Basic Clinical Radiobiology

Dose-response relationships in radiotherapy

Drew Hope Thanks to Michael Joiner!





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Toronto 2025

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







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





Examples of dose response relationships

Sigmoid curves

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Bentzen and Overgaard (1991)

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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





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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:

$$P(x) = \frac{e^{-1} |^{x}}{x!}$$

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







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$$P(x) = \frac{e^{-1} |^{x}}{x!}$$
tumors.

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

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

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

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 $P(x) = \frac{e^{-1} |^{x}}{x!}$ 100 tumors.

Average number of surviving clonogens per tumor = $0.5 \qquad \lambda$ (average # per 'treatment')

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

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

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 $P(x) = \frac{e^{-1} |^{x}}{x!}$

100 tumors. Average number of surviving clonogens per tumor = $0.5 - \lambda$ (average # per 'treatment')

Each box indicates the number of surviving clonogens actually in that tumor $\checkmark x$ (actual # per 'treatment')

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:

$$TCP = P(0) = \frac{e^{-1} | ^{0}}{0!} = e^{-1} = \exp(-1)$$

 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:

$$\mathbf{S} = \mathbf{I} / N_0 = \mathbf{e}^{-n\left(\partial d + bd^2\right)} = \exp\left(-\partial \mathbf{D} - b d\mathbf{D}\right)$$

Therefore:

$$TCP = \exp\left[-N_0 \exp\left(-\partial D - b dD\right)\right]$$



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Definition of dose-response curve slope



Normalized dose response gradient, γ :

$$\mathsf{D}\boldsymbol{P} \approx \mathrm{g} \, \frac{\mathsf{D}\boldsymbol{D}}{\boldsymbol{D}}$$

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:

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

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





Logistic model of response



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

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)

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Beware: γ changes with response level

	Response level, %								
950	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

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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)



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Balancing risks and benefits: The therapeutic window

Example: protraction of overall treatment time is detrimental!

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Modifying the steepness of the dose-response

Oropharyngeal cancer

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

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Alfaraj, F. et al. Treatment outcomes in oropharynx cancer patients who did not complete planned curative radiotherapy. Oral Oncology 97, 124–130 (2019).





Clinical data to test modeling

G 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







Overgaard, J. et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet **362**, 933–940 (2003).





From change in dose to change in RR

$$DR \approx g \times \frac{DD}{D} \times 100\%$$
$$= 1.6 \times \frac{4.9}{66} \times 100 = 12\%$$







Overgaard, J. et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet **362**, 933–940 (2003).





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	<i>e.g.</i> 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





Prevalence of confluent mucositis



Overgaard, J. et al. Five compared with six fractions per week of conventional radiotherapy of squamous-cell carcinoma of head and neck: DAHANCA 6 and 7 randomised controlled trial. Lancet **362**, 933–940 (2003).





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)







Radiation dose

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





ORN Late Toxicity



Voroney, J.-P. J. *et al.* Chest Wall Pain and Rib Fracture after Stereotactic Radiotherapy for Peripheral Non-small Cell Lung Cancer. *Journal of Thoracic Oncology* **4**, 1035–1037 (2009). Caparrotti, F. *et al.* Osteoradionecrosis of the mandible in patients with oropharyngeal carcinoma treated with intensity-modulated radiotherapy. *Cancer* **123**, 3691–3700 (2017).



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



<u>Cyclophosphamide</u> <u>Methotrexate</u> <u>Fluorouracil</u>

No such change with cyclophosphamide as single agent

Bentzen et al (1989)

Impaired shoulder movement after post-mastectomy R/T



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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

$$NTCP(D,v) = \frac{1}{\sqrt{2\rho}} \times \tilde{0}_{-\neq}^{u(D,v)} \exp(-x^2/2) dx$$
$$u(D,v) = \frac{D - D_{50}(v)}{m \times D_{50}(v)} \qquad \begin{array}{l} 0 < n < 1\\ \text{Larger } n, \text{ more volume effect} \end{array}$$
$$D_{50}(v) = \frac{D_{50}(1)}{v^n} \qquad (\text{see BCR5 book, Ch 7.6})$$

 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

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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

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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

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