-N_0 \exp\left(-\alpha D - \beta d D\right)\right]$$

Definition of dose-response curve slope



Normalized
dose response gradient, γ :

$$\Delta P \approx \gamma \frac{\Delta D}{D}$$

1% change in dose gives
increase in response = γ %

Usually defined at
the steepest part of curve:
With Poisson model,
at Response = 37% (0.3679…, e^{-1})

Interesting consequence of Poisson

It can be shown that:

$$\gamma_{37} = \frac{\ln N_0}{e}$$

This may be used for deducing the number of “tumor clonogens” but any relevance to normal tissue response is doubtful

Logistic model of response

$$P = \frac{\exp(u)}{1+\exp(u)} \qquad u = \ln\left(\frac{P}{1-P}\right)$$

$$u = a_0 + a_1 D + a_2 D d + \ldots$$

P/(1-*P*) is called the ***odds*** of the response,
u is called the ***logit*** of *P*

With Logistic, the inflection (max slope) occurs at Response = 50% (*P* = 0.5, *u* = 0)

Beware: γ changes with response level

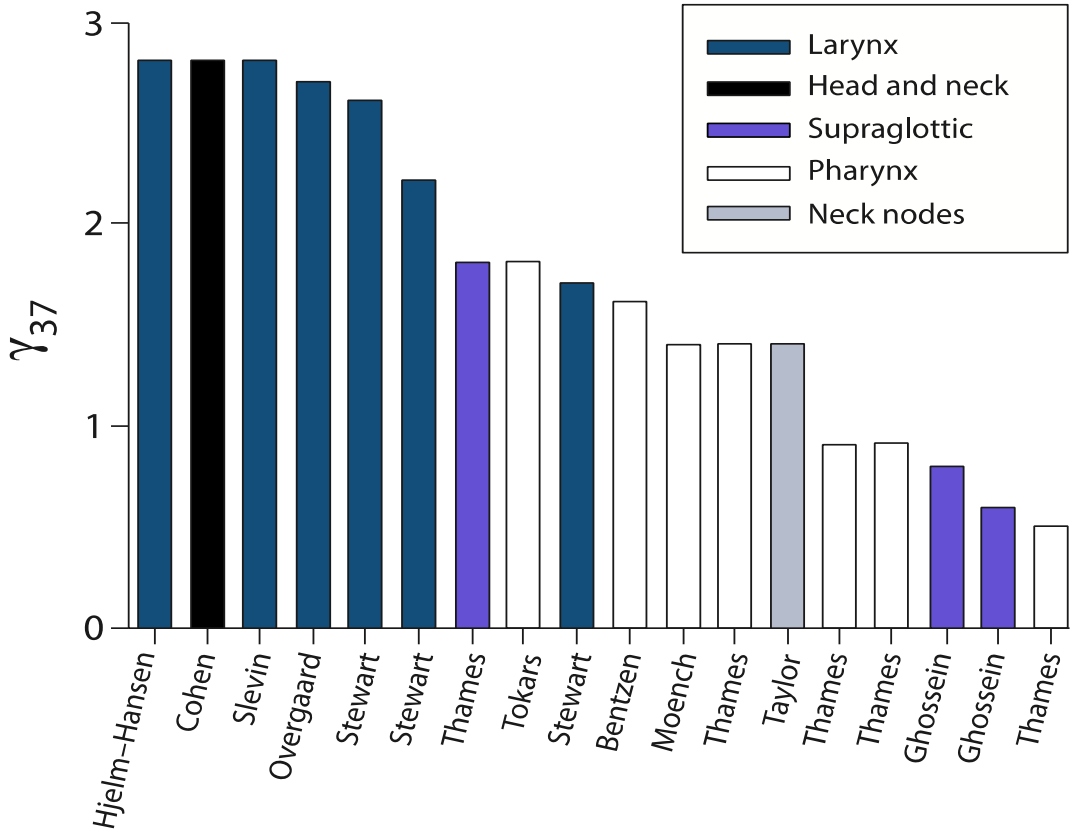
γ_{50}	Response level, %								
	10	20	30	40	50	60	70	80	90
1	0.2	0.4	0.7	0.9	1.0	1.1	1.0	0.9	0.6
2	0.5	1.1	1.5	1.8	2.0	2.0	1.9	1.5	0.9
3	0.9	1.7	2.3	2.8	3.0	3.0	2.7	2.1	1.3
4	1.2	2.3	3.2	3.7	4.0	3.9	3.5	2.8	1.6
5	1.6	3.0	4.0	4.7	5.0	4.9	4.4	3.4	2.0

γ is only useful when you are “on the curve”!

Clinical estimates of γ

Average γ_{37} for H&N ≈ 2%

From studies where dose per fraction was fixed

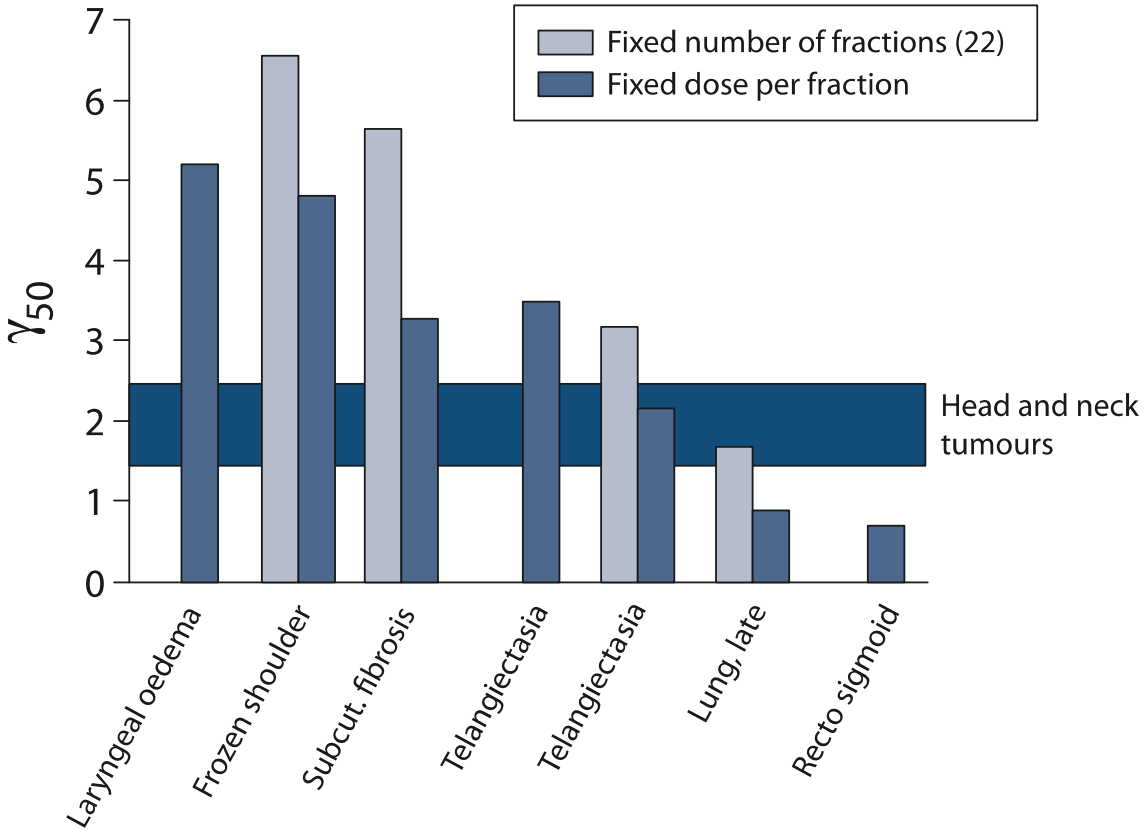


Bentzen (1994)

Value of γ in some late-reacting tissues

Compared with tumors, γ is usually larger

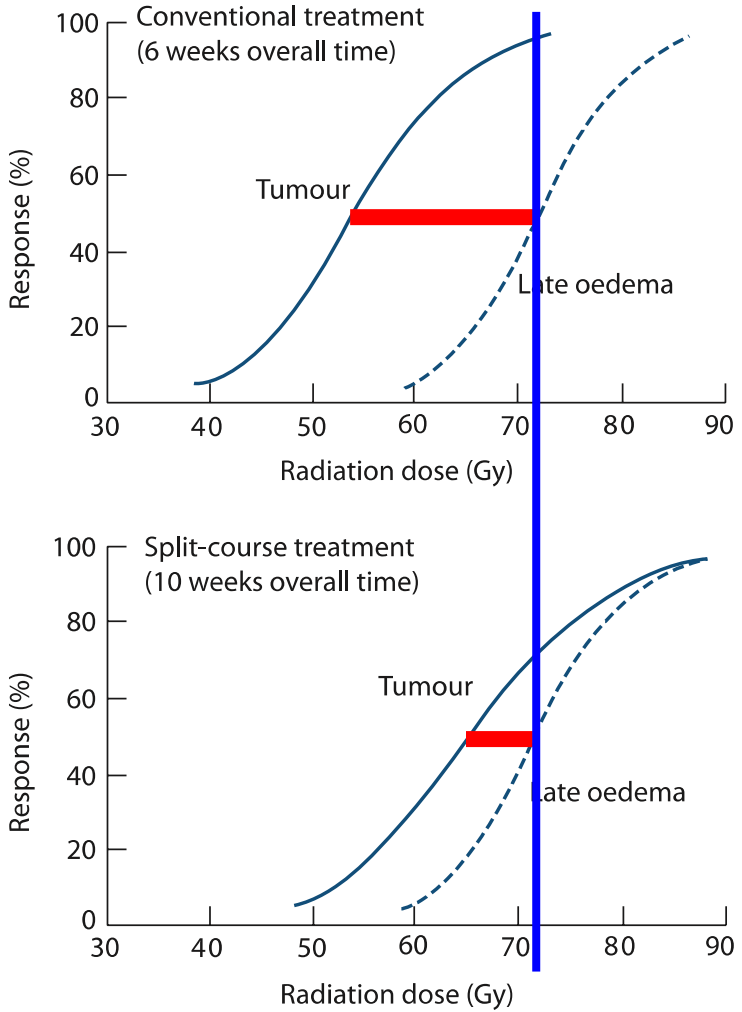
Dose response curves can be steeper, more so when fixed fraction number, *i.e.* higher dose per fraction



Bentzen (1994)
Bentzen and Overgaard (1996)

Balancing risks and benefits: The therapeutic window

Example: protraction of overall treatment time is detrimental!

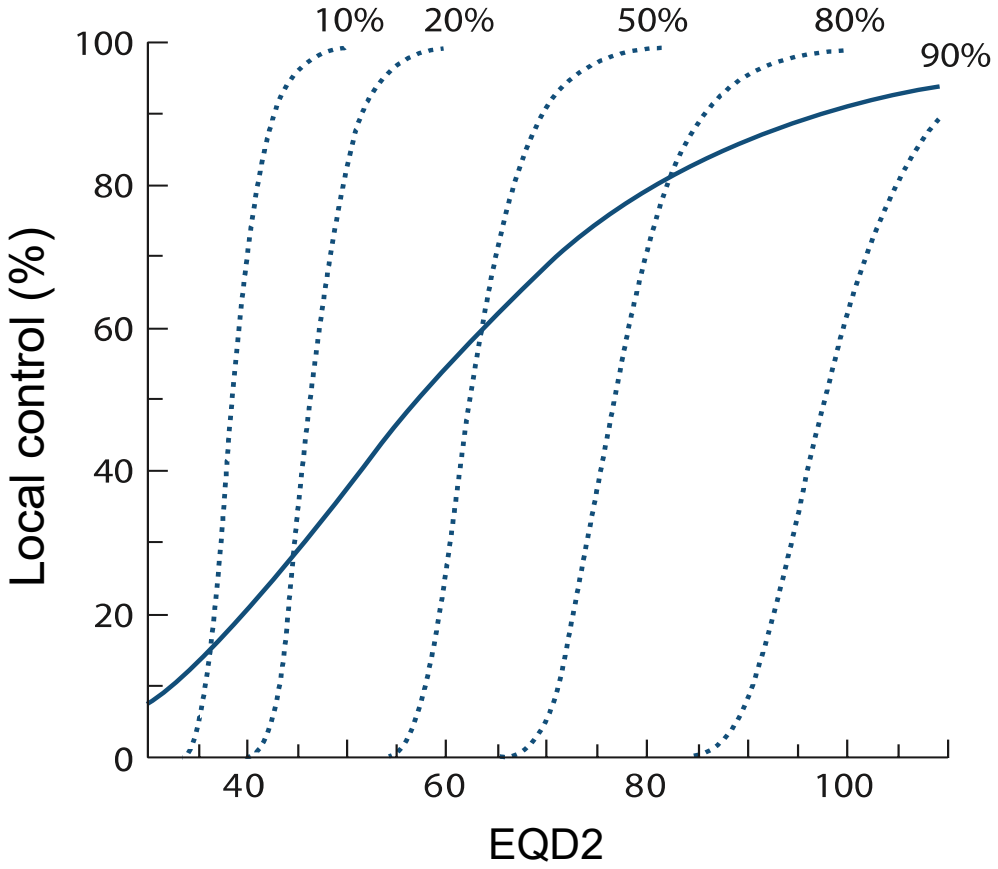


Bentzen and Overgaard (1996)

Modifying the steepness of the dose-response

Oropharyngeal cancer

Homogeneous patient populations with radiosensitivity equal to selected percentiles of radiosensitivity distribution in total population



Bentzen (1994)

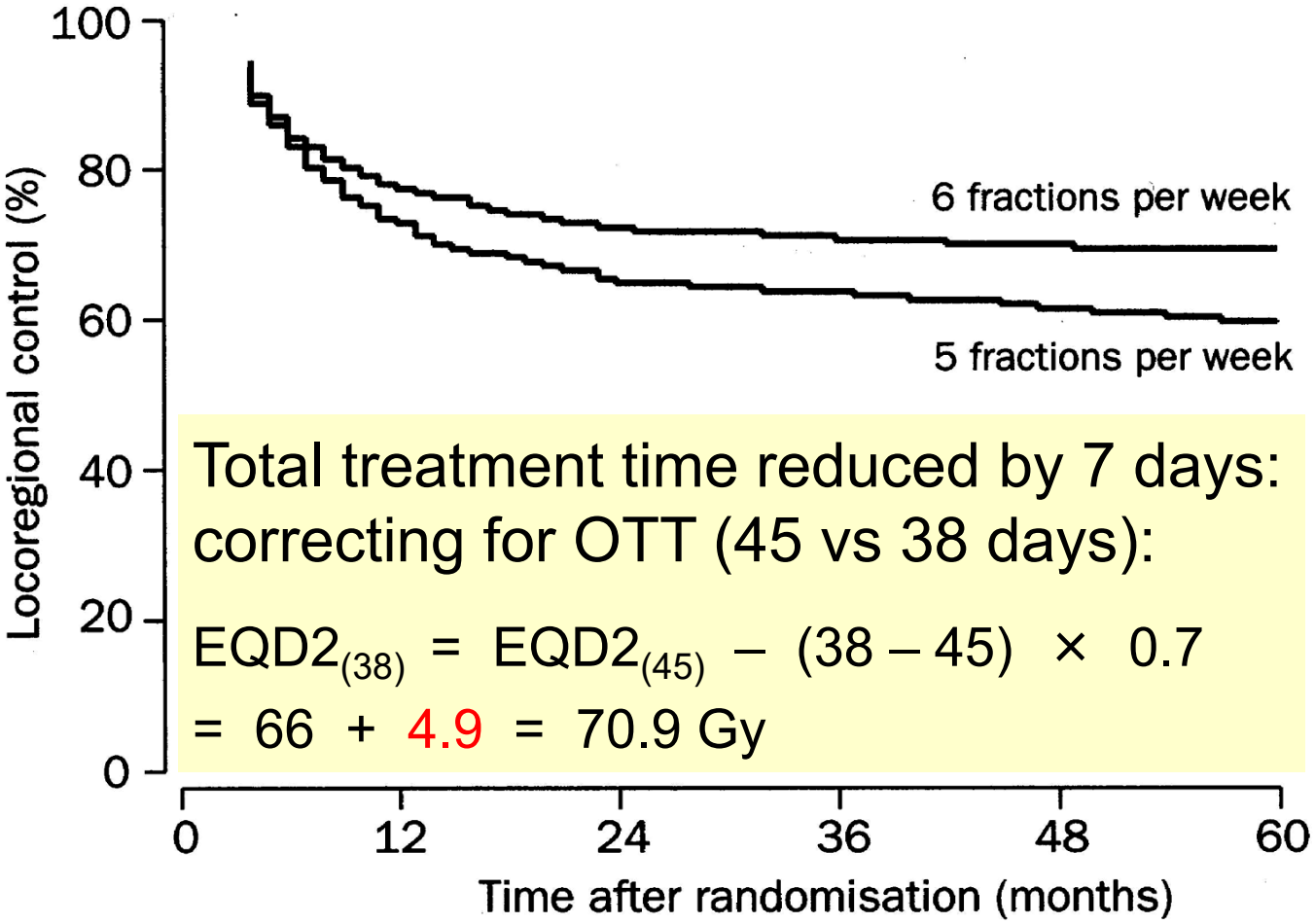
Clinical data to test modeling

Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6&7 randomised controlled trial

Jens Overgaard, Hanne Sand Hansen, Lena Specht, Marie Overgaard, Cai Grau, Elo Andersen, Jens Bentzen, Lars Bastholt, Olfred Hansen, Jørgen Johansen, Lisbeth Andersen, Jan F Evensen, on behalf of the Danish Head and Neck Cancer Study Group

Lancet 2003;362:933-40

Convert from a change in dose
to a change in response rate



Total treatment time reduced by 7 days: correcting for OTT (45 vs 38 days):

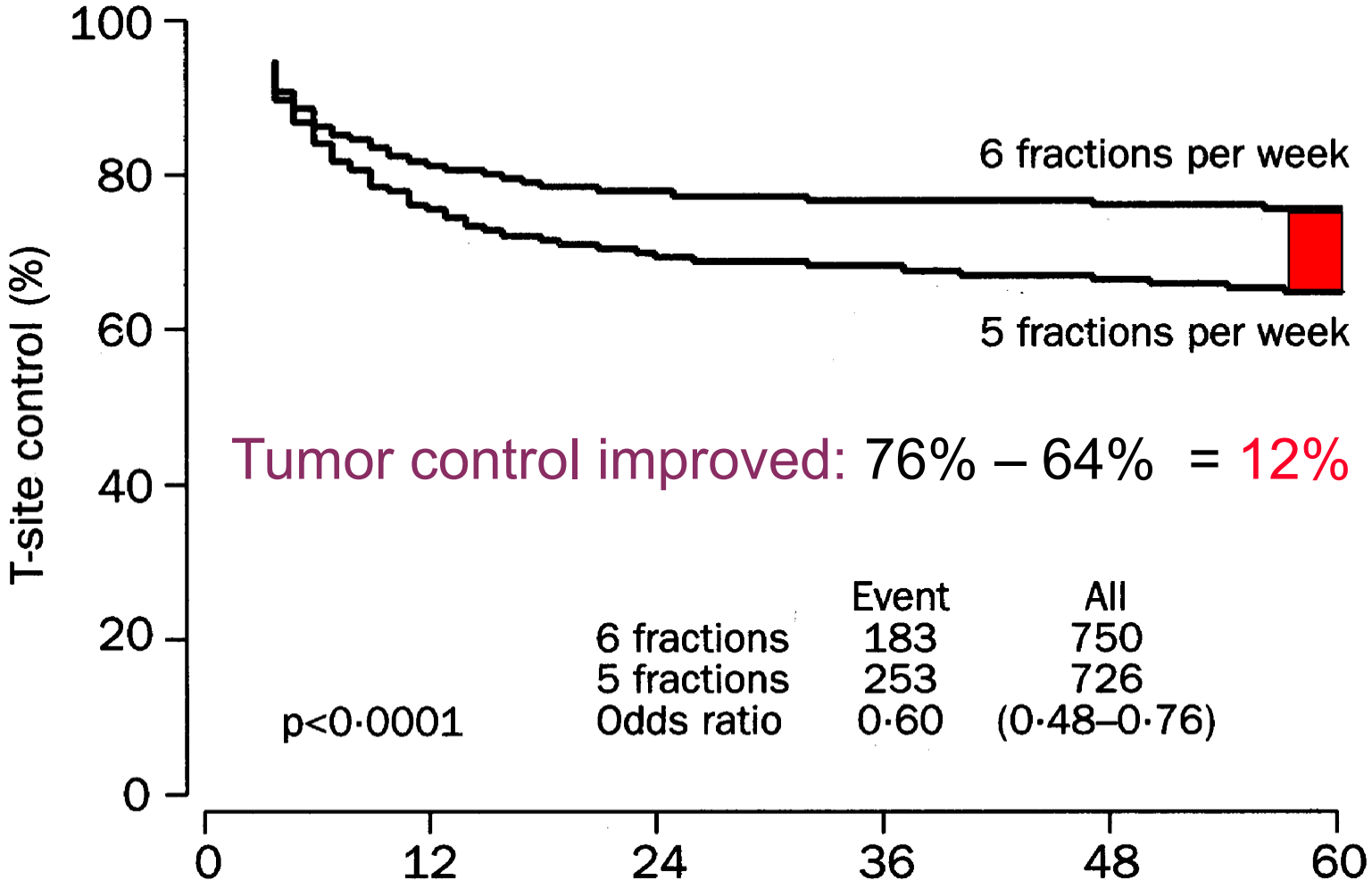
$EQD2_{(38)} = EQD2_{(45)} - (38 - 45) \times 0.7$

$= 66 + 4.9 = 70.9$ Gy

From change in dose to change in RR

$$\Delta R \approx \gamma \times \frac{\Delta D}{D} \times 100\%$$

$$= 1.6 \times \frac{4.9}{66} \times 100 = 12\%$$


100
80
60
40
20
0
T-site control (%)
6 fractions per week
5 fractions per week
Tumor control improved: 76% – 64% = 12%
Event
All
6 fractions
183
750
5 fractions
253
726
p<0·0001
Odds ratio
0·60
(0·48–0·76)
0
12
24
36
48
60

Clinical manifestations of normal tissue damage

Remember…

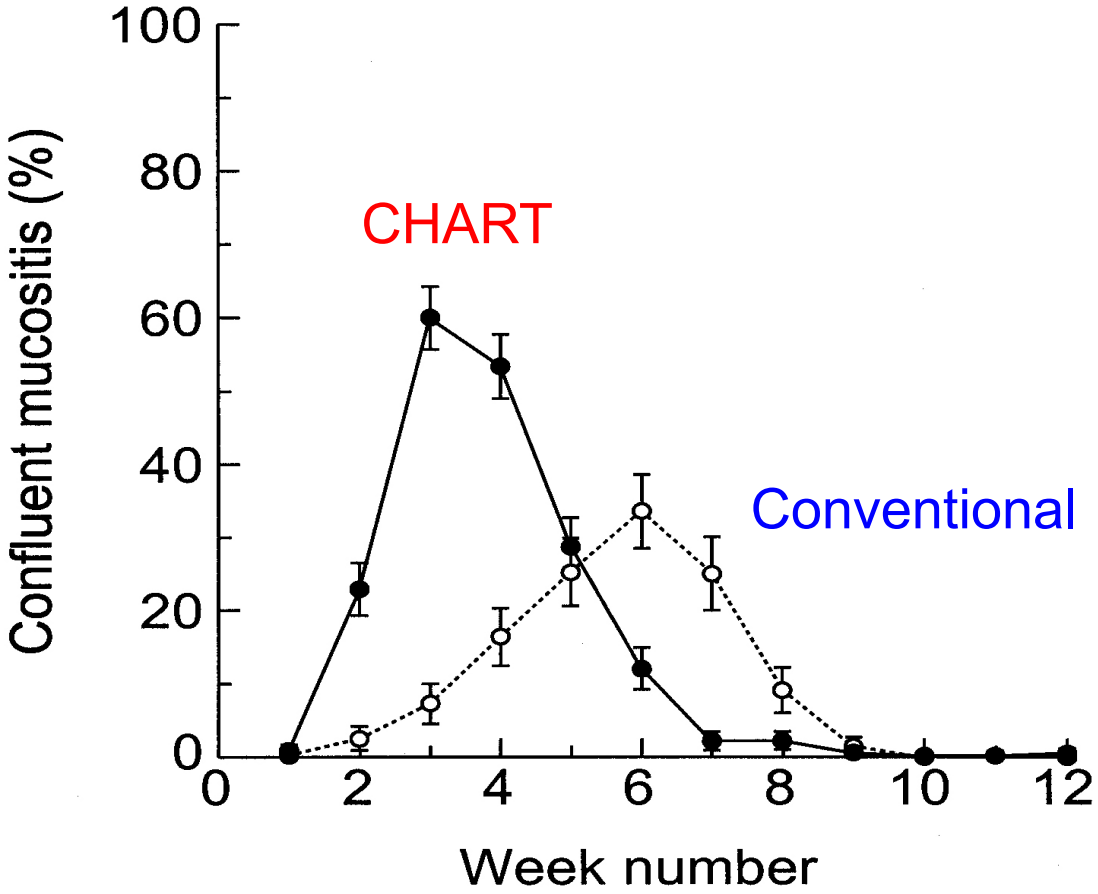
Document *tumor response*

Document *normal tissue reactions*

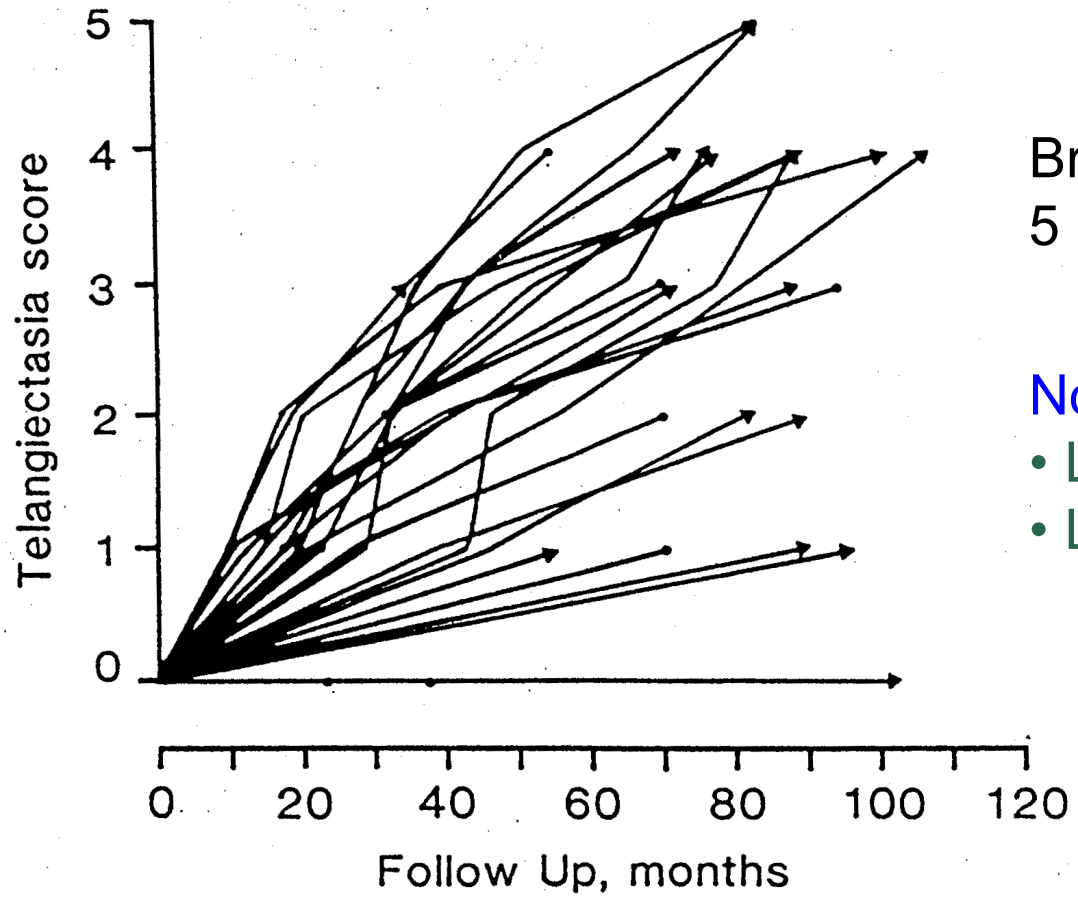
Three types of clinical toxicity data

Type of end-point	Statistical data type	Scoring system	Examples
Binary	**Categorical** all-or-nothing response	Yes / No	Radiation-induced second tumors
Graded	**Ordinal** ranking of severity	*e.g.* None / mild / moderate / severe	Telangiectasia; subcutaneous fibrosis
Continuous	**Continuous**	"Laboratory value"	Kidney ^{51}Cr-EDTA clearance; CT density of pulmonary fibrosis

Prevalence of confluent mucositis



Progressive nature of late reactions

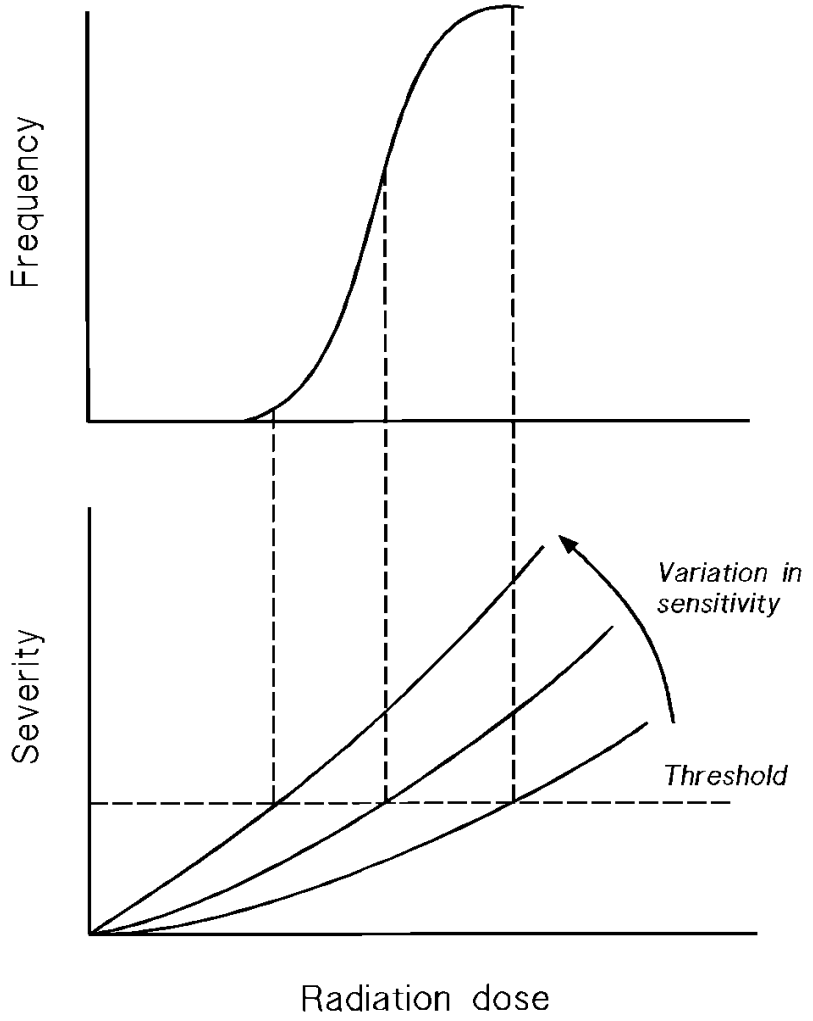


Breast Ca, post-op R/T
5 × 1.8 Gy/w, N = 35

Note:
- Long latent times
- Large inter-individual variation

Turesson (1990)

Conversion of continuous (deterministic or non-stochastic) into all-or-nothing (stochastic) responses



Field and Upton (1985)

Crude versus actuarial estimates of complications

End-point	Primary tumour	Crude estimate	Actuarial	Remarks	Reference
Radiation myelopathy	Lung	4 ± 1% at 3 years	30 ± 15%	Median survival 9 months	Hatlevoll
Marked telangiectasia	Breast	39 ± 6%	62%	Follow-up 1.5-6 years; long latent period	Bentzen
Severe rectosigmoid complications	Uterine cervix: FIGO IIb FIGO IIIb+IVa	 9 ± 5% 15 ± 3%	 10 ± 6% at 5y 39 ± 8% at 5y	Patients with IIIb and IVa disease received a higher dose but had fewer complications	Unpublished

Conclusion: Always quote actuarial values

https://ctep.cancer.gov/protocolDevelopment/electronic_applications/docs/

Common Terminology Criteria for Adverse Events (CTCAE)

Version 5.0

Published: November 27, 2017

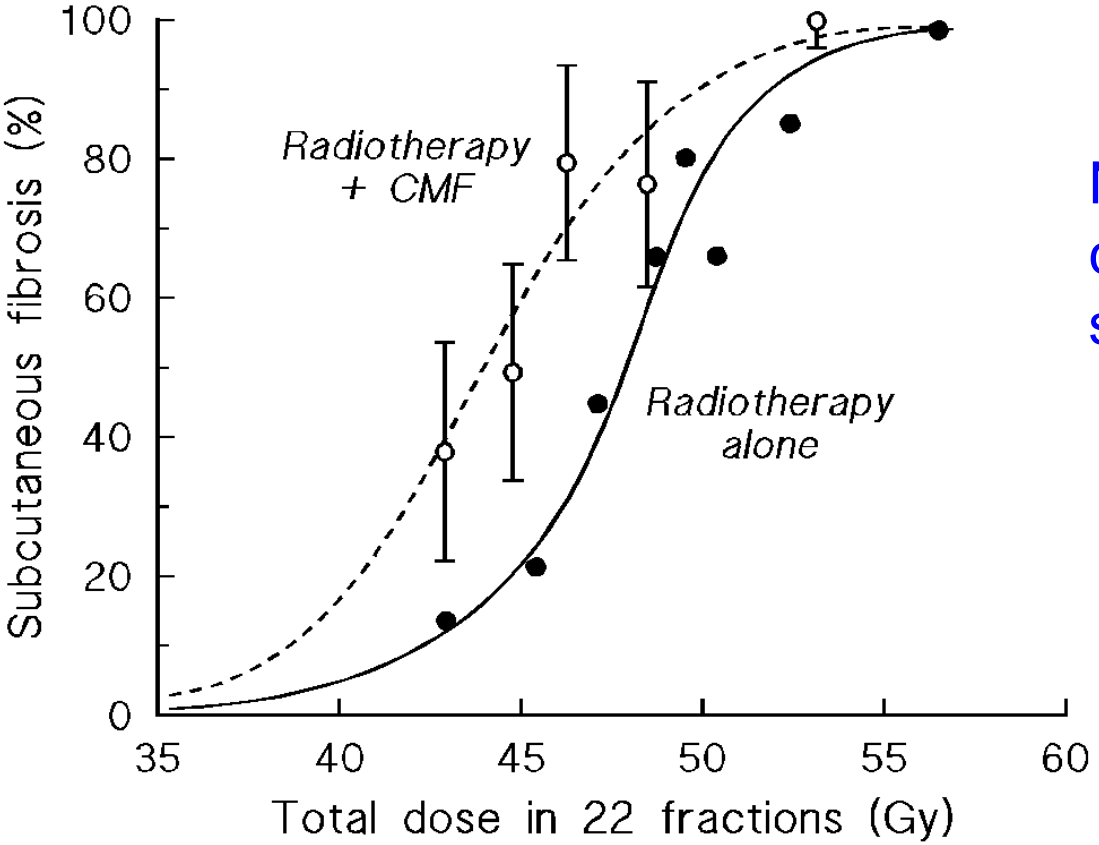
CTCAE_v5_Quick_Reference_8.5x11.pdf

U.S. DEPARTMENT OF HEALTH AND HUMAN SERVICES

National Institutes of Health

National Cancer Institute

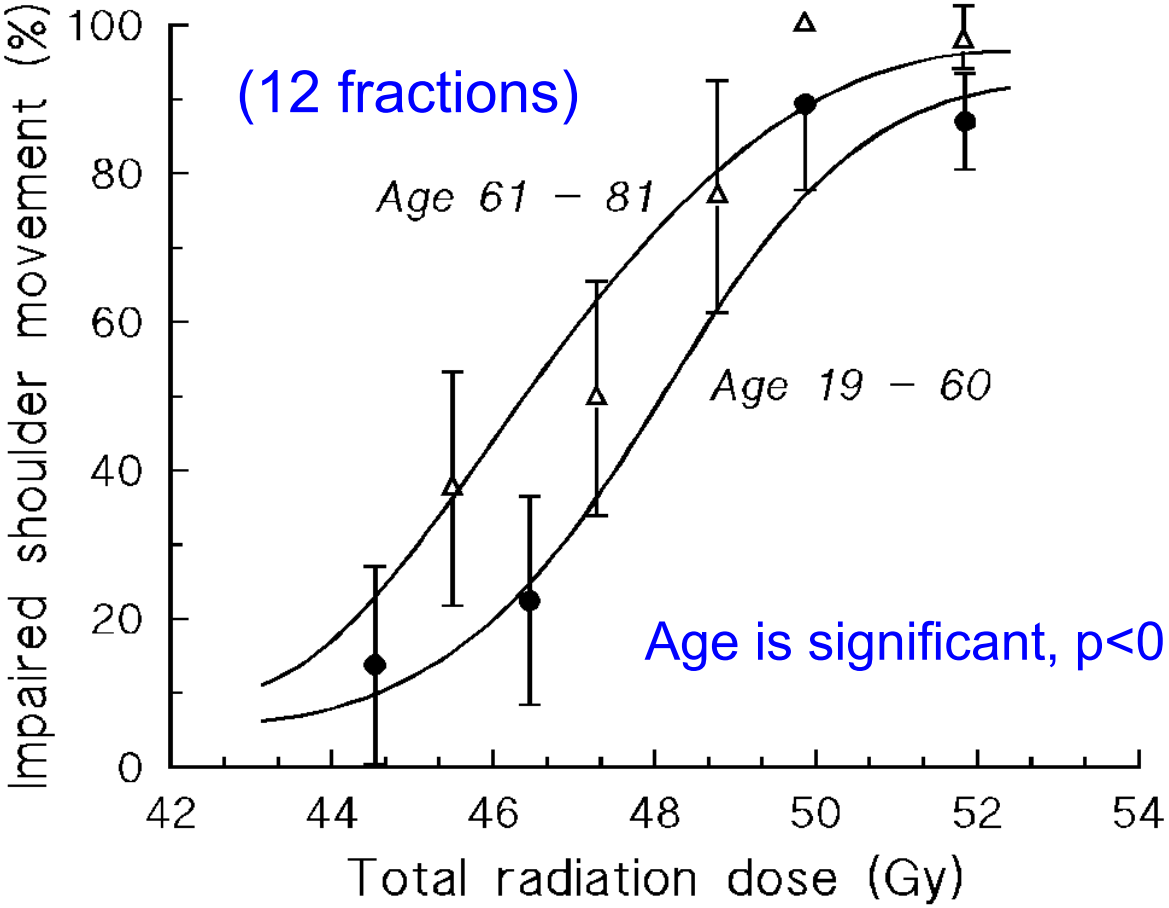
Treatment-related factors: influence of adjuvant chemo in post-mastectomy R/T



No such change with cyclophosphamide as single agent

Bentzen *et al* (1989)

Impaired shoulder movement after post-mastectomy R/T



Bentzen *et al* (1989)

Dose-volume models for normal tissues

- Predicting normal tissue toxicity has become more complicated by the use of IMRT, non-uniform dose distributions and partial organ irradiation
- Mathematical and biophysical models are developed to describe late normal tissue toxicity
- Toxicity is assessed from the complete dose distribution throughout an OAR in an integrative manner

NTCP models

Example:

The Lyman model of dose-volume effects in normal tissue

- Relates NTCP to dose and volume irradiated
- Assumes a normal distribution of complications as a function of dose for each uniformly irradiated fractional organ volume

Lyman model of dose-volume effects in normal tissue

$$NTCP(D,v) = \frac{1}{\sqrt{2\pi}} \cdot \int_{-\infty}^{u(D,v)} \exp(-x^2/2)\,dx$$

$$u(D,v) = \frac{D - D_{50}(v)}{m \cdot D_{50}(v)}$$

$0 < n < 1$

Larger n, more volume effect

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

(see BCR5 book, Ch 7.6)

D_{50} = uniform dose producing 50% incidence of specific effect

n = denotes influence of volume effect in organ of interest

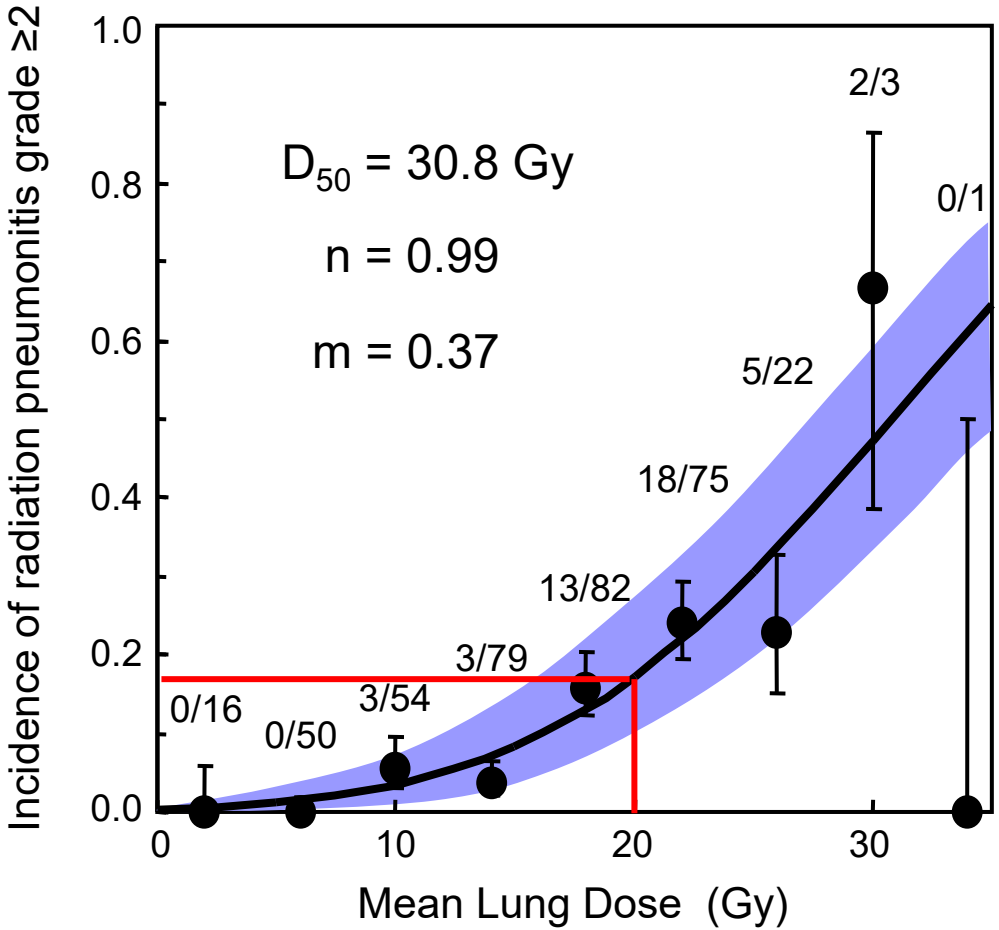
m = inverse of dose response curve gradient

NTCP models

Organ	**Toxicity**	**D_{50}**	**Volume effect** (n)	**Dosimetric descriptor**
Parotid gland	Xerostomia	28.4 Gy	large (1)	mean dose
Lung	gr ≥ 2 pneumonitis	30.8 Gy	large (0.99)	V20, MLD
Heart	RIHD		intermediate (0.35–0.64)	Vd, MHD
Spinal cord	myelopathy		marginal (except very small volumes)	EQD2
Liver	RILD	40-45 Gy	large (0.69–0.97)	MLD, Vd
Rectum	proctitis, ulceration	80 Gy	small (serial)	V70, V50

Kong et al. *Semin Radiat Oncol* 2007;17:108-20

Complications versus mean lung dose



Seppenwoolde et al.
Int J Radiat Oncol Biol Phys 2003;55:724-35

Summary

- Dose-response data usually defined in terms of probability
- Steepness of the dose response at a defined level can be used to convert change in dose to response
- Dose-response curves for normal tissues are steeper than those for tumors
- Heterogeneity in population data (particularly tumors) tend to make dose-response curves less steep
- NTCP models are not well validated and require caution when applied to clinical data; simpler dosimetric descriptors may be more useful