The Linear-Quadratic ("Alpha-Beta") Isoeffect Model

A. The seeds of what became the LQ isoeffect model were planted in the mid-to-late 1970s, and matured during the 1980s, but what was used for isoeffect analysis *before* that time?

1. ANSWER: The "**Nominal Standard Dose**" or **NSD** model which was based on decades of historical information about how skin reactions (and the control of skin cancers) changed with changing time, dose and fractionation patterns

a] the NSD equation related the total dose (D), the number of fractions (N) and the overall treatment time (T) in the form of a power function

$$D = (NSD)\, N^{0.24}\, T^{0.11}$$

2:1 ratio for the relative "weights" of the number of fractions (N) and the overall treatment time (T) in determining an isoeffective total dose (Note that a larger number of fractions implies a smaller dose per fraction, and vice versa)

...where NSD is a proportionality constant related to normal tissue tolerance; it is expressed in units called "**rets**" or "**r**adiation **e**quivalents for **t**herapy"

b] a simplification of the NSD equation, which eliminated the need for doing power function calculations (with a slide rule 😱) was the TDF formula ("time-dose-factors")

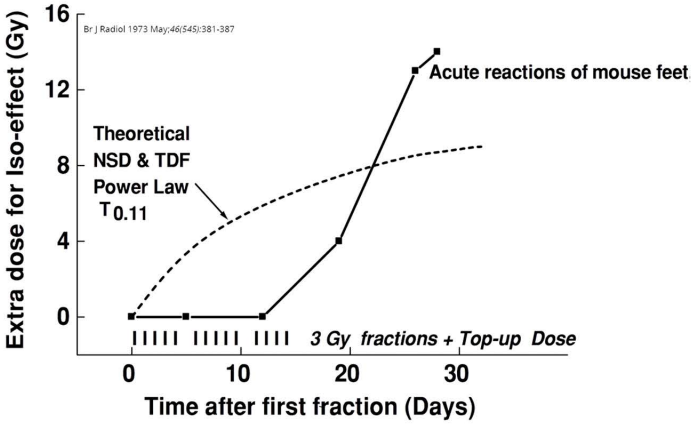
2. **The NSD equation and its derivatives - what's wrong with them?**

1) in the decade following the introduction of Ellis' NSD equation (and TDF tables), it became clear that some of the model's assumptions didn't hold up

(a) **the model did not do a good job predicting late effects**, that is, treatment schedules supposedly isoeffect according to TDF tables weren't

(b) **the model fell apart at the extremes of fraction number and overall treatment time** - this became more of a problem as more radiation oncologists toyed with "altered fractionation"

(c) **the NSD equation did not correctly model the patterns of repopulation in either early or late responding normal tissues, or tumors, during and after radiation therapy**



In early responding normal tissues and many carcinomas, there is a delay before repopulation begins following the start of radiotherapy, which the "T" factor in the NSD equation models incorrectly

Meanwhile, there's effectively no time factor at all for late responding normal tissues

2. meanwhile, **late-responding normal tissues have no time factor at all**, due to their repopulation rates, if any, taking much longer than the duration of radiation therapy

B. 1970's and early 1980's: Laying the Groundwork for the Linear-Quadratic Model

1) the first salvo in what ultimately became the alpha-beta model came from *clinicians*, French radiation oncologists named **Dutreix and Wambersie** (see: Eur J Cancer *9*: 159-167, 1973)

(a) they conducted clinically-oriented fractionation studies in a cohort of women receiving post-mastectomy chest wall irradiation; their experiments went something like this:

> *each planned chest wall field was subdivided in two, with half of it receiving a range of single doses per day (some of them quite large), and with the other half receiving two smaller doses per day, separated by 6-12 hours; overall treatment times were identical, and on the short side, so as to "equalize" any possible proliferation in the skin*

each of the fields was evaluated daily for the development and resolution of skin reactions, and a table of "isoeffects" was generated

"Recovered Dose" as a Function of Dose per Fraction for Skin Reactions in Human Radiotherapy Patients

Single Dose (Ds)	Split Dose (2 Di)	Recovered Dose (Dr = 2Di - Ds)
15 Gy	2 x 8.5 Gy	2 Gy
13 Gy	2 x 7.5 Gy	2 Gy
6 Gy	2 x 4 Gy	2 Gy
3.5 Gy	2 x 2 Gy	≤ 0.5 Gy

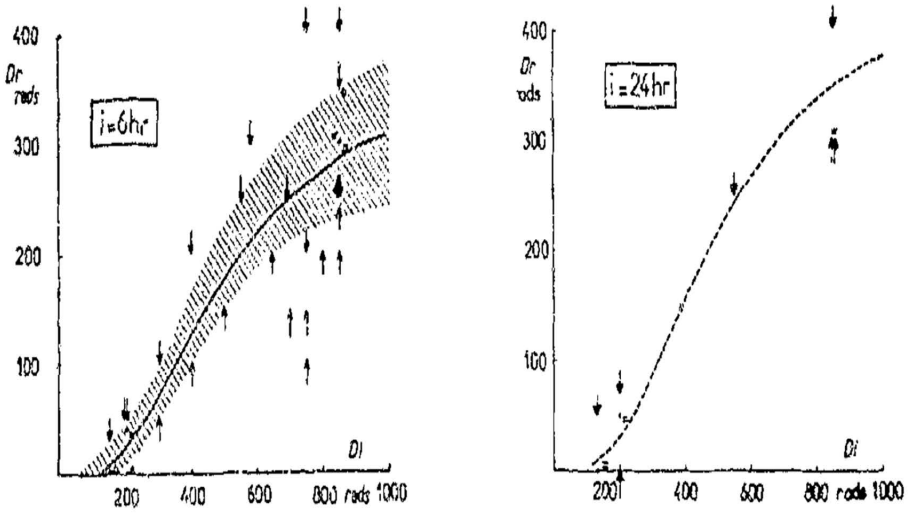
Interfraction interval (i) was 6 hours.

So for example, a single dose of 15 Gy (Ds) is isoeffective with 2 doses of 8.5 Gy (2 Di), separated by 6 hours.

But, 2 x 8.5 Gy = 17 Gy, which means that compared to the single dose of 15 Gy, 2 Gy was "recovered" (Dr) by fractionating.

as the sizes of Ds and Di decreased, so did Dr...until it finally reached ZERO RECOVERED DOSE...

or, if you prefer, shown graphically:



Recovered dose (**Dr**, y-axis) as a function of the size of the first dose (**Di**, x-axis) of a split dose treatment. Dutreix's chest wall skin data are shown for split dose intervals of either 6 or 24 hours.

But what does it all mean?!!

1. *for doses per fraction less than about 2 Gy, there is no more "recovered dose" achieved by splitting it into smaller and smaller sized fractions, that is, 2 x 2 Gy = 4 x 1 Gy = 8 x 0.5 Gy, etc.*

2. *this implies that some component of radiation damage must be irreparable, and that this is most evident at low radiation doses; thus, there should be a dose per fraction below which, no additional sparing would occur with further fractionation*

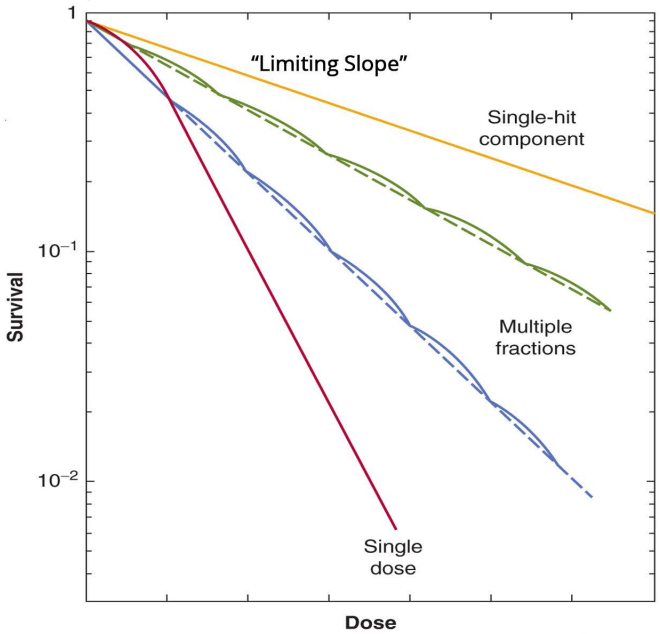
3. this was a novel idea for clinical radiotherapy at the time, because it had always been assumed that further fractionation = further sparing, indefinitely

   a] it also helped explain why the NSD formula tended to fall apart when large numbers of very small fractions were used

4. **the consensus was that survival and dose response curves must have NON-ZERO initial slopes**...

   this effectively doomed the old target theory model because that model predicted that cell survival and tissue dose response curves have initial slopes equal to zero

5. **for sufficiently small dose fractions (or continuous low dose rate), cell survival should "trace" this initial slope...you'd know you reached the initial or "limiting" slope when further fractionation failed to yield an even shallower survival curve** (again, similar to the Dutreix findings)



The influence of fractionating the radiation treatment on the shape of cell survival curves. When repair occurs between the fractions, the shoulder of the survival curve is repeated for every fraction.

Please note that this would only be true if:

1. No proliferation was occuring during treatment; and

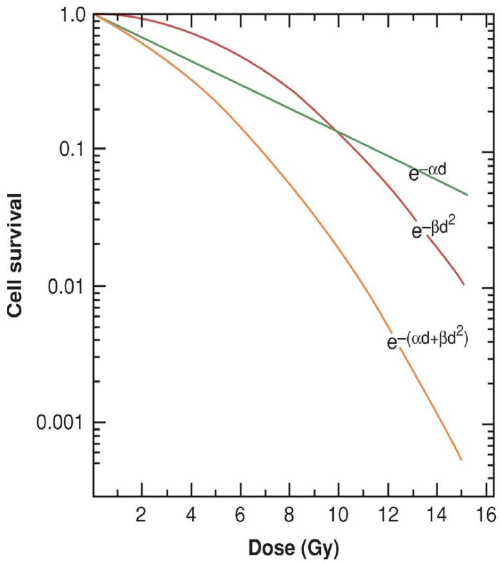
2. There was enough time between fractions to allow for maximal repair of sublethal damage

(c) **it follows from this idea that very small differences in the initial slopes of survival curves for different cell types would be greatly magnified if many small dose fractions were used**

1. one mathematical model that provided a good fit to survival curves – especially in the low dose, initial slope region – was the linear-quadratic survival expression:

a] this model had been used previously to describe the induction of chromosome aberrations, and later, to model cell survival after irradiation

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



"$S = e^{-\alpha D}$" represents the fraction of cell killing caused by single-hit, irreparable damage that is invariably fatal

"$S = e^{-\beta D2}$" represents the fraction of cell kill caused by accumulating, two-hit, sublethal damage that only becomes lethal if more sublethal damage is added before the original damage can be repaired

3) Douglas and Fowler (1976) - decided to expand upon the studies of Dutreix and Wambersie (but with mice instead of patients) by looking at an even wider range of doses per fraction, different times between fractions, different overall treatment times, and several different levels of skin reactions (see: Radiat Res *66*: 401-426, 1976)

(a) **they analyzed their data in what was then a very novel fashion, a method that ended up becoming the *de facto* standard for determining a tissue's α/β ratio:**

the RECIPROCAL DOSE or "Fe" PLOT

1. a reciprocal dose or Fe plot is a variation on a Strandqvist-type isoeffect curve, in which the reciprocal of the total dose (D) required to reach an isoeffect is plotted as a function of the dose per fraction (d) on linear-linear axes

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

where D is replaced by n (number of fractions) x d (dose per fraction)

2. $\ln S = -n(\alpha d + \beta d^2)$

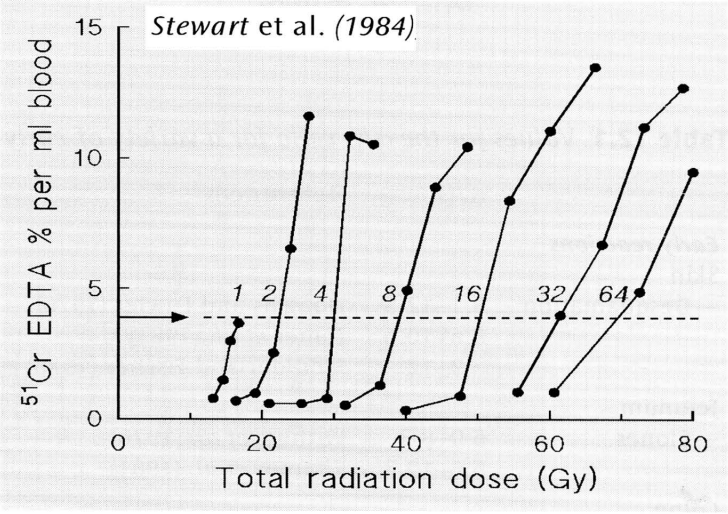
3. $\ln S = -nd(\alpha + \beta d)$

4. $-\ln S / nd = \alpha + \beta d$

5. $\mathbf{-1 / nd = -1 / D = \alpha / \ln S + \beta d / \ln S}$

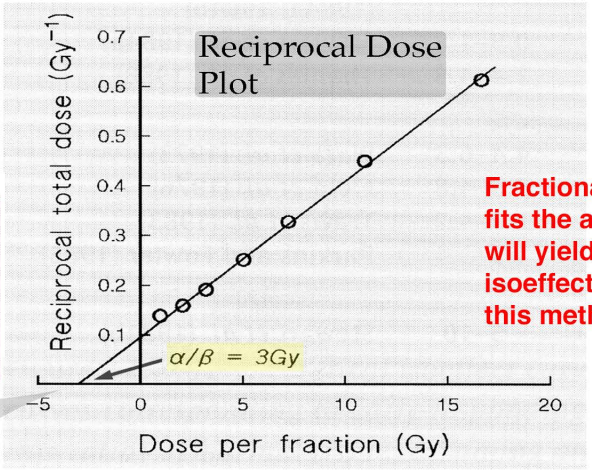
By plotting 1/D as a function of d, you should get a straight line with an intercept of α/ln S, and a slope of β/ln S.

taking the ratio of intercept:slope of the reciprocal dose plot does give you a knowable value, the α/β ratio (in units of "Gy"), and from that, you can work backwards and construct a presumptive dose response curve for the tissue



Sample Fractionation Data
(Endpoint = mouse kidney damage)

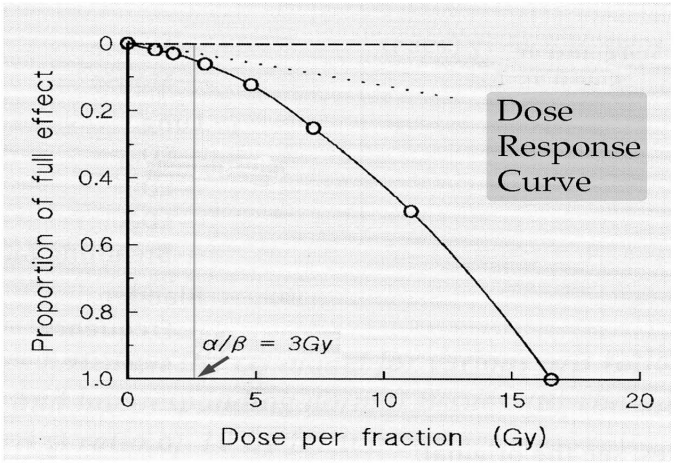
Replot data as a reciprocal dose isoeffect curve



easier method for determining the α/β ratio: back-extrapolate the reciprocal dose curve to the X-axis

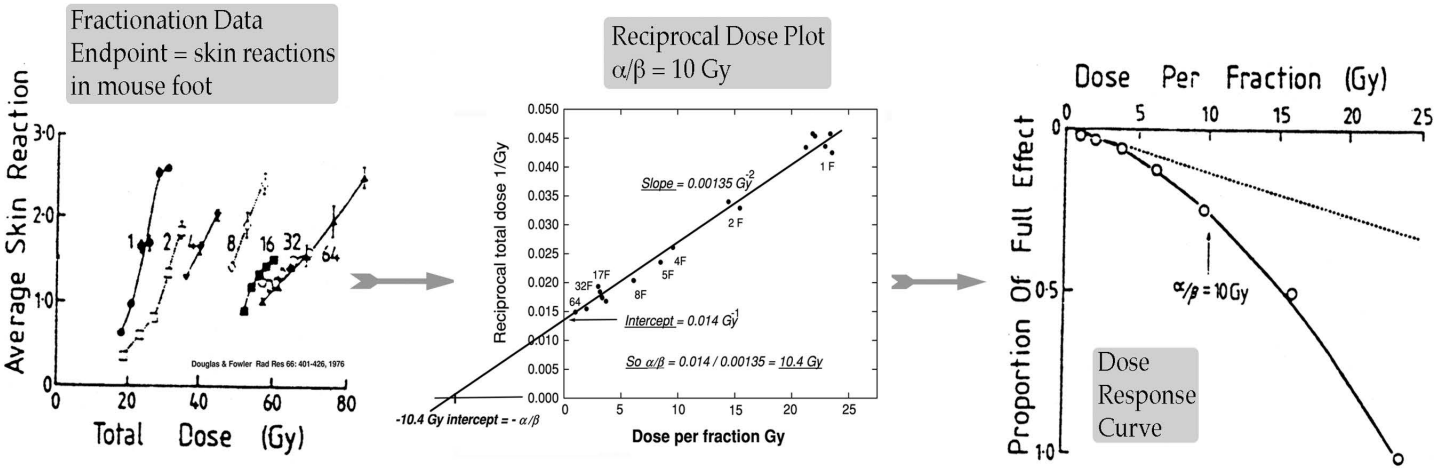
Fractionation data that fits the alpha-beta model will yield a LINEAR isoeffect curve when using this method

use derived value of α/β to work backwards and generate a (pseudo-) dose response curve for the tissue at risk



From: Stewart *et al.* Radiat Res 98:407-420, 1984

(1) thus, in the above example, it was determined that the α/β ratio for kidney damage, a late effect, equaled approximately 3 Gy; but what about early effects?



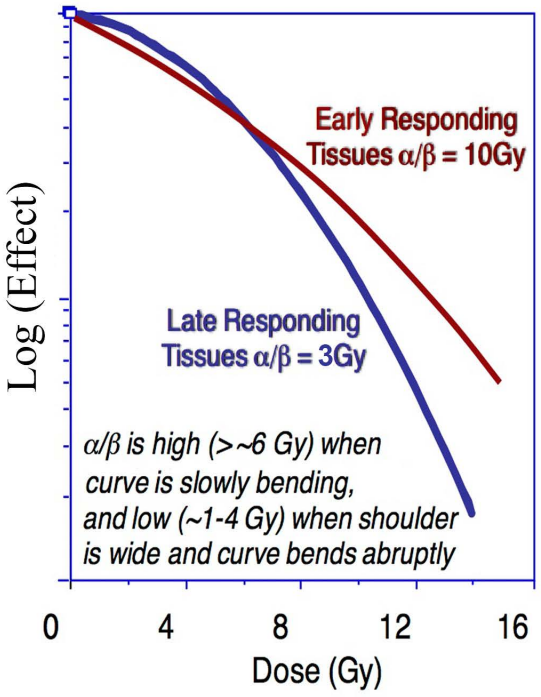
2. the technique of isoeffect analysis pioneered by Douglas and Fowler was used extensively to determine α/β ratios for many early and late responding normal tissues in laboratory rodents, and over time, in humans as well

a] the general trend (NOT without exceptions) was that early-responding tissues were found to have high α/β ratios (greater than about 6 Gy; an average of 10 Gy), and late-responding tissues were found to have low α/β ratios (less than 6 Gy; average around 3 Gy)

(1) the prevailing explanation for this is that the underlying dose response curves for early and late responding tissues are different, particularly in their low dose, regions

Ratio of linear to quadratic terms from multi-fraction experiments

Early reactions		α/β (Gy)
Skin		
Desquam	Douglas & Fowler (1976)	9.1–12.5
	Joiner *et al.* (1983)	8.6–10.6
	Moulder & Fischer (1976)	9–12
Jejunum		
Clones	Withers *et al.* (1976)	6.0– 8.3
	Thames *et al.* (1981)	6.6–10.7
Colon		
Clones	Tucker *et al.* (1983)	8–9
Wt. loss	Terry & Denekamp (1983)	10–12
Testis		
Clones	Thames & Withers (1980)	12–13
Callus		
50d	Hayashi & Suit (1971)	9–10
Mouse lethality		
30d	Kaplan & Brown (1952)	7–10
30d	Mole (1957)	13–17
30d	Paterson *et al.* (1952)	11–26
Late reactions		
Spinal cord		
Cervical	Van der Kogel (1979)	1.8–2.7
Cervical	White & Hornsey (1978)	1.6–1.9
Cervical	Ang *et al.* (1983)	1.0–1.5
Lumbar	Van der Kogel (1979)	3.7–4.5
Lumbar	White & Hornsey (1978)	4.1–4.9
	Leith *et al.* (1981)	3.8–4.1
	Amols, Yuhas (quoted by Leith *et al.*, 1981)	2.3–2.9
Kidney		
Rabbit	Caldwell (1975)	1.7–2.0
Pig	Hopewell & Wiernik (1977)	1.7–2.0
Mouse	Williams & Denekamp (In press)	2.1–2.4
Mouse	Meistrich *et al.* (submitted)	1.5–2.1
Lung		
LD_{50}	Wara *et al.* (1973)	4.4–6.3
LD_{50}	Field *et al.* (1976)	2.8–4.8
LD_{50}	Travis *et al* (1983*a*)	2.0–4.2
Br. rate	Fowler & Parkins (submitted)	2.5–5.0
Bladder		
Frequency, Elasticity	Stewart *et al.* (1981)	3–7
Tumour bed		
45d	Begg (pers. comm.)	6–7



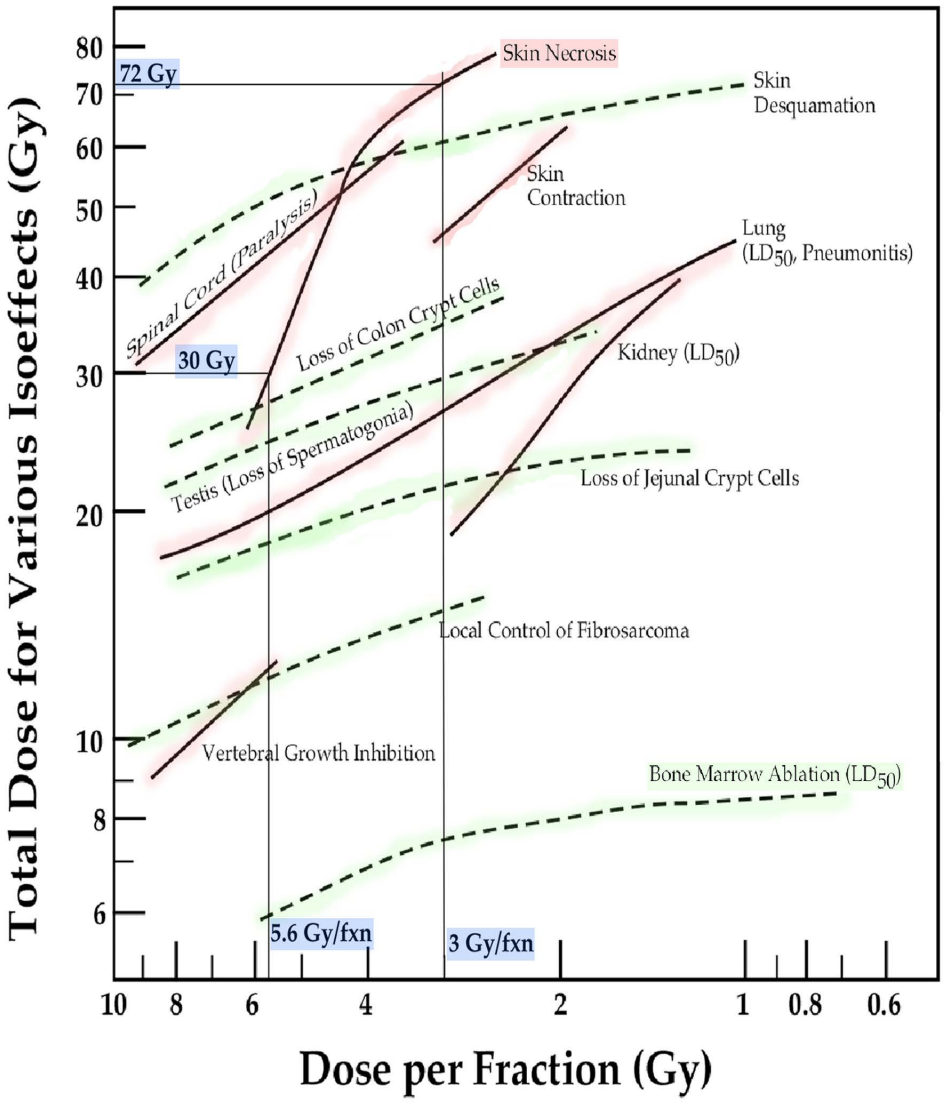
3. OK, so what about tumors, human or otherwise?

a] ***most* tumors evaluated to date tend to have high α/β ratios, similar to early-responding normal tissues**

1) in humans, it is much more difficult than in rodents to derives α/β ratios, usually because the data does NOT include a wide range of fraction sizes and numbers; as such, lots of statistical analyses (and assumptions) are involved

4) **Thames, Withers, Peters and Fletcher (1982**, see: IJROBP *8*: 219-226, 1982) - were among those calculating α/β ratios for experimental animal and human tissues, and were the first to report the apparent systematic difference between early versus late responding tissues

(a) however, these authors didn't really like the reciprocal dose plot method of data presentation, claiming that the "reciprocal total dose" (1/D) was an unwieldy, confusing concept; they preferred more traditional isoeffect curves like Strandqvist's, ***with the log of the total dose (D) on the y-axis, and, in their case, log of the dose per fraction (d) on the x-axis***:



Isoeffect curves in which the total dose necessary for a certain effect in various tissues is plotted as a function of dose per fraction. Late effects are plotted with solid lines, early effects with dashed lines.

The data were selected to exclude conditions (i.e., long overall treatment times) where proliferation could have influenced the total isoeffect dose.

Whether these isoeffect curves are steep (late effects and a few tumors), or shallow (early effects and most tumors) is governed by the tissue's* α/β *ratio; low α/β = steep isoeffect curve and high α/β = shallow isoeffect curve

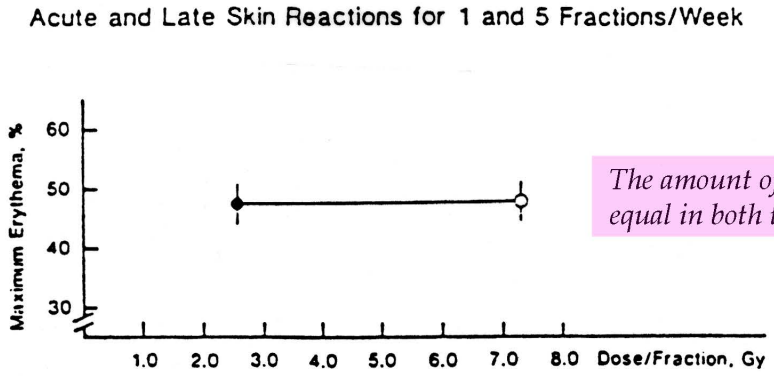
In this example, if the $TD_{5/5}$ for skin necrosis (late effect) is ~30 Gy when given in 5.6 Gy fractions, it's 72 Gy when given in 3 Gy fractions. A *huge* difference!

However, for bone marrow ablation (early effect), the change in tolerance dose in going from 5.6 Gy to 3 Gy fractions is quite small (~6 Gy to ~7.5 Gy).

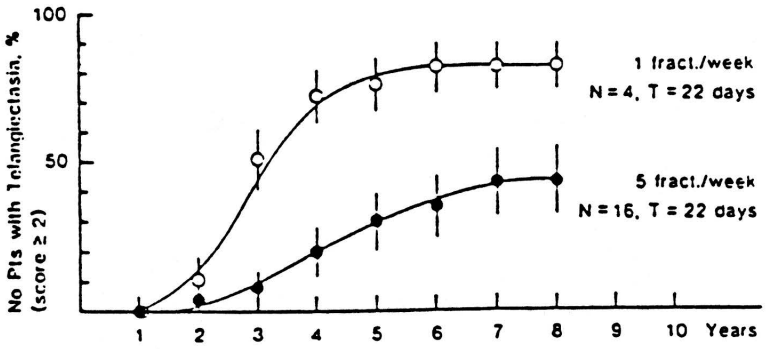
From: Withers, Cancer *55*: 2086, 1986

5) **Turesson and Notter (1984**; see: IJROBP *10*: 607-618, 1984) - Swedish radiation oncologists who were the first to complete a *prospective* clinical trial testing the tenets of the α/β isoeffect model

(a) in their study, *women receiving post-mastectomy radiation therapy were evaluted for early (erythema) and late (telangiectasia) skin reactions as a function of dose per fraction, 6-8 Gy given once per week versus 2-3 Gy given 5 days per week, with the overall time for both arms of the study kept constant at 22 days*

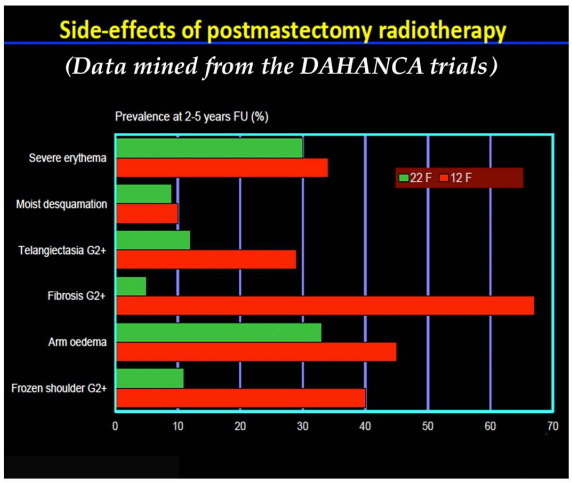


The amount of skin erythema was equal in both treatment arms...



...however, late telangiectasia was much worse in the treatment arm using one large fraction per week, in keeping with the predictions of the α/β model

(b) meanwhile, other investigators were mining old, retrospective clinical data for instances where one or a few large dose fractions were compared to many, small dose fractions, both in terms of normal tissue reactions and tumor control; in most cases:



EARLY AND LATE INJURY AFTER TWO SCHEDULES APPLYING A DIFFERENT DOSE PER FRACTION[a]

Post-mastectomy radiotherapy to the chest wall

End point	Field	36.5 Gy total dose 12 fractions (n = 73)	(~41 Gy total dose) 22 fractions (n = 66)	p-value
Erythema grade 3	Electrons	34%	30%	n.s.
Moist desquamation grade ≥1	E	10%	9%	n.s.
Telangiectasia grade ≥2	E	29%	12%	0.009
Fibrosis grade ≥2	E	67%	5%	$<10^{-8}$
Pneumonitis grade ≥2[c]	Photons	43%	23%	0.01
Lung fibrosis grade ≥2[c]	P	32%	17%	0.04
Persistent arm edema		45%	33%	0.14
Spontaneous rib fractures[c]	P + E	19%	2%	0.0003
Frozen shoulder grade ≥2		40%	11%	$2 \cdot 10^{-5}$

[a] Data from Overgaard *et al.* (1987) and Bentzen *et al.* (1989)

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early reactions were similar
tumor control was similar
late effects were much worse when large dose fractions were used

C. The Linear-Quadratic Isoeffect Model Today: Clinical Implications and Applications

1) in keeping with some of the ideas originally put forth by the α/β model, the day-to-day practice of radiation oncology has changed accordingly over the years

...but first, let's clear up a few of the most common misconceptions when it comes to the clinical application of the linear-quadratic model

a. just because the LQ cell survival curve model was adapted for use in measuring the fractionation response of normal tissues and tumors, ***it doesn't mean that the α/β ratios determined in animal models or clinically were derived from, or have anything to do with, cell survival curves or cellular radiosensitivity***.

1] in other words, the α/β ratio calculated from the absolute values of α and β of a cell survival curve for human hepatocytes isn't necessarily the same as the α/β ratio measured for liver *in vivo* based on fractionation experiments

b. likewise, ***the α/β ratios measured clinically for tissues*** – unlike for cell survival curves – ***have NO mechanistic underpining***

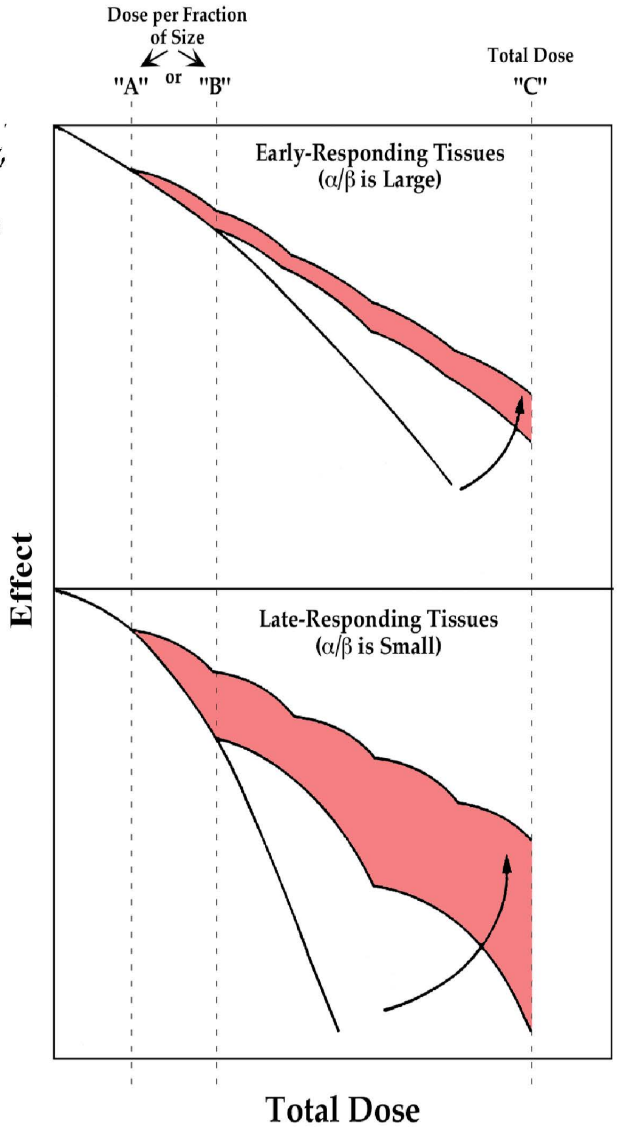
c. clinical studies that suggest the linear-quadratic model "fails" at high doses per fraction (i.e., hypofractionation) and attempt to fix this discrepancy by adding new survival curve parameters to the model ***are misguided*** (unless this is being done strictly for pragmatic reasons)

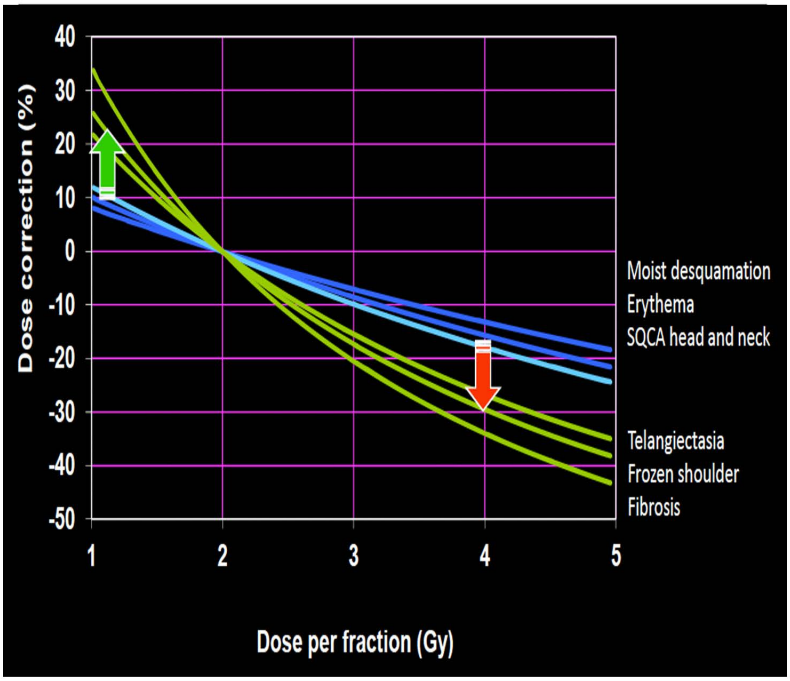
OK then, let's review some of the major concepts that guide the clinical use of the LQ model...

(a) Major Concept #1: **there is a steep increase in late complications with increasing dose per fraction, because the underlying dose response curves have different shapes in their low-dose regions (α components); specifically, the dose response curve for late-responding tissue is more "curvy" than that for its early-responding tissue counterparts**

1. meanwhile, **early-responding normal tissues and tumors are relatively insensitive to changes in fraction size, meaning that they'd barely notice if a change was made from say, standard fractionation to hyperfractionation, while late-responding tissues would benefit from much more sparing**

2. therefore, **large doses per fraction should be avoided and hyperfractionation encouraged** (provided the overall treatment time isn't too long–see below), except in special circumstances





Influence of fraction size on complications in early- vs. late-reacting tissues. The α/β ratio for the early tissue (*blue curve*) was set at 10 in this example; the α/β ratio for the late tissue (*red curve*) was 2.5. The tissues were presumed to have equal reactions to 40 Gy delivered at 2 Gy per fraction. Note that for equal reactions, the early-reacting tissue is far less dependent on fraction size. For large daily fractions, the late-reacting tissue will require substantial dose reduction to maintain equal clinical effects. Conversely, if fraction size is reduced, the late-reacting tissue will tolerate substantially higher doses of radiation.

Total doses for radiotherapy schedules calculated to keep late effects constant, as a function of dose per fraction. Standardized to 200 cGy per fraction

Dose per fraction (cGy)	Total doses for constant late effects					
	30F × 200 = 6000 cGy			35F × 200 = 7000 cGy		
	α/β = 2 Gy	3 Gy	4 Gy	2 Gy	3 Gy	4 Gy
120	7500	7143	6923	8750	8333	8080
140	7059	6818	6667	8235	7955	7778
160	6667	6522	6429	7778	7609	7500
180	6316	6250	6207	7368	7292	7241
200	6000	6000	6000	7000	7000	7000
220	5714	5769	5807	6667	6731	6774
240	5455	5556	5625	6364	6482	6563
260	5217	5357	5455	6087	6250	6364
280	5000	5172	5294	5833	6035	6177
300	4800	5000	5143	5600	5833	6000
350	4364	4615	4800	5091	5385	5600
400	4000	4286	4500	4667	5000	5250
450	3692	4000	4235	4308	4667	4941
500	3429	3750	4000	4000	4375	4667
600	3000	3333	3600	3500	3889	4200
700	2667	3000	3273	3111	3500	3818
800	2400	2727	3000	2800	3818	3500

This table is only a guide. It should not be used to preempt clinical judgement.

From Fowler, Br J Radiol 62: 679-694, 1989

This is a reboot of an old-school NSD/TDF table of isoeffective treatments... except instead of a single presumed value of NSD, it uses tisssue-specific α/β ratios

All equivalent doses normalized to:

30 x 2 Gy = 60 Gy, or
35 x 2 Gy = 70 Gy

(b) Major Concept #2: although not immediately addressed in the original incarnation of the linear-quadratic isoeffect model, we have since learned a lot more about normal tissue and tumor proliferation patterns during and after radiation therapy that can help guide us in its appropriate use

1. **there is no time factor for late responding normal tissues** - *so, in order to keep the risk of late effects constant, no increase in total dose should be made if the overall treatment time is extended*

2. **the time factor for early responding normal tissues is sigmoid-shaped, and characterized by a delay period before repopulation begins**

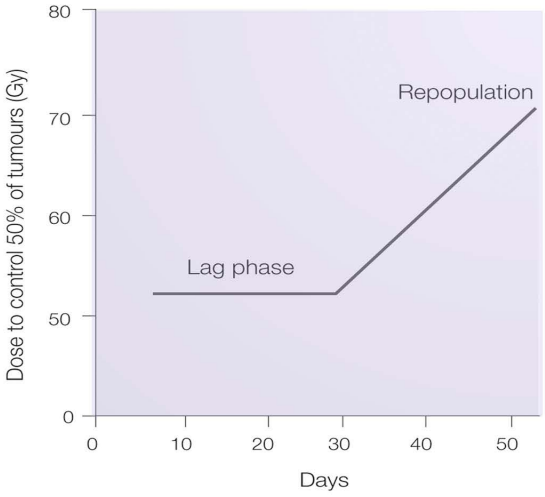
    a) the delay period varies with the tissue, but is typically in the range of 2-4 weeks in humans

    b) **once this proliferation begins in earnest though, it is capable of counteracting anywhere from about 30% to nearly 50% of each daily dose fraction of ~1.8 - 2.0 Gy**

        (1) if this had been a normal tissue capable of repopulation during radiotherapy, this would be considered a good thing...but what about tumors?

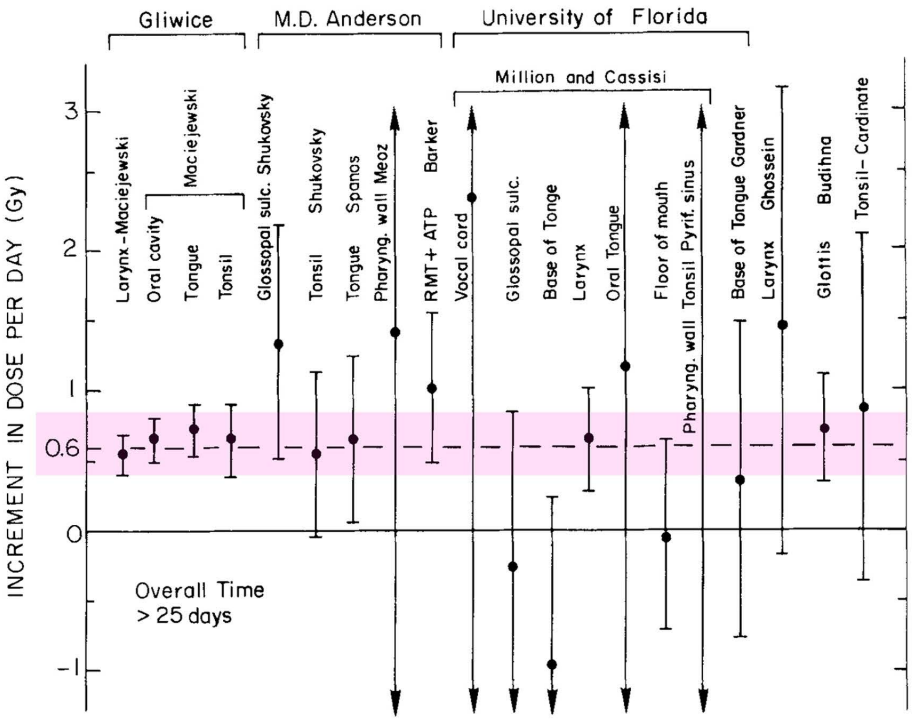
3. **many tumors are likewise able to compensate for cell killing by mounting a proliferative response, but not all of them, and certainly, some more than others** (especially head & neck and cervix carcinomas)

    a) ***like some normal tissues, some tumors also appear to show a lag period before proliferation begins, generally in the 3-4 week range, and again, especially carcinomas and especially head & neck tumors (best answer for the Boards, ~28 days)***



The relationship between total dose of radiation to control 50% of oropharyngeal cancers and duration of fractionated radiotherapy. For courses of radiotherapy that last up to about one month the line is flat (lag phase), indicating that there is little or no repopulation in the tumour. When treatment time is extended beyond about 1 month, repopulation between dose fractions increases the number of tumour cells that must be killed, which means that increasing doses of radiation must be given. Line is fitted to data for oropharyngeal cancers. Modified from Withers et al., Acta Oncol *27*: 131-146, 1988

This proliferative response in tumors, also estimated to counteract about 60 cGy per treatment would correspond to a 1-2% loss of local control per treatment day beyond the lag phase

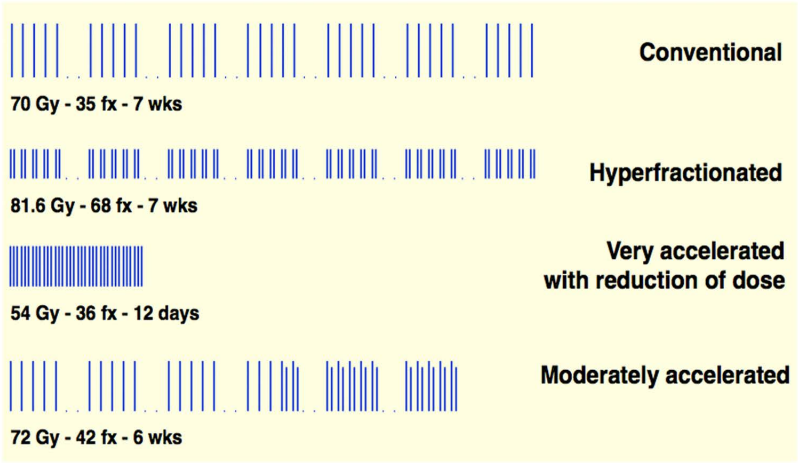


Results of large retrospective studies of head and neck tumors estimating the amount of repopulation (in terms of "dose counteracted per day") when overall treatment times were longer than 25 days.

So, armed with all this new information about fractionation sensitivity and proliferative response, what becomes the goal of radiotherapy?

- Deliver the dose in the shortest possible time without exceeding early-responding tissue tolerance
  - This will improve tumor control because the time available for (accelerated) tumor cell proliferation is minimized
- Use as low dose per fraction as possible without prolonging overall treatment time
  - This will increase the biological effect on tumors relative to late-responding normal tissues

1. this is often easier said than done, but even so, these ideas led to several new approaches to fractionation



1. **<u>hyperfractionation</u>: the use of smaller than conventional-sized dose fractions delivered 2 or 3 times daily (i.e., 2 doses of 1.3 Gy per day vs. one dose of 2.0 Gy per day) in the same overall treatment time, but to a somewhat higher total dose**

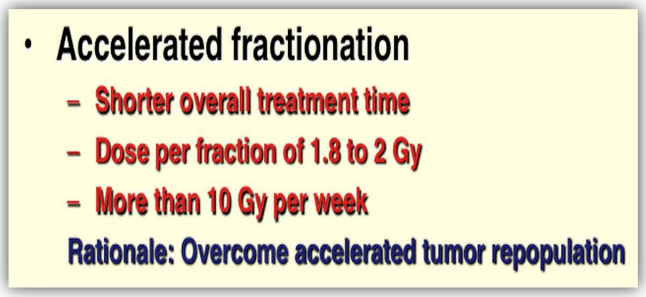
a] hyperfractionation is indicated in the case where you want to take advantage of differences in α/β ratios between tumors and late-responding normal tissues, knowing that they can tolerate higher total doses if delivered in smaller increments

- **Conventional fractionation**
  - **Daily doses (d) of 1.8 to 2 Gy**
  - **Dose per week of 9 to 10 Gy**
  - **Total dose (D) of 40 to 70 Gy**
- **Hyperfractionation**
  - **The number of fractions (N) is increased**
  - **T is kept the same**
  - **Dose per fraction (d) less than 1.8 Gy**
  - **Two fractions per day (t)**

Rationale: Spares late responding tissues

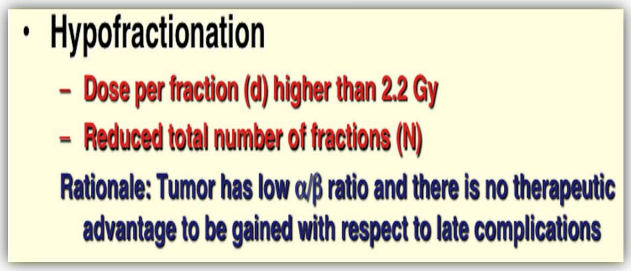
2. **<u>accelerated fractionation</u>: the use of 2 or 3 dose fractions per day, of about the conventional size, and to the same total dose, but in a shorter overall treatment time**

a] **accelerated fractionation is indicated in the case where you want to combat a tumor that proliferates rapidly, in other words, where the production of new tumor cells over the course of 6-7 weeks partially negates the killing effects of radiation**



3. **<u>hypofractionation</u>: the use of fewer (or one), larger-than-conventional-sized dose fractions, and in shorter overall treatment times and/or somewhat lower total doses** (e.g., SRS/SBRT/SABR, intraoperative radiotherapy, etc.)

a] **hypofractionation is indicated for tumors thought to have LOW α/β ratios, that is, are more late responding normal tissue-like and would therefore be preferentially damaged by larger dose fractions - prostate cancer falls into this category, and to a lesser extent, breast cancer**



1) why is there current controversy about hypofractionation?

<u>Answer</u>: the issue is NOT whether hypofractionation works - because there have been some impressive clinical results - but rather, ***what kind of biology governs the response to high/very high dose fractions***?

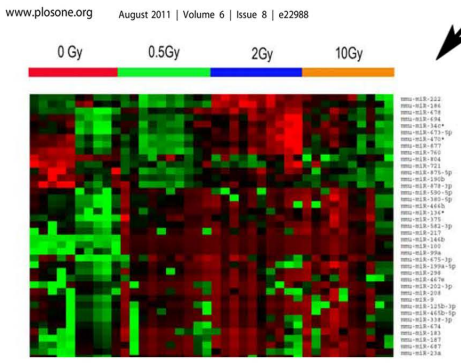
2) two opposing camps:

- **The "Hypofractionation works because 'new biology' happens after high doses, but not after low doses. As such, the linear-quadratic isoeffect model doesn't apply (or needs to be changed)" camp.**

vs.

- **The "There's no need to invoke 'new biology' to explain the success of hypofractionation, and the linear-quadratic model works just fine over a broader range of doses than we originally thought" camp.**

Evidence FOR 'new biology':



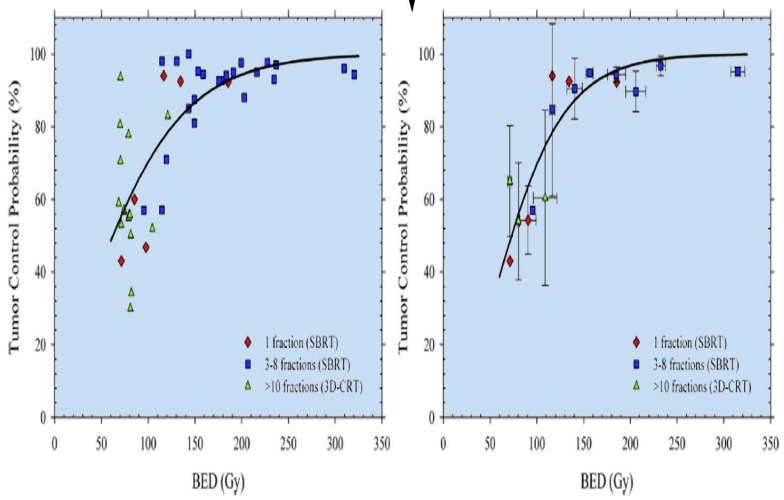
Select miRNA expression profiles in murine plasma 6 hours following TBI with low vs. high single doses of γ-rays. Compared to control, the same miRNA may be up- or down-regulated differentially depending on radiation dose.

(Red = an up-regulated miRNA; Green = a down-regulated miRNA; Black = little or no change compared to control)

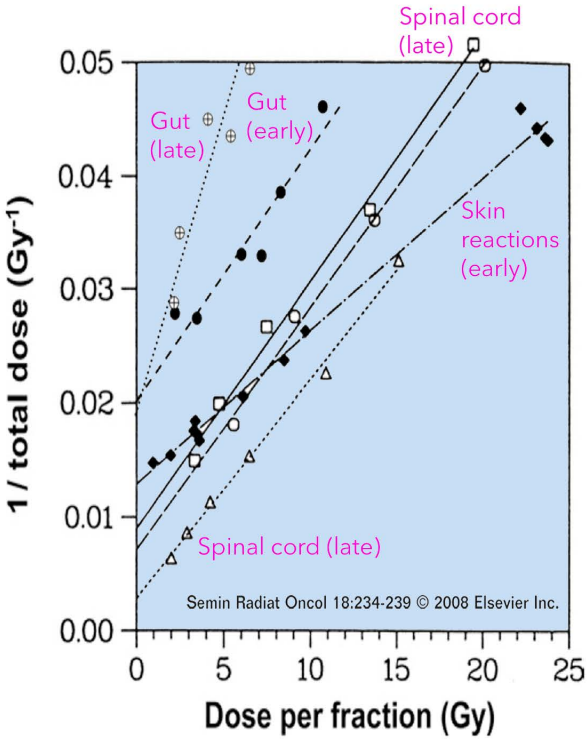
- **Different patterns of gene expression after high radiation doses than low radiation doses.**
- **Immunological response to tumor cell killing differs after high vs. low doses. (SRS/SBRT doses more likely to cause a vigorous immune response than lower doses.)**
- **Some evidence that effects on tumor vasculature and stroma (apoptosis?) are different at high doses.**
- **The alpha-beta model significantly overestimates toxicity to surrounding normal tissues, particularly late-responding ones, so it must be wrong.**
- **Some evidence that human tumors have lower α/β ratios than first thought, which would limit the utility of hyperfractionation**

Evidence AGAINST 'new biology':

- **Many (older) fractionation experiments with rodents show that reciprocal dose isoeffect curves remain linear up to single doses of ~25 Gy. (This would only be true if the alpha-beta model *did* work.)**
- **For a given BED "dose" (i.e., also part of the alpha-beta model), the same amount of tumor control is achieved *regardless of how that dose was delivered, i.e., conventional, hyper- or hypofractionated.* This argues against there being anything unique and different about hypofractionation.**



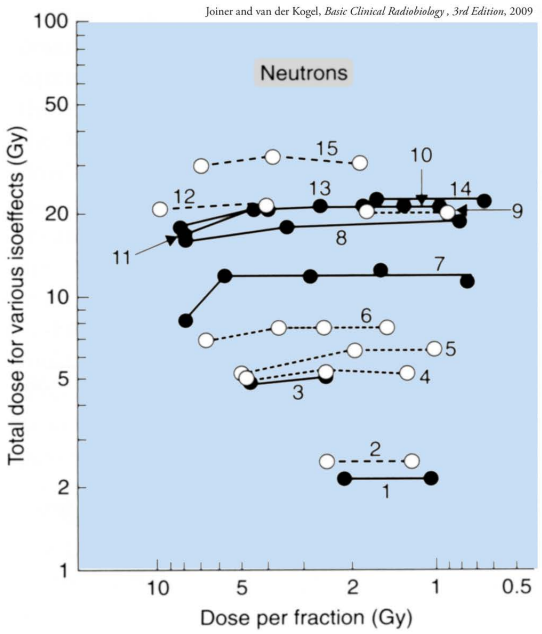
Tumor control probability (TCP) as a function of biologically effective dose (BED) for stage I non-small cell lung cancer. Left, symbols show local control rates (≥2 years) from a pooled analysis reported by Mehta et al (27) with symbols distinguishing conventional and stereotactic body radiation therapy (SBRT) fractionations. Right, weighted mean TCP probabilities calculated to compensate for the different numbers of patients in each study. Solid lines show linear quadratic-based fits to the data showing that within the limits of clinical data, the efficacy of single doses, a few SBRT fractions, and conventional radiation therapy produce the same overall TCP for the same BED.



Isoeffect data for late response from 3 (□ ○ Δ) different regions of the rat spinal cord, for acute skin reactions (♦) in mice, and for early (●) and late (⊕) murine intestinal damage. The data are plotted in a "reciprocal-dose F_e" form such that, if they follow an LQ relationship, the points fall on a straight line.

The α/β model and high LET radiotherapy

There isn't much information available on α/β ratios or isoeffect curves for high LET radiotherapy (because it's uncommon), but as might be expected for tissues with exponential survival/dose response curves, ***the resulting isoeffect curves for, in this case, neutrons, are essentially flat (very high α/β ratio)***



Summary of published data on isoeffect curves for neutrons as a function of dose per fraction in various tissues of mice and rats. Broken lines indicate data on acute-responding tissues; solid lines are for late-responding tissues. Key: 1, thyroid function; 2, haemopoietic colonies; 3, vertebral growth; 4, spermatogenic colonies; 5, fibrosarcomas; 6, jejunum colonies; 7, lung LD_{50}; 8, lumbar nerve root function; 9 and 12, skin desquamation; 10, skin contraction; 11, skin late changes; 13, spinal cord; 14, oral mucosa necrosis; 15, skin necrosis.

Withers et al., IJROBP *8*:2071-2076, 1982

D. **Common Clinical Scenarios**: illustrating the day-to-day use of the linear-quadratic model

1. ***Changing/"Equivalent-izing" the Dose per Fraction*** - simplest case in which, for whatever reason, the dose per fraction needs to be changed from what was originally planned and a new, biologically-equivalent total dose needs to be calculated for the new dose per fraction (assumes overall treatment time remains approximately the same)

a] assuming the α/β ratio is known for the tissue at risk...

$$\text{TOTAL DOSE \#2 / TOTAL DOSE \#1} = n_2\, d_2 / n_1\, d_1$$

$$= \frac{1 + d1\,(\beta/\alpha)}{1 + d2\,(\beta/\alpha)}$$

$$= \frac{\alpha/\beta + d_1}{\alpha/\beta + d_2}$$

b] variation on a theme: increasingly, radiation dose information in clinical trials is reported in terms of *"equivalent total dose in 2 Gy fractions"*, aka EQD_2

$$EQD_2 = D\,[d + \alpha/\beta \;/\; 2 + \alpha/\beta\,]$$

where D = total dose actually delivered, and d = dose per fraction actually used

c] BUT, isn't it necessary to assess how a planned change in dose per fraction effects *both* the tumor and critical normal tissue(s) simultaneously, not just one of them? Answer: absolutely!

1. to accomplish this, you need to determine a **Biologically Effective Dose** (**BED**) for each tissue at risk, calibrated to that tissue's own α/β ratio

$$\text{"(Iso)Effect"} = e^{-(\alpha D + \beta D^2)}$$

$$E = nd\,(\alpha + \beta d)$$

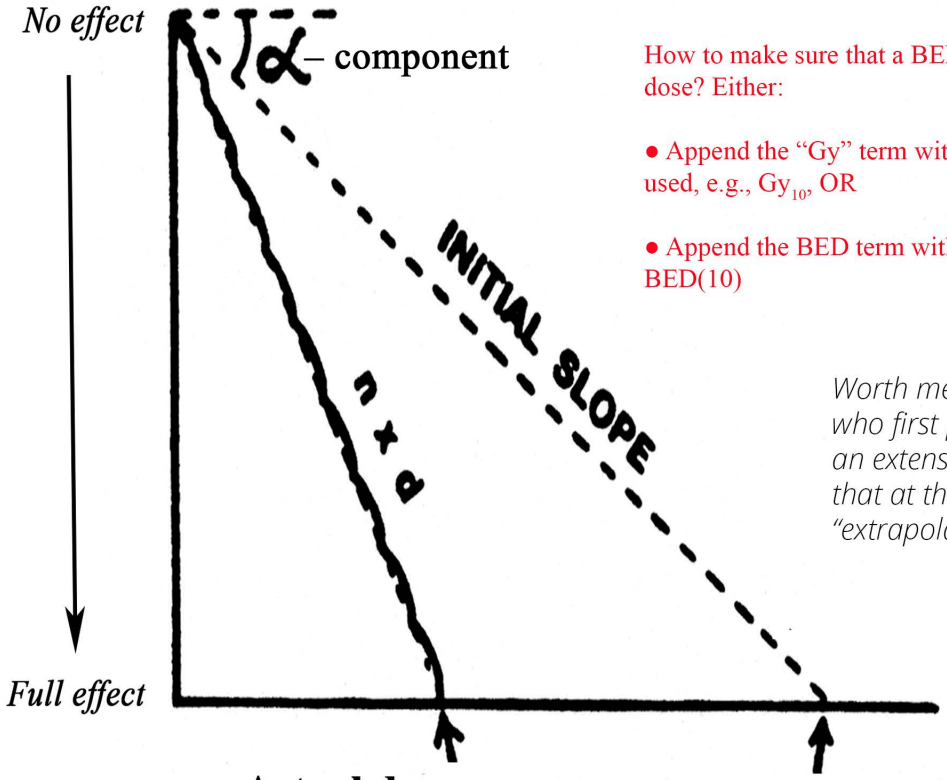
$$BED = nd\,(1 + d/_{\alpha/\beta})$$

Biologically Effective Dose — Total Dose — "Relative Effectiveness" Correction

n = number of fractions
d = dose per fraction
D = total dose (n x d)

BED = in units of dose, but corrected for the particular α/β ratio, i.e., (Gy_{10} or Gy_3)

PLEASE remember that the BED is an extrapolate pegged to a particular value of α/β and as such is not a literal dose



Actual dose, *i.e., number of fractions (n) times dose per fraction (d) to achieve the "full" endpoint*

BED "dose", *which is based on an extrapolate of the initial slope of the tissue's dose response curve*

How to make sure that a BED is not confused with an actual dose? Either:

- Append the "Gy" term with a subscript indicating the α/β ratio used, e.g., Gy_{10}, OR
- Append the BED term with the α/β ratio in parentheses, e.g., BED(10)

Worth mentioning: It was Dr. Barendsen who first proposed the BED concept as an extension of the α/βmodel (except that at the time, he called it "ERD", "extrapolated response dose")

Barendsen, IJROBP 8:1981-1997, 1982

How to work with BED's

30 x 2 Gy = 60 Gy :	BED of 72 Gy_{10} and 100 Gy_3	**Conventional**
35 x 1.8 Gy = 63 Gy :	BED of 74.3 Gy_{10} and 100.8 Gy_3	
68 x 1.2 Gy = 81.6 Gy :	BED of 91.4 Gy_{10} and 114 Gy_3	**Hyperfractionated**
70 x 1.15 Gy = 80.5 Gy :	BED of 89.8 Gy_{10} and 111.4 Gy_3	
20 x 2.8 Gy = 56 Gy :	BED of 71.7 Gy_{10} and 108 Gy_3	
16 x 3.4 Gy = 54.4 Gy :	BED of 73 Gy_{10} and 116.1 Gy_3	**Hypofractionated**
3 x 15 Gy = 45 Gy :	BED of 112.5 Gy_{10} and 270 Gy_3	

- Calculate the BED's for conventional fractionation, and compare them to the new BED's for hyper- or hypofractionation

- Gy_3's can be compared ***qualitatively*** wth Gy_3's, and Gy_{10}'s wth Gy_{10}'s, but NOT Gy_3's with Gy_{10}'s (because they're based on different dose response curve shapes)

- If Gy_{10} values increase, it suggests that the new treatment regimen could yield better tumor control (for most tumors), but also the possibility of worse acute reactions in normal tissues

- If Gy_3 vaules increase, it suggests the possibility that late normal tissue complications would increase, and/or that control of tumors with low α/β ratios would be improved

- Given the variability in individual patient (and tumor) response however, **in practice, it would take an increase in BED of at least 15% in order to detect clinically an increase in complication frequency or tumor control**

Changing the Overall Treatment Time - such a correction might be needed for longer overall treatment times where rapid tumor cell repopulation threatens to compromise the effectiveness of radiotherapy

1. historically, the α/β model has been criticized because it didn't incorporate a parameter that could account for the effects of repopulation on BEDs

2. today though, there is a way to do this, but it requires knowledge of additional tumor parameters that aren't readily available...but can be *estimated* for calculation purposes

$$BED = nd\left(1 + \frac{d}{\alpha/\beta}\right) - \left(\frac{0.693\ (T\text{-}T_k)}{\alpha\ T_p}\right)$$

Note that this term is subtracted from the BED, i.e. that *the effect of cell proliferation will decrease the BED (and EQD2)*

where T = overall treatment time, and T_k = delay time before proliferation begins

Tp = the "effective clonogen doubling time" which is akin to Tpot, except determined during treatment instead of prior to the start of treatment

a) **performing this calculation (using representative values for Tp, Tk and α) allows an estimation of how much of the BED is "lost" to cell proliferation**

1. if the overall treatment time is long (or the treatment interrupted), and Tp is short, the loss of biological effectiveness could be quite large, as much as 25%

What about "incomplete repair"?

Over time, it has become clear that at least some normal tissues (late-responding ones in general, CNS in particular) repair damage more slowly than originally thought, meaning that even a 6 hour interval between twice daily fractions might not be sufficient for all the repair to occur

a. therefore, a correction to the BED equation (and a modified way of calculating the EQD2) has been proposed to account for this

$$EQD_2 = D\frac{d(1 + H_m) + (\alpha/\beta)}{2 + (\alpha/\beta)}$$

...with "H_m" defined as the incomplete repair correction factor.

1. these factors vary with the assumed half time of repair for the tissue at risk (for CNS, ~5 hours might be the most appropriate and maybe ~4 hours for subcutaneous fibrosis), and the interfraction interval used

2. ***Note that the effect of incomplete repair will increase the BED (and EQD2)***

BED's have been around for over 35 years...is there now enough data available for human solid tumors to come up with any kind of "consensus statement(s)"?

1. An α/β ratio of 10 Gy is now routinely used for calculation purposes for most acutely responding normal tissues and tumors, and 3 Gy for most late-responding normal tissues. Exceptions: Breast cancer = 4 Gy; Prostate cancer ≈ 1.8 Gy; Melanoma ≈ 0.6 Gy; NSCLC ≈ 20 Gy; CNS and kidney ≈ 2 Gy.

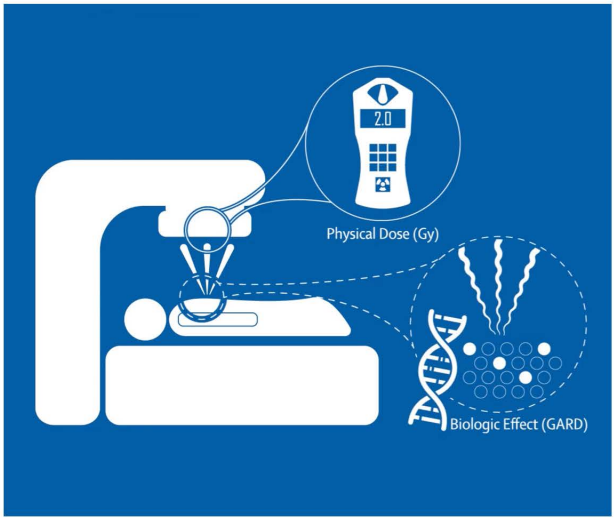
2. More robust values of α (~0.35 Gy^{-1}), Tk (~7 days for most mucosal linings, twice that for skin, and ~27 days for tumors) and Tp (~3 days for mucosa and rapidly proliferating tumors) are now available and can be used for modeling purposes.

3. BED's corresponding to tolerance limits for late responding normal tissues have become better defined. For most late responding tissues (assuming α/β = 3 Gy), **117 Gy_3**'s shouldn't be exceeded, unless the treatment volume can be significantly reduced.

→ Arguably, all these new numbers are best applied to treatment planning for head and neck cancer.

E. **The Future of the Linear-Quadratic Model...** what would be needed to make it more useful than it already is?

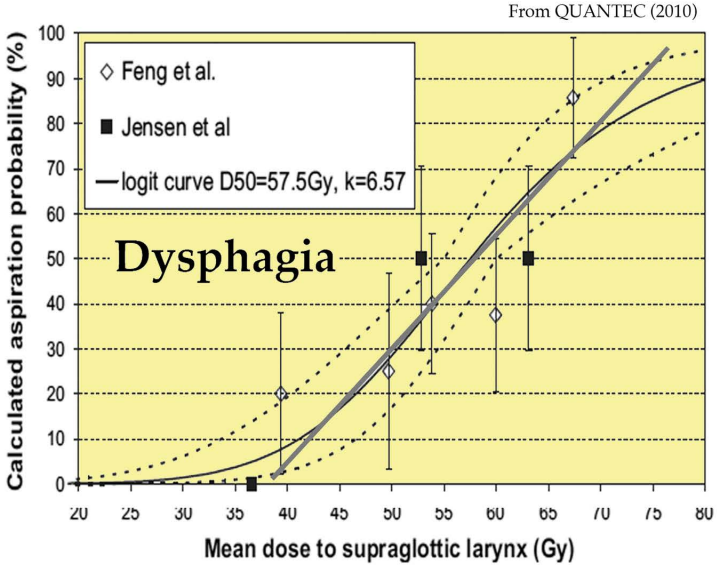
1) **ultimately, what we'd like to be able to do is paint a biological dose distribution on top of all our physical dose distributions** – are we there yet? Answer: we have a *fair* handle on a few pieces of the puzzle (e.g., α/β ratios for various normal tissues and tumors, proliferation patterns after irradiation, dose response curve shapes, etc.), but for others, our knowledge is limited (half-times of repair), rudimentary (volume effects) or non-existent (what happens when other treatment modalities are added to radiation, patient-related factors, what if it's a retreatment rather than an initial treatment, novel radiotherapy techniques, etc.)



a. one step in this direction has been the development of GARD, the "genome-adjusted radiation dose", which can be used to adjust tumor BEDs on a patient-by-patient, tumor-by-tumor basis; ***across a number of tumor types, GARD was associated with time to recurrence and overall survival in patients treated with radiation whereas physical dose was not***

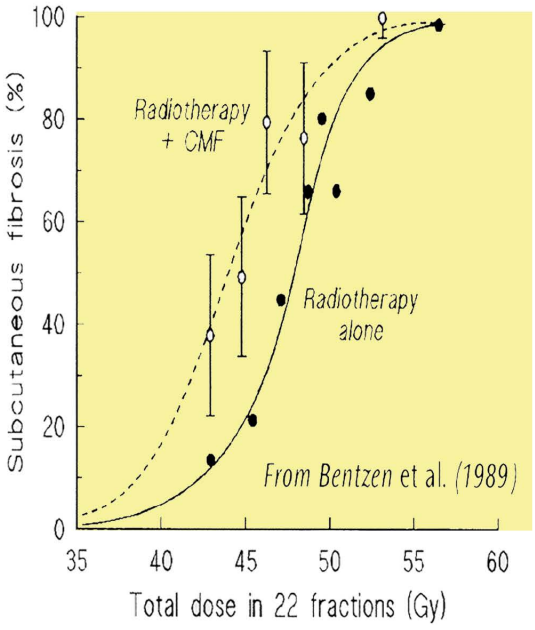
b. in addition, ***GARD isn't simply a predictor of outcomes in general, but rather is a predictor of outcomes after radiotherapy specifically***

b. another factor of importance for the calculation of normal tissues complication and tumor control probabilities (NTCP and TCP) is the shape of the clinical dose repsonse curves, and in particular, the steepness of these curves (the γ factor); we have reasonable info for some normal tissues and tumors, but nowhere near all of them!

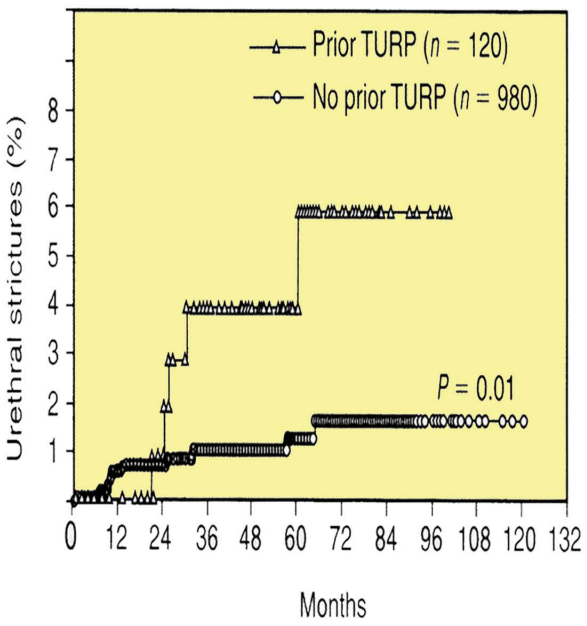


c. and last but by no means least, **there are all sorts of other treatment- and patient-related factors that also can influence outcome that we currently have little or no idea how to model**, including:

1. tumor hypoxia; combinations and sequencing of chemotherapy, targeted therapy, immunotherapy and/or surgery; whether the radiotherapy is *de novo* or a retreatment, etc.



Effect of adjuvant chemotherapy on the incidence of radiation-induced subcutaneous fibrosis. ●, Post-mastectomy radiotherapy alone; ○, radiotherapy plus adjuvant CMF



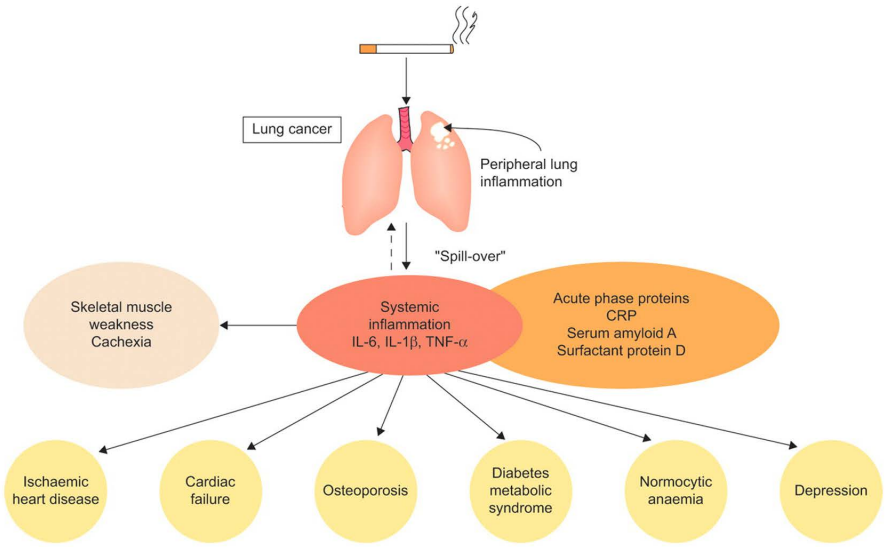
Actuarial incidence of urethral stricture after 3D conformal radiotherapy for prostate cancer among patients with and without a prior history of transurethral resection of the prostate. From Sandhu et al. (2000)

How the 4R's can affect α/β ratios

Int. J. Radiation Oncology Biol. Phys., Vol 11, pp. 87–96, 1985

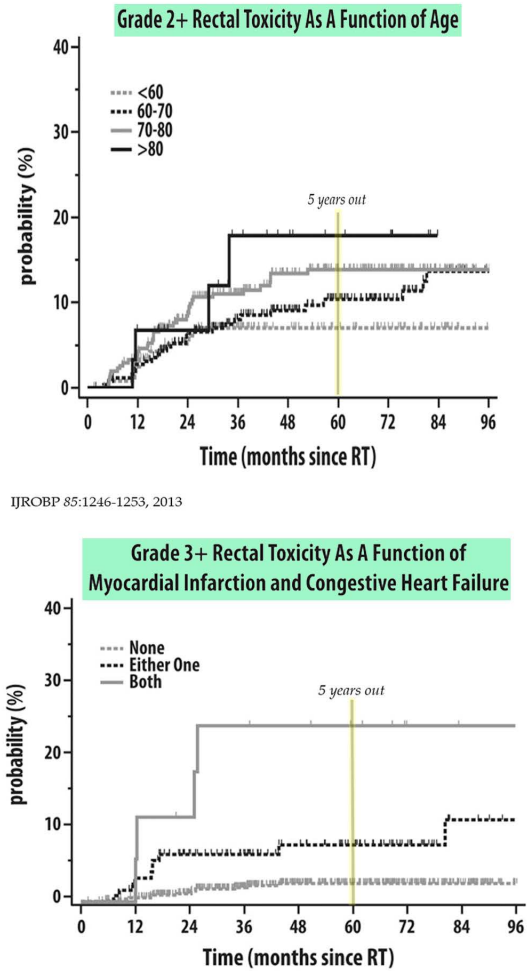
Factor	Effect	Influence on α/β ratio
Reoxygenation	Increased cell killing in fractionated regimens relative to single dose	Increase
Repopulation	Increased isoeffect dose in protracted regimens	Decrease
Redistribution	Enter *more* sensitive phases of cell cycle in fractionated regimens	Increase
Redistribution	Enter *less* sensitive phases of cell cycle in fractionated regimens	Decrease
Repair	Short intervals between fractions might lead to incomplete repair	Increase
Repair	Slow repair might occur only with fractionated regimens	Decrease

2. and if anything, the patient-related factors are even more confounding:



Lung cancer patients are particularly prone to having at least one comorbidity (>50%), and often, more than one...these can pre-date the cancer, or else be caused by it. No big surprise, but most are related - directly or indirectly - to a history of smoking.

For other types of cancer, obesity is a common comorbid condition (not to mention a likely causative factor), and it can give rise to a whole bunch of others.



Likelihood of experiencing rectal complications of prostate cancer radiotherapy as a function of patient's age (upper panel) or concurrent heart disease (lower panel)

3) **A further consideration for the future of the LQ model is how well it will hold up in the face of novel ways of delivering radiotherapy**

a. What about things like ***GRID***, ***Mini-Beam*** or ***Microbeam Radiotherapy*** ***(MRT)***, where the daily dose is delivered non-uniformly in volume, i.e., that the entire treatment volume is "striped" by beamlets of differing sizes, but with unirradiated zones in between?

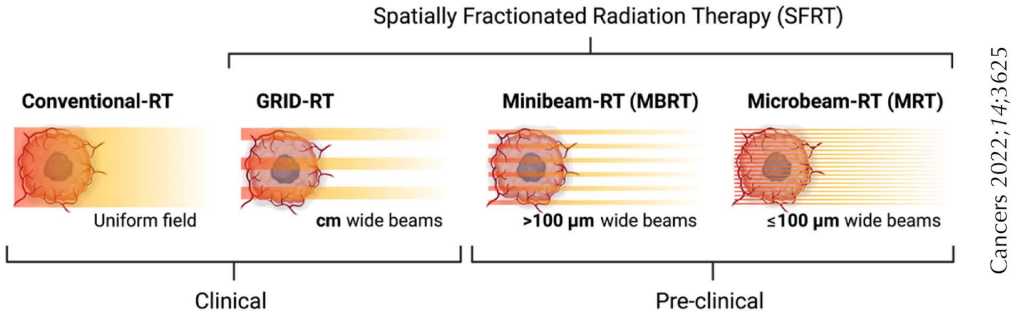


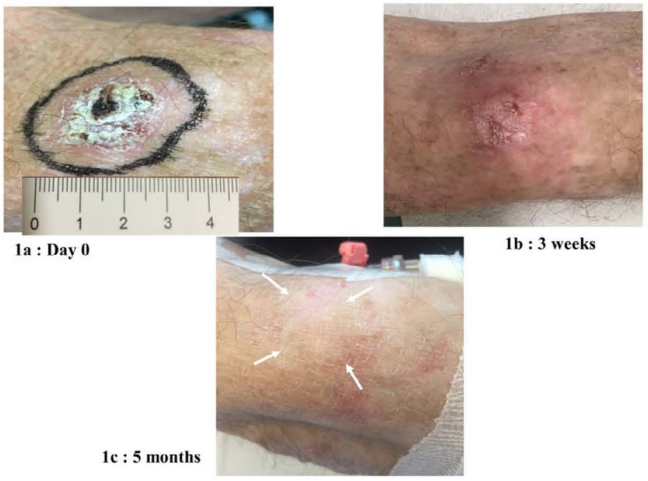
Illustration of radiation **spatial distribution of SFRT.** Starting from conventional RT where radiation is seamless, SFRT radiation is spatially fractionated in increasing smaller scales – from clinical GRID-RT (and Lattice therapy not shown) to preclinical MBRT to MRT.

b. Or things like ***FLASH radiotherapy***, where the total dose is delivered to the treatment volume at an extremely high dose rate (at least 40 Gy/second), either all at once, or in pulses separated in time?

Cat with deeply-infiltrating SCC of the nose treated with a single dose of 27 Gy FLASH (electrons)

First human patient, a 75 year old male with heavily-pretreated cutaneous T-cell lymphoma of ~20 years duration, received a single dose of 15 Gy FLASH electrons. (Overall treatment time = 90 ms.)

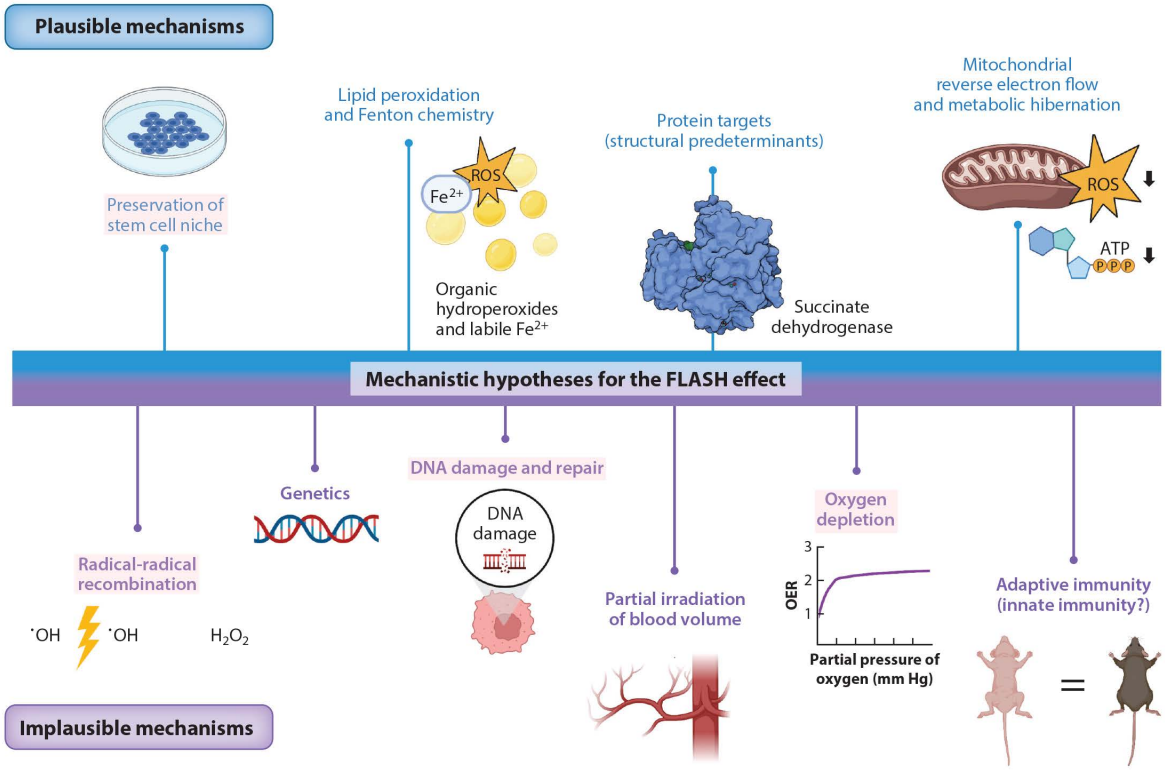
Patient claimed he saw a blue flash coming from the linac during/after treatment!



Temporal evolution of the treated lesion: (a) before treatment; the limits of th PTV are delineated in black; (b) at 3 weeks, at the peak of skin reactions (grade 1 epithelitis NCI-CTCAE v 5.0); (c) at 5 months.

1] *Both of these novel techniques spare normal tissues but not tumors – suggesting a therapeutic advantage – although the exact mechanisms involved remain up for debate*

Possible Mechanisms for the FLASH effect?



Mechanistic summary: Why does FLASH kill tumors? (*Top*) Plausible mechanisms that can account for the FLASH effect include stem cell niche preservation, differential lipid peroxidation and Fenton chemistry, structural predeterminants in specific protein classes, and changes in mitochondrial metabolism such as reverse electron flow or metabolic hibernation. (*Bottom*) Implausible mechanisms include those involving radical-radical recombination, genetic predisposition, DNA damage and repair, partial blood volume irradiation, oxygen depletion, and adaptive immunity (not exclusive of innate immunity).

Annu. Rev. Cancer Biol. 2023.7:1-21

Appendix Materials

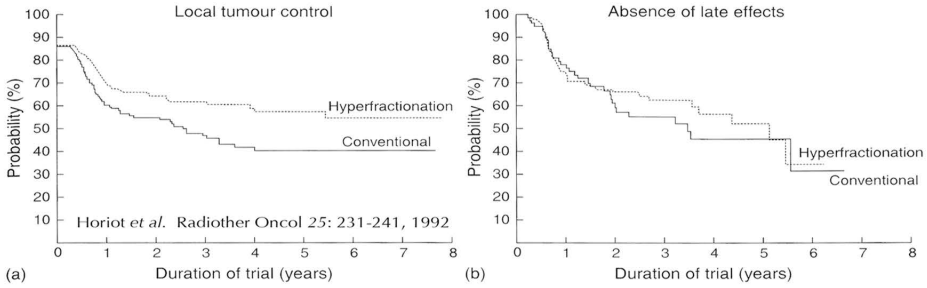
Clinical Trials about Fractionation

1. **EORTC #22791** - a dose escalation study of hyperfractionation in squamous cell carcinoma of the oropharynx (see: Horiot *et al*. Radiother Oncol *25*: 231-241, 1992)

a] the question asked was: *Can we achieve improved tumor control by escalating the total dose, yet with little or no change in late effects, by using smaller-than-conventional doses per fraction? (Overall treatment time kept constant at 7 weeks)*

Conventional Arm = 35 daily fractions of 2 Gy to a total dose of 70 Gy

Hyperfractionated Arm = up to 70 fractions of 1.15 Gy twice per day, to a total dose of 80.5 Gy



Results of the EORTC (22791) trial of dose-escalated hyperfractionation. (a) Loco-regional tumour control (log-rank $p = 0.02$); (b) patients free of late radiation effects, grade 2 or worse (log-rank $p = 0.72$).

Improved tumor control

Little or no change in late effects

2. **RTOG #9003** - similar to the EORTC trial above, but with **additional accelerated fractionation arms**

(see: IJROBP *48*: 7-16, 2000; 15 year update: IJROBP *89(1)*: 13-20, 2014)

Standard Fractionation = 35 daily fractions of 2 Gy to 70 Gy, in 7 weeks

Hyperfractionation = 68 twice daily fractions of 1.2 Gy to 81.6 Gy in 7 weeks

Accelerated Fractionation with Concomittant Boost = 42 fractions of 1.7 Gy to 72 Gy in 6 weeks

Accelerated with Break = 42 fractions of 1.6 Gy to 67.2 Gy in 6 weeks, with 2 week break after 38.4 Gy

Results:

a) **both hyperfractionation and accelerated fractionation decreased the locoregional failure rate by 19% compared to standard fractionation** in patients (nearly 1,100 of them!) with locally-advanced SCC of the head and neck

b) **the change from an overall treatment time of 7 weeks to 6 weeks was associated with a significant increase in Grade 3, 4 and 5 acute complications** (e.g., prolonged feeding tube use)...even with the break

1. the severe acute complications also precipitated worse late effects (”***consequential late effects***”)

c) after 15 years of followup, **the only treatment that showed a therapeutic gain compared to standard fractionation was the hyperfractionated arm**, i.e., that it improved tumor control but without also making normal tissue complications worse

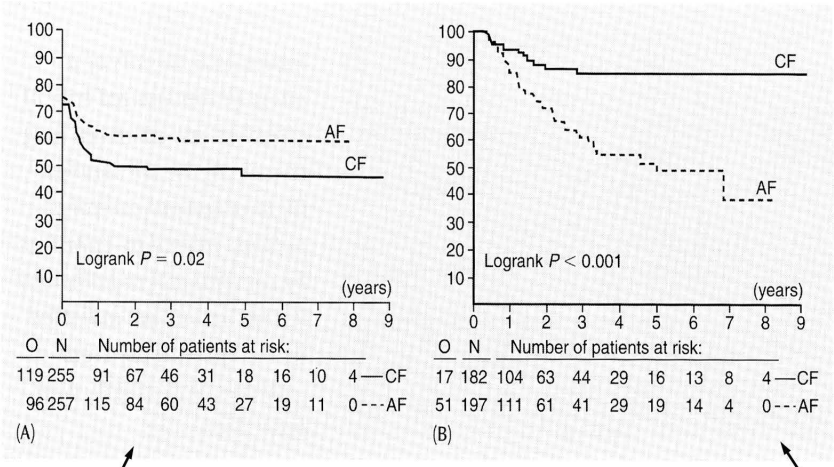
3. **EORTC #22851** - a study of accelerated fractionation, asking the question *"Does shortening the overall treatment time (with everything else being approximately equal) produce better tumor control in head and neck cancer, yet with little or no change in late effects (and also, to get an idea of how much worse early reactions would be when treatment was accelerated)"*?

Conventional Arm = 35-40 daily fractions of 1.8-2.0 Gy each in an overall time of 54 days (maximum total dose of 80 Gy)

Accelerated Arm = 45 fractions of 1.6 Gy given 3x daily (with 4-6 hour interval) in an overall time of 35 days (total dose of 72 Gy, given as split course with treatments on days 1-8, break of 7-10 days, treat again for 17 days)

a] early effects were also quite bad (as expected) - 38% of patients required hospitalization for Grade 3-4 mucositis, compared to only about 7% in the conventional arm

Radiother Oncol 44(2):111-121, 1997



Results of the EORTC (22851) trial of accelerated fractionation. (A) Loco-regional tumour control (logrank P = 0.02); (B) patients free of severe radiation effects, grade 3 and 4 (logrank P < 0.001).

18% increase in local tumor control at 5 years in the accelerated arm compared to the conventional arm

Much worse late effects in the accelerated arm (only 63% free of complications at 3 years) compared to the conventional arm (85% free of Grade 3-4 complications at 3 years)

More consequential late effects and possibly, incomplete repair as well (i.e., 4 hours between fractions)

BOTTOM LINE: *accelerated fractionation does improve tumor control even for lower total doses, but at the expense of severe early reactions that could make late complications worse; also, cannot get away with anything less than 6 hours between fractions when using multiple fractions per day, or else you risk incomplete repair in late-responding tissues, also likely to make late complications worse*

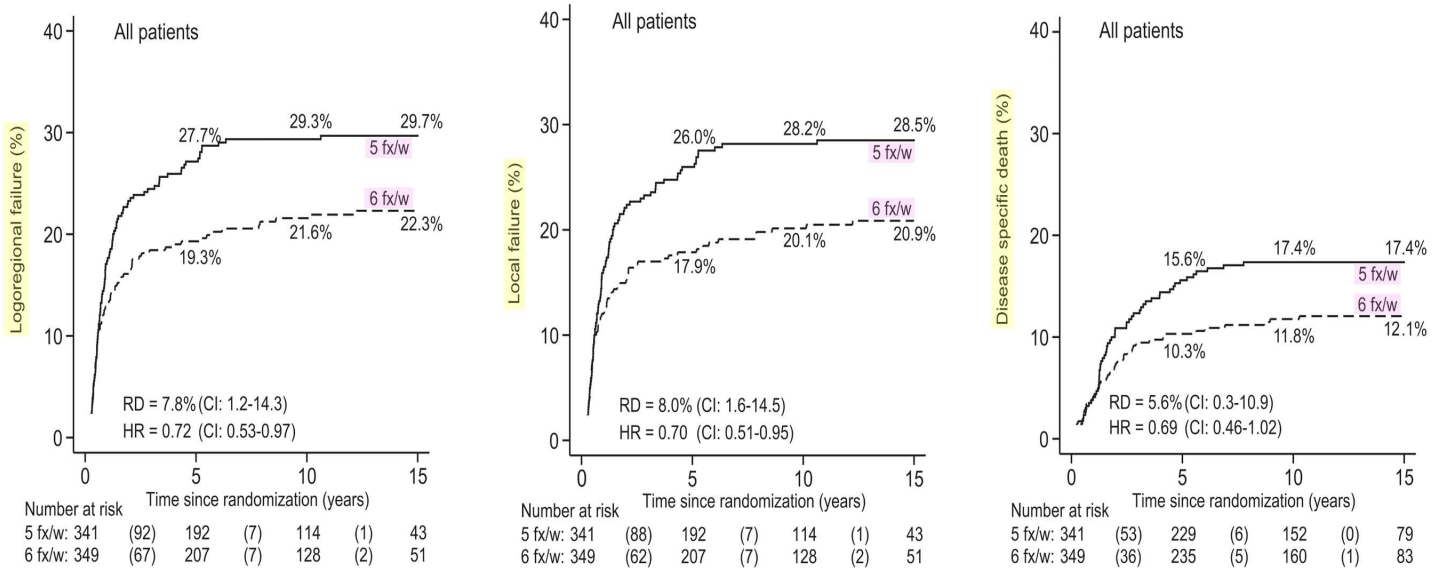
4. **DAHANCA 6 & 7** - large, accelerated fractionation trials in head and neck cancer, seeing the effect of shortening the overall treatment time by about a week (by delivering 6 fractions per week instead of 5)

Eligibility criteria: previously untreated Stages I-IV squamous cell carcinoma of the glottic larynx, with no distant disease (Total accrual = 1,485 patients)

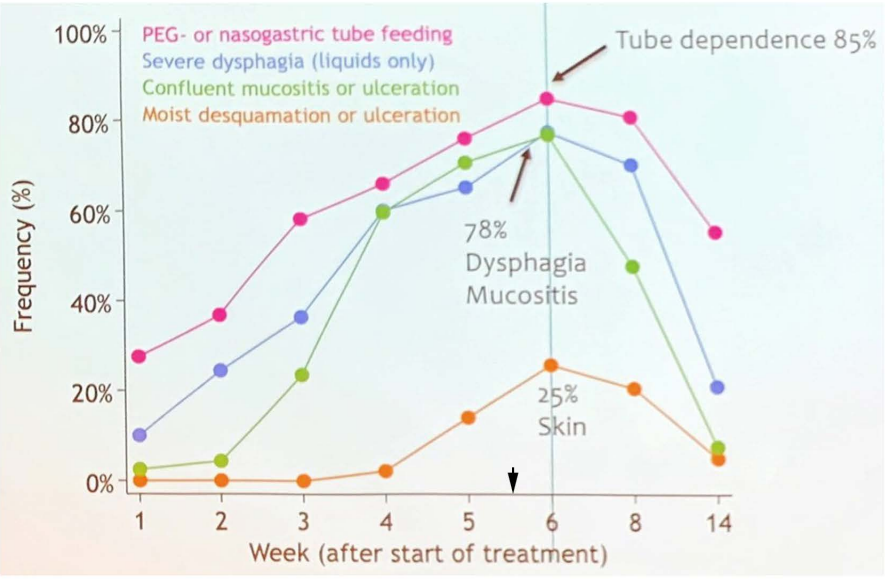
Control Arm: 62-68 Gy in 2 Gy fractions, 5 fractions per week, median overall time = **46 days**

Accelerated Arm: 62-68 Gy in 2 Gy fractions, 6 fractions per week (6-8 hours between fractions on the day two fractions were given), median overall time = **38 days**

N.M. Lyhne et al./Radiotherapy and Oncology 117 (2015) 91–98

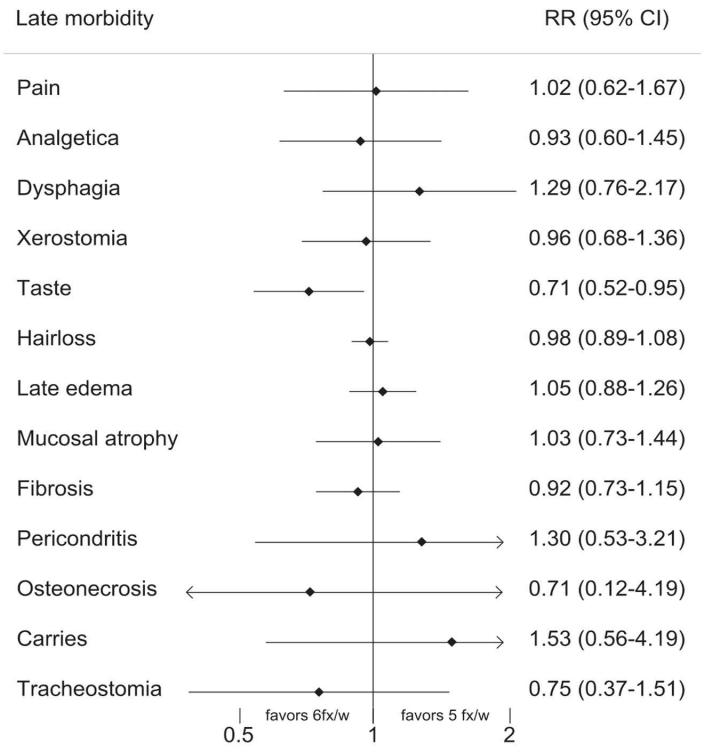


For three tumor endpoints (locoregional failure rate, local failure rate and disease-specific death), the accelerated arm was superior, although not for overall survival.



Time course for, and frequency of, Grade 3+ acute complications in H&N cancer patients randomized to the accelerated arms of the DAHANCA 6 and 7 clinical trials. (Frequencies were about half this, or less, in the control arms.)

Treatment was complete at about the 5.5 week point.



Also as expected, there was little or no change in the incidence of late effects in the accelerated arm compared to the control arm, assessed 6 months after the completion of treatment.

4. **Continuous Hyperfractionated Accelerated Radiotherapy (CHART)** - a "hybrid" trial using both low doses per fraction multiple times per day and highly accelerated treatment; designed to really test the limits of the alpha-beta model!

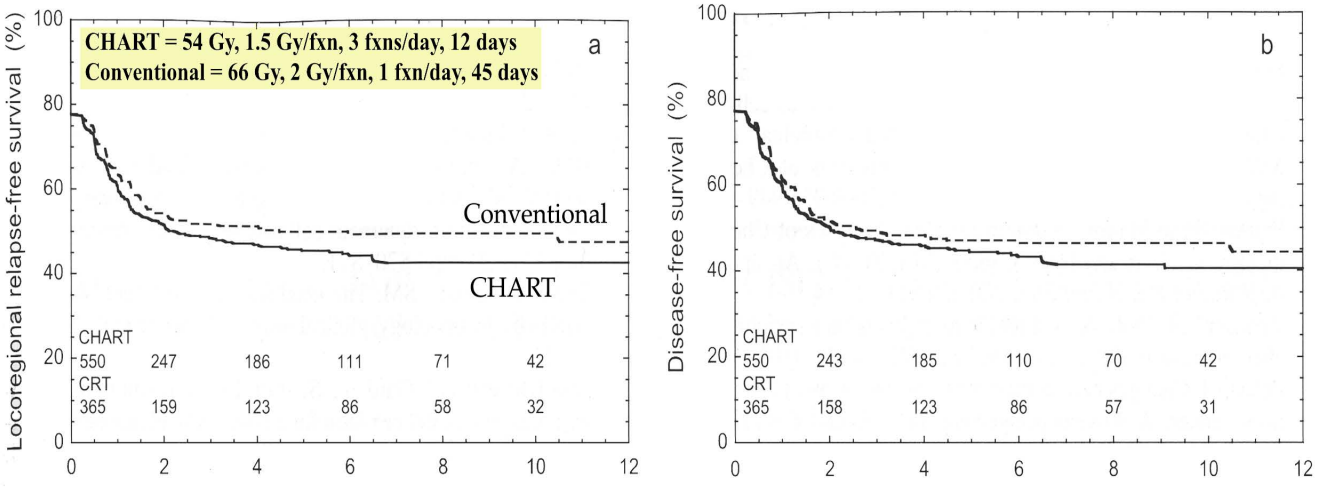
a] two large trials were completed during the 1990's, one in SCC of the head and neck (918 patients) and one in non-small cell lung cancer (563 patients)

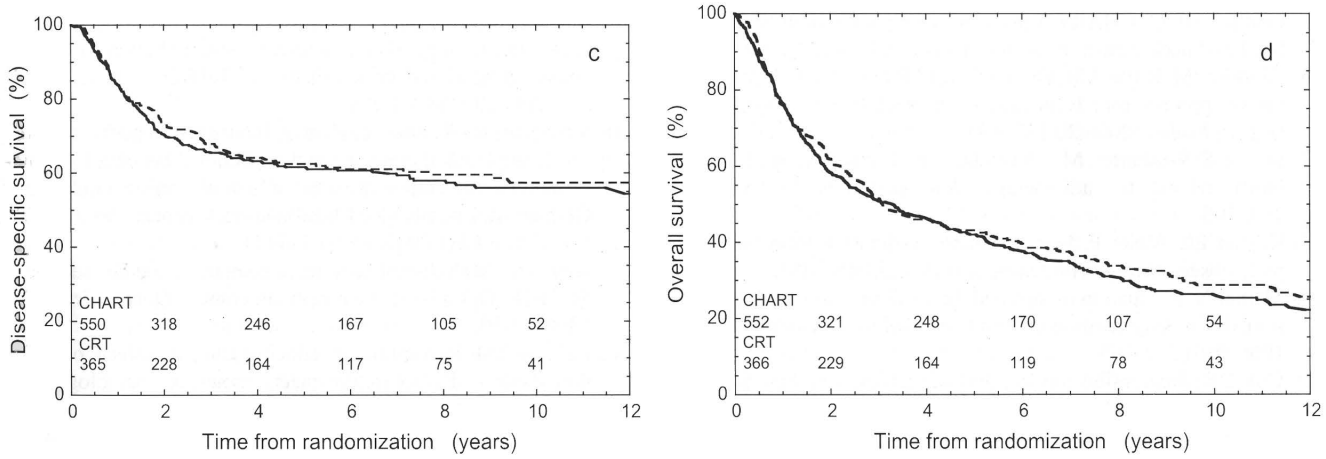
b] head and neck trial (see: Dische *et al.* Radiother Oncol *44*: 123-136, 1997) -

CHART = **36 fractions of 1.5 Gy, given 3x per day (6 hours between fractions), 7 days per week to a total dose of 54 Gy...all in 12 days!**

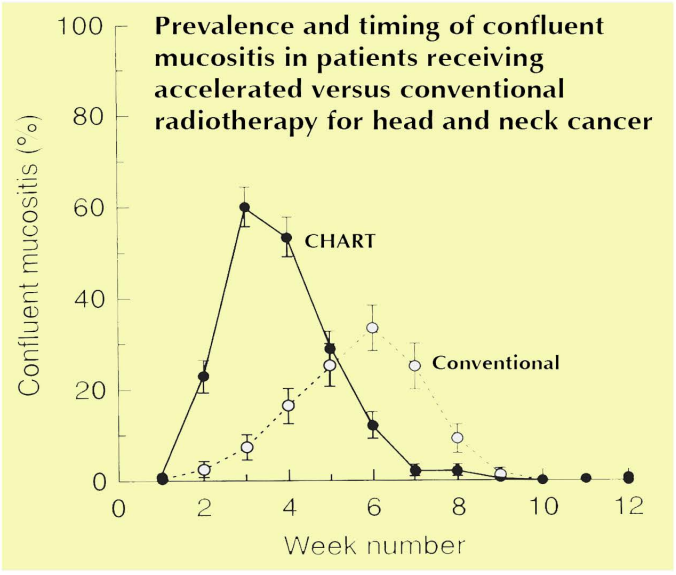
Conventional = 33 daily fractions of 2 Gy, 5 days per week, to a total dose of 66 Gy in a total of 45 days

Saunders *et al.* IJROBP 77: 3-8, 2010





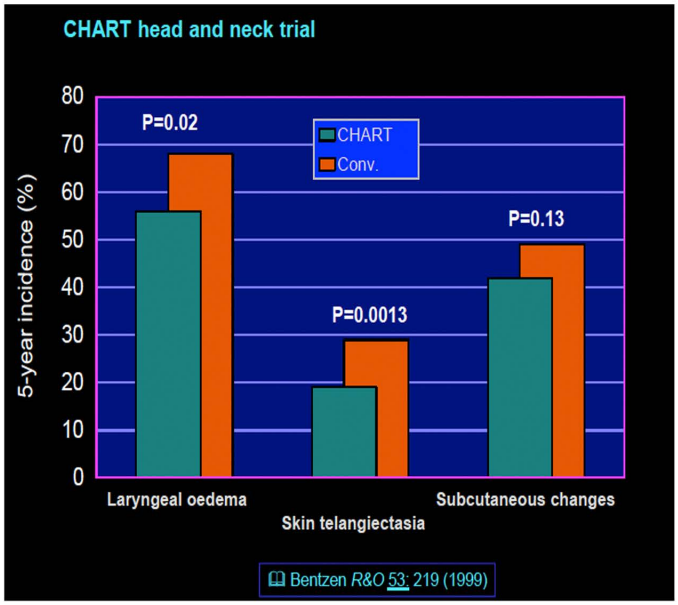
Locoregional relapse-free survival (a), disease-free survival (b), disease-specific survival (c), and overall survival (d) after continuous, hyperfractionated, accelerated radiotherapy (CHART) alone (solid lines) or after conventional radiotherapy (CRT) (dashed lines). The number of patients at risk of relapse or death is shown from randomization to 12 years after CHART or CRT at 2-year intervals.



Joiner and van der Kogel, *Basic Clinical Radiobiology, 4th Edition*, 2009

early reactions after CHART - predictably, mucositis was severe and required hospitalization, *however* this did not affect patient compliance, because the entire treatment was completed before the mucositis kicked in (sneaky!)

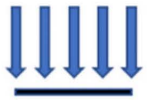
Late effects - significantly lower incidence of late effects for a few endpoints in the CHART arm of the head and neck trial, but all endpoints considered, *there was no case where CHART produced more late effects than conventional* (provided the interfraction interval was no shorter than 6 hours)



UK Breast Hypofractionation Trials - a case study in very carefully designed and executed, radiobiology-driven clinical trials that have changed the standard of care for radiotherapy (after surgery) in early stage breast cancer

Strahlenther Onkol (2021) 197:269–280

10-Year Evolution of Hypofractionated Breast Cancer Treatment in the UK

Regimen	Treatment schedule over the course of 5 weeks	$EQD_{2\,Gy}$ ($\alpha/\beta = 3.5$ Gy)
Conventional 25 × 2 Gy		50 Gy
START A 13 × 3.0/3.2 Gy		46.1 Gy/50.4 Gy
START B 15 × 2.67 Gy		44.9 Gy
FAST 5 × 5.7/6.0 Gy		47.7 Gy/51.8 Gy
FAST-Forward 5 × 5.2/5.4 Gy		41.1 Gy/43.7 Gy

$EQD_{2\,Gy}$ Dose equivalent delivered in 2 Gy-fractions without time loss-factor.

Pertinent References: Whelan *et al.*, N Eng J Med 2010;*362*:513-520
Yarnold *et al.*, Radiother Oncol 2011;*100*:93-100
Haviland et al., Lancet Oncol 2013;*14*:1086-1094
Brunt et al., Lancet 2020; *395*:1613–1626
Brunt et al., J Clin Oncol 2020; *38*:3261-3272

What about "extreme hypofractionation"?

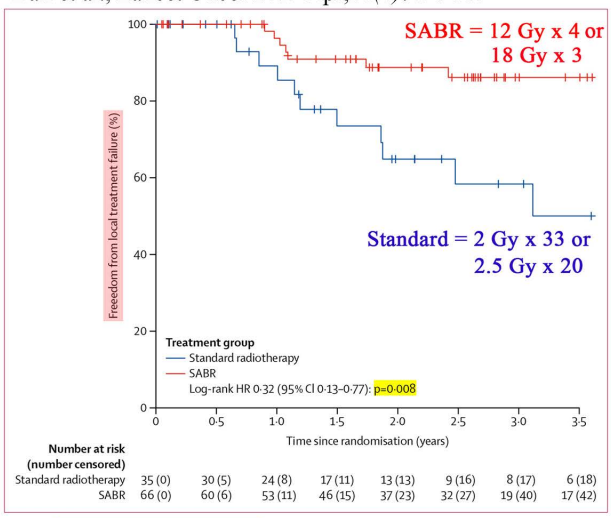
1. One of the first only-a-few-big-fractions SABR/SBRT randomized Phase 3 trials that made a big splash was the CHISEL trial out of Australia and New Zealand

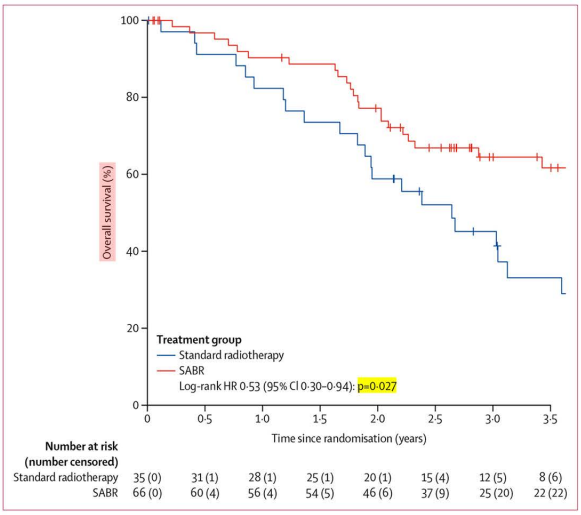
Population: about 100 patients with inoperable, Stage 1 NSCLC randomized ~2:1 to either SABR or standard treatment

Standard treatment = 66 Gy in 33, 2 Gy fractions or 50 Gy in 20, 2.5 Gy fractions (overall times of 4-6 weeks)
SABR = 54 Gy in 3, 18 Gy fractions or 48 Gy in 4, 12 Gy fractions (overall times of 1-2 weeks)

Endpoints: primary endpoint was local treatment failure; secondary endpoints were overall survival, disease-specific survival, treatment toxicity and patient quality of life

Ball et al., Lancet Oncol 2019 Apr;*20(4)*:494-503





Local treatment failure and overall survival endpoints clearly favored the SABR group(s), out to 3.5 years after treatment

Treatment-related complications were mild overall, and certainly no worse in the SABR group than the control group

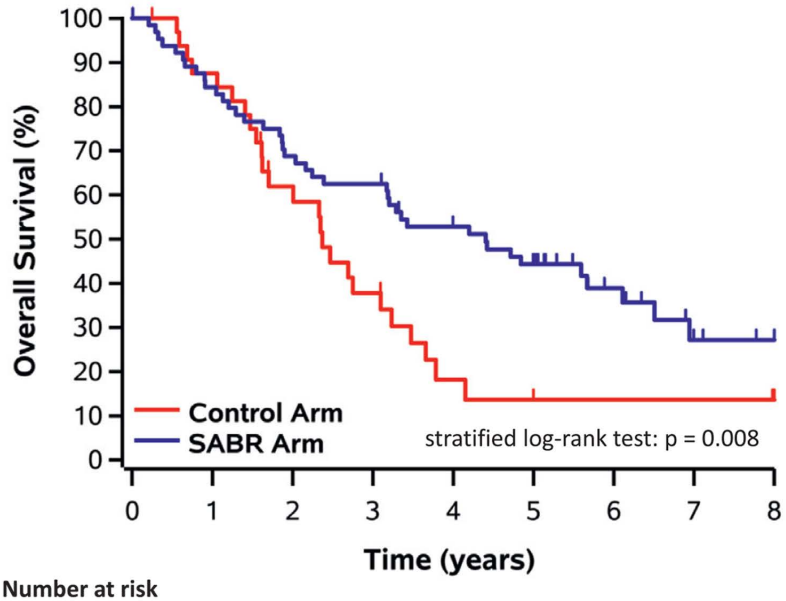
	SABR group (n=66)			Standard radiotherapy group (n=35)	
	Grade 1–2	Grade 3	Grade 4	Grade 1–2	Grade 3
Dyspnoea	22 (39%)	1 (2%)	1 (2%)	18 (58%)	0
Cough	33 (59%)	2 (4%)	0	15 (48%)	0
Fatigue	32 (57%)	1 (2%)	0	21 (68%)	0
Chest wall pain	21 (38%)	0	0	4 (13%)	1 (3%)
Lung infection	3 (5%)	1 (2%)	0	0	0
Pain	2 (4%)	0	0	0	1 (3%)
Cataract	0	1 (2%)	0	0	0
Hypoxia	0	1 (2%)	0	0	0
Weight loss	0	1 (2%)	0	0	0
Pulmonary fibrosis	22 (39%)	0	0	9 (29%)	0
Dermatitis radiation	6 (11%)	0	0	17 (55%)	0
Nausea	9 (16%)	0	0	5 (16%)	0
Atelectasis	9 (16%)	0	0	4 (13%)	0
Pneumonitis	10 (18%)	0	0	1 (3%)	0
Pleural effusion	7 (12%)	0	0	1 (3%)	0
Fracture	5 (9%)	0	0	1 (3%)	0
Anorexia	0	0	0	4 (13%)	0
Dysphagia	3 (5%)	0	0	1 (3%)	0
Bronchopulmonary haemorrhage	2 (4%)	0	0	1 (3%)	0
Dizziness	0	0	0	3 (10%)	0
Dry mouth	1 (2%)	0	0	2 (6%)	0

2. Another high profile trial of extreme hypofractionation is the SABR-COMET trial(s) - a Phase 2, randomized multi-institutional trial

Population: 99 patients with assorted primary tumors and 1-5 metastases; *primary tumors were controlled*, so the idea was to assess outcomes after treating all of the metastatic sites

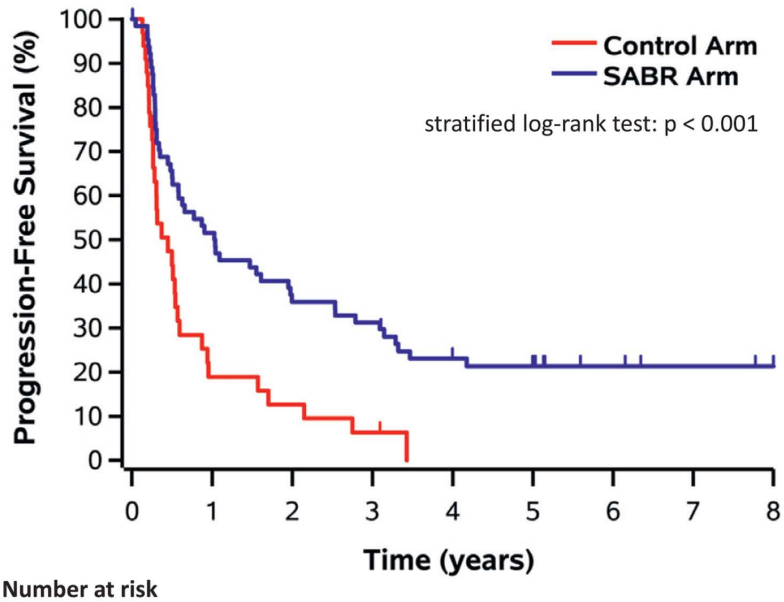
Standard treatment = 8 Gy single fraction or else 30 Gy in 10 fractions
SABR = 16-24 Gy single dose for brain and verterbral mets; otherwise, 30-60 Gy in 3-8 fractions

Endpoint(s): mainly overall survival, but progression-free survival and normal tissue toxicity also assessed



Number at risk

Control	33	28	18	11	4	2	2	2	1
SABR	66	54	44	40	31	25	12	5	3



Number at risk

Control	33	6	4	2					
SABR	66	33	23	20	13	11	5	3	2

Results:

- More than a doubling of overall and progression-free survival as of 8 years out
- Noticeably worse toxicity was the downside, including a nearly 5% fatality rate from radiation-related complications
  - ≥Grade 2 toxicity in 61% of SABR patients versus 46% in the control group
- Proof of concept that an oligometastatic state must exist, and that a few patients are even curable when sites of metastases are treated aggressively

Int J Radiation Oncol Biol Phys, Vol. 114, No. 4, pp. 611–616, 2022

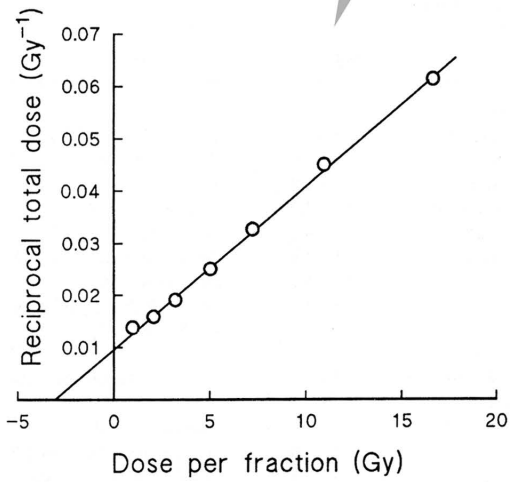
Summary of the Linear-Quadratic Isoeffect Model Parameters and Concepts

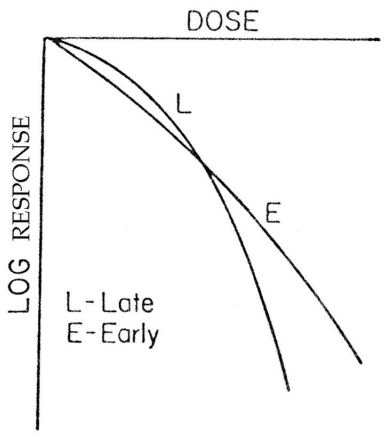
Tissue Type	α/β Ratio[a]	Dose Response Curve Shape[b]	Isoeffect Curve Shape[c]
Early-Responding Normal Tissues and Most Tumors	**High (6 - 30 Gy)**	**Steep Initial Slope (α is large)**	**Shallow**
Late-Responding Normal Tissues	**Low (1 - 6 Gy)**	**Shallow Initial Slope (α is small)**	**Steep**

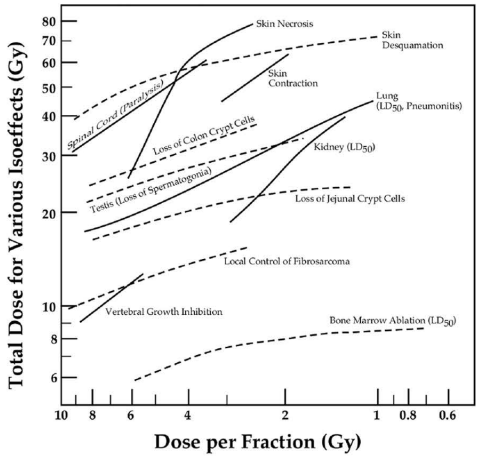
[a] Determined from the reciprocal dose plot technique of Douglas and Fowler

[b] Based on the assumption that differences in the calculated α/β ratio are usually caused by differences in α rather than β

[c] Using the Thames *et al.* isoeffect curve plot







Current Status of Existing and Proposed Parmeters of the LQ Isoeffect Model for Human Normal Tissues and Tumors

Parameter	Property Governed	Availability of Data with Respect to:		
		Early Effects	Late Effects	Tumors
α/β Ratio	Fractionation sensitivity	Can assume 10 Gy for most (Some evidence that α/β = 10 Gy for early effects and tumors is too high)	Can assume 3 Gy for most	Can assume 10 Gy for most
$T_{1/2}$ (Repair Half-Time)	Repair kinetics	Poor/Fair (Growing body of evidence that repair half-times in normal tissues are longer than originally thought)	Poor/Fair	None/Poor
T_p/T_{eff} (Effective Clonogen Doubling Time) and/or T_k ("Kickoff" Time - time proliferation begins relative to the start of treatment)	Dose lost to accelerated proliferation during radiotherapy	Fair	Poor/N.A.	Poor/Fair
Volume Effect	Variation in tissue tolerance with increasing target volume	Poor	Poor	None/Poor
γ (Normalized Dose Response Gradient)	Steepness of dose-response curve for effect; can be used to estimate the normal tissue complication probability	Fair	Fair	Fair

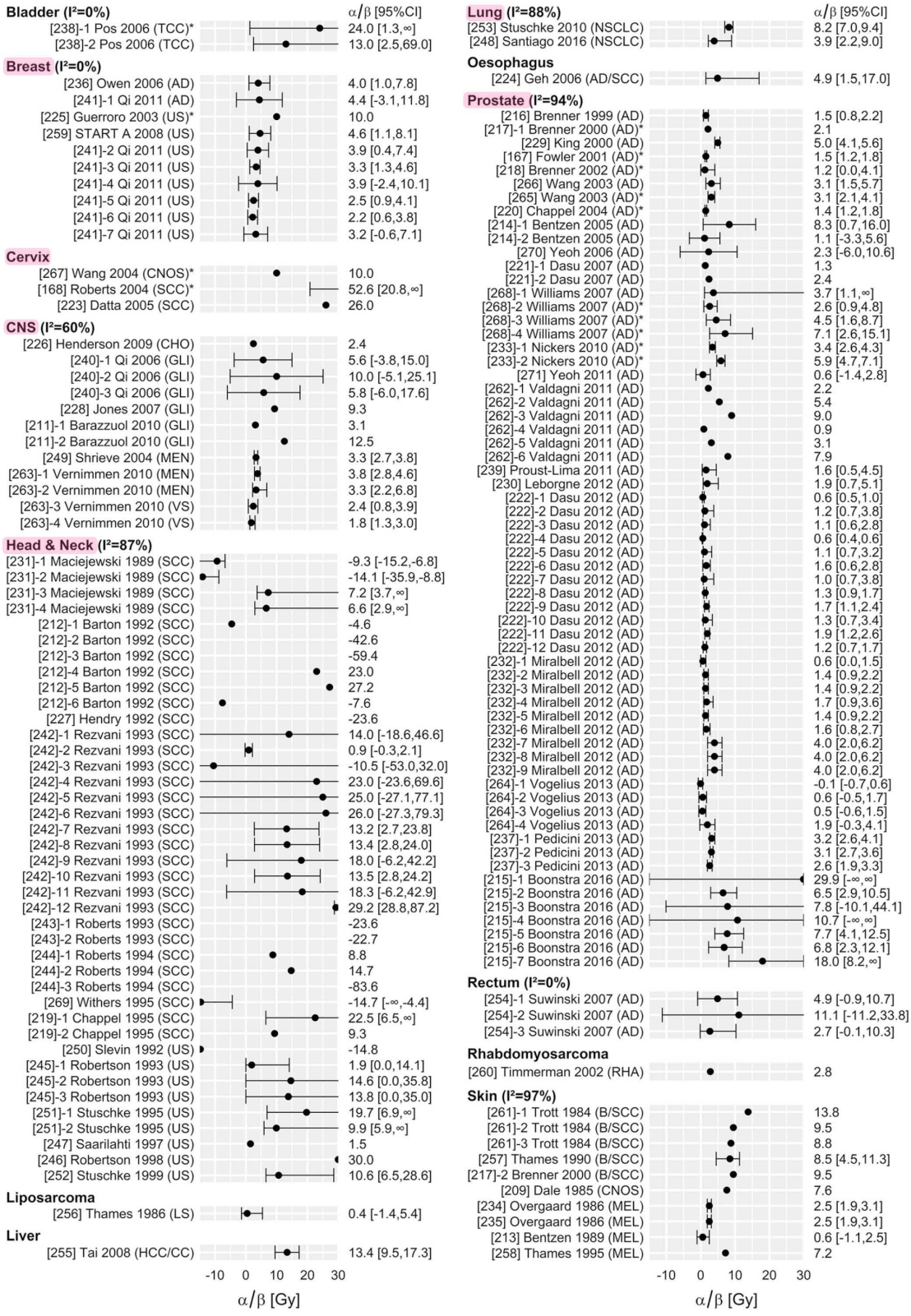
Best Estimate α/β Ratios for Human Normal Tissues and Tumors

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.

From Joiner & van der Kogel, *Basic Clinical Radiobiology, 4th Edition*, 2009.

More Recent Compilation of α/β Ratios for Human Tumors (note wide variability in some cases)



Overview of 149 reported estimates of a/β, stratified by tumour site. Within tumour sites, studies are sorted by histology, and then by date of publication. TCC: transitional cell carcinoma; AD: adenocarcinoma; US: unspecified; CNOS: carcinoma, not otherwise specified; SCC: squamous cell carcinoma; CHO: chordoma; GLI: glioma; MEN: meningioma; VS: vestibular schwannoma; LS: liposarcoma; HCC/CC: Hepatocellular carcinoma & Cholangiocarcinoma; NSCLC: Non small cell lung carcinoma; RHA: Rhabdomyosarcoma; B/SCC: Basal-cell carcinoma & Squamous cell carcinoma; MEL: melanoma. *Included data of patients treated with brachytherapy as part of the treatment.

Even More α/β Ratios for Human Tumors (note discordance between *in vitro* and *in vivo* values)

	In Vivo Range of (α/β) [Gy]	*In Vitro* Range of (α/β) [Gy]
Breast	2.2-4.6	
Breast adenocarcinoma	4-4.4	
CNS	1.8-12.5	
CNS chordoma	2.4	
CNS glioma	3.1-12.5	1.83
CNS meningioma	3.3-3.8	
CNS vestibular schwannoma	1.8-2.4	
H&N	0.9-30	
H&N squamous cell carcinoma	0.9-29.2	1.46-47.5
H&N squamous cell carcinoma (larynx)	0-29.2	1.82-7.65
H&N squamous cell carcinoma (nasopharynx)	16	
H&N squamous cell carcinoma (oropharynx)	6.5-10.3	
H&N salivary gland		0.58-10.89
GI liver	13.4	
GI esophagus	4.9	
GI esophagus adenocarcinoma		
GI esophagus squamous cell carcinoma		
GI pancreas adenocarcinoma		
GU prostate adenocarcinoma	0-20	5.8
GU colorectal		3.08-69.5
GU colon		
GU cervix	10-52.6	6.9-7.1
GU cervix squamous cell carcinoma	26-52.6	
GU rectum	2.7-11.1	
GU bladder	13-24	
Sarcoma	0.4	7.61
Lung (Non-small cell)	3.9-8.2	3.0-52.23
Pediatric rhabdomyosarcoma	2.8	
Pediatric medulloblastoma		4

Int J Radiation Oncol Biol Phys, Vol. 112, No. 1, pp. 222–236, 2022