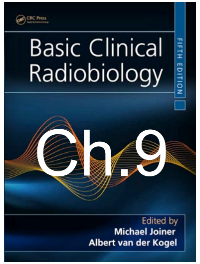
Basic Clinical Radiobiology

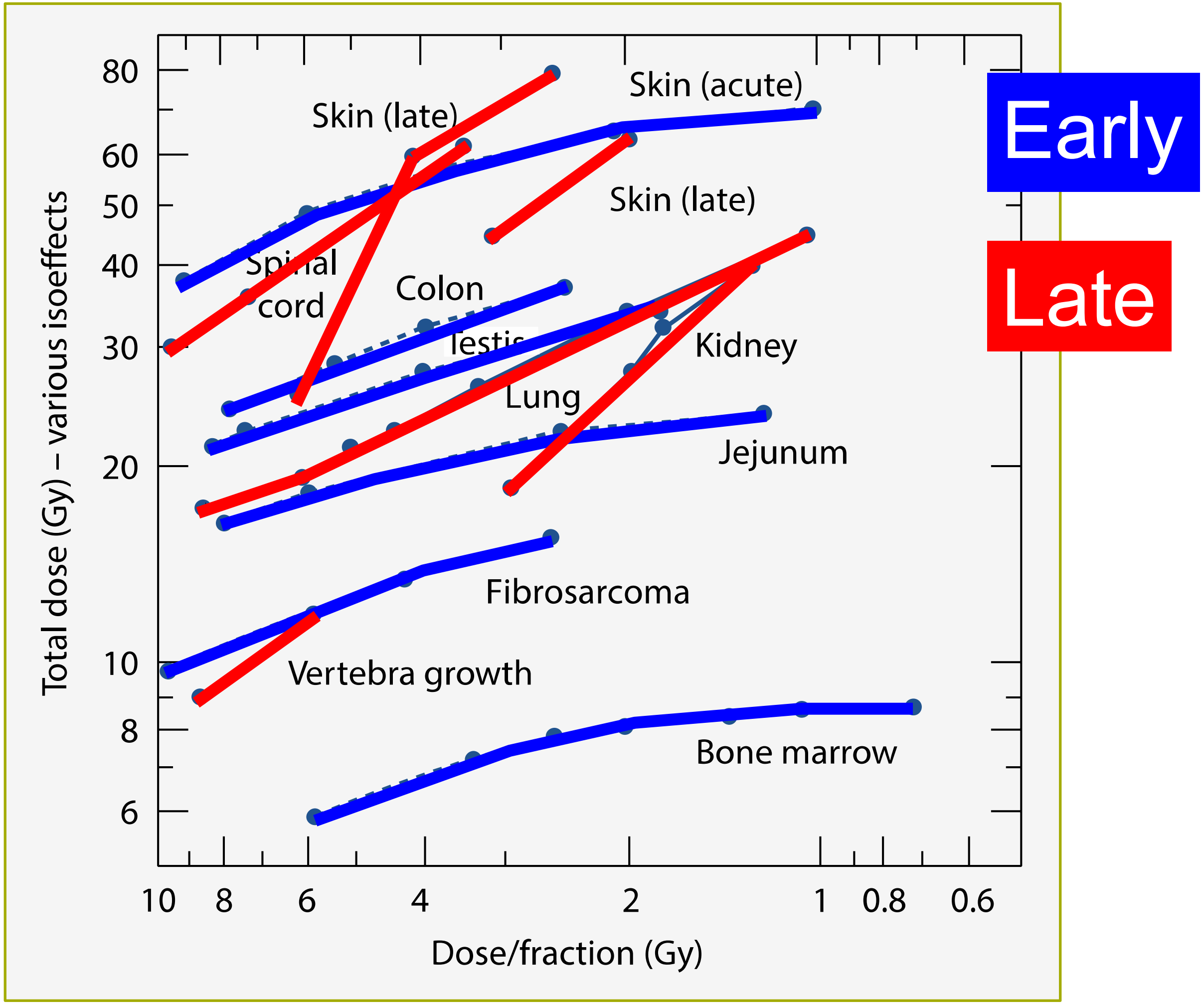
The Linear-Quadratic approach to fractionation

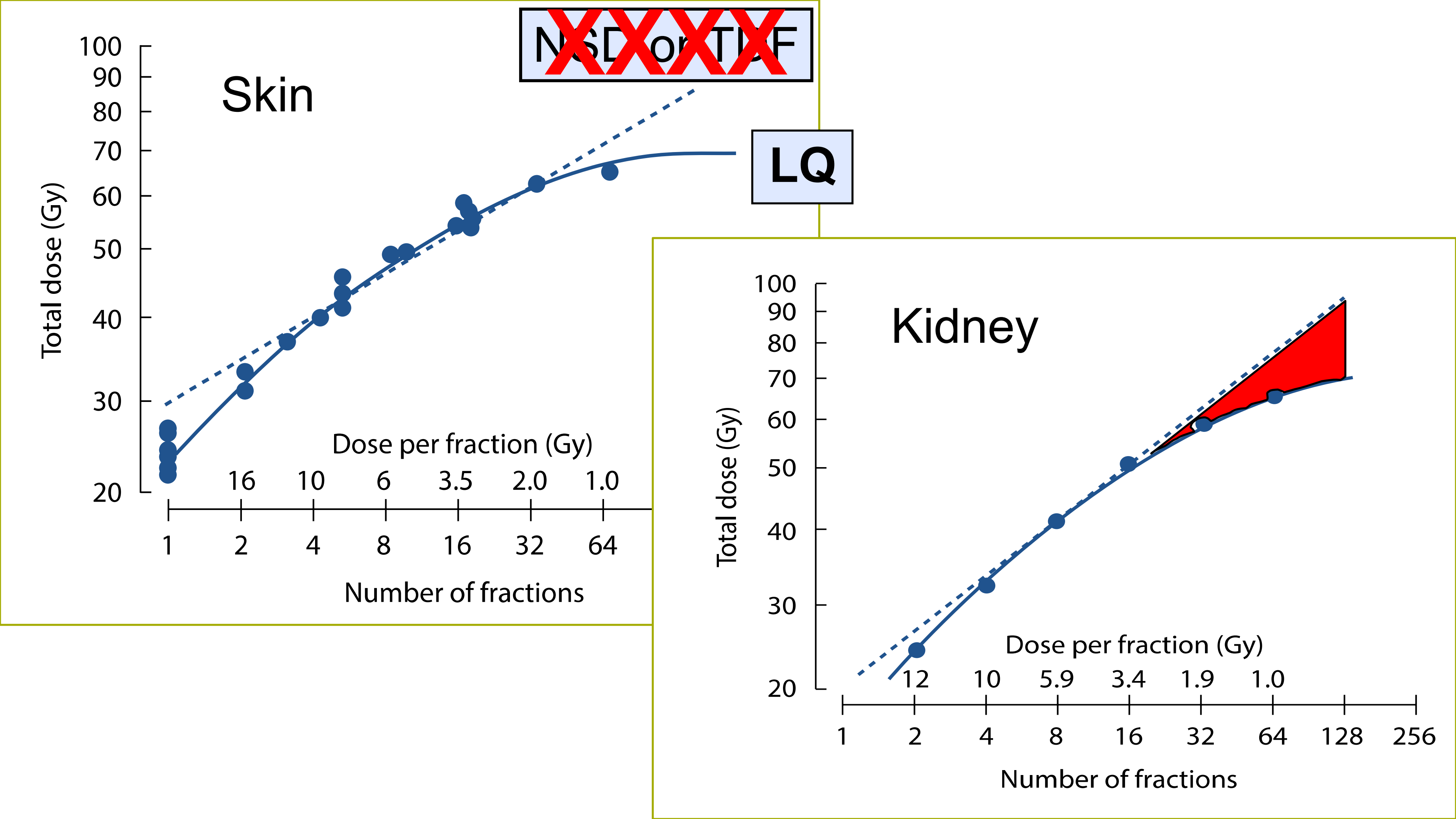
Michael Joiner

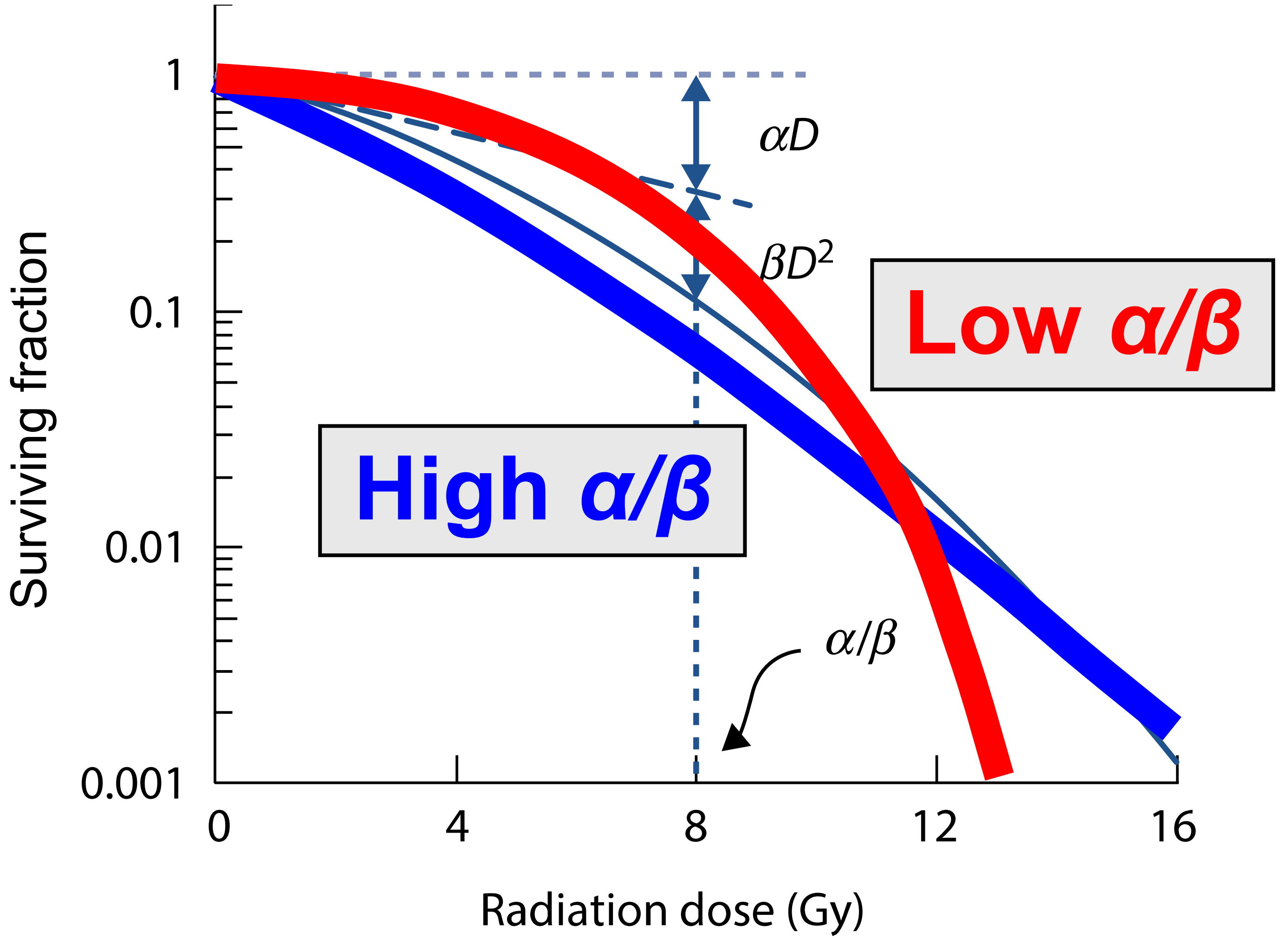
Toronto 2023



Thames HD, Withers HR, Peters LJ, Fletcher GH. *Int J Radiat Oncol Biol Phys* 1982;8:219

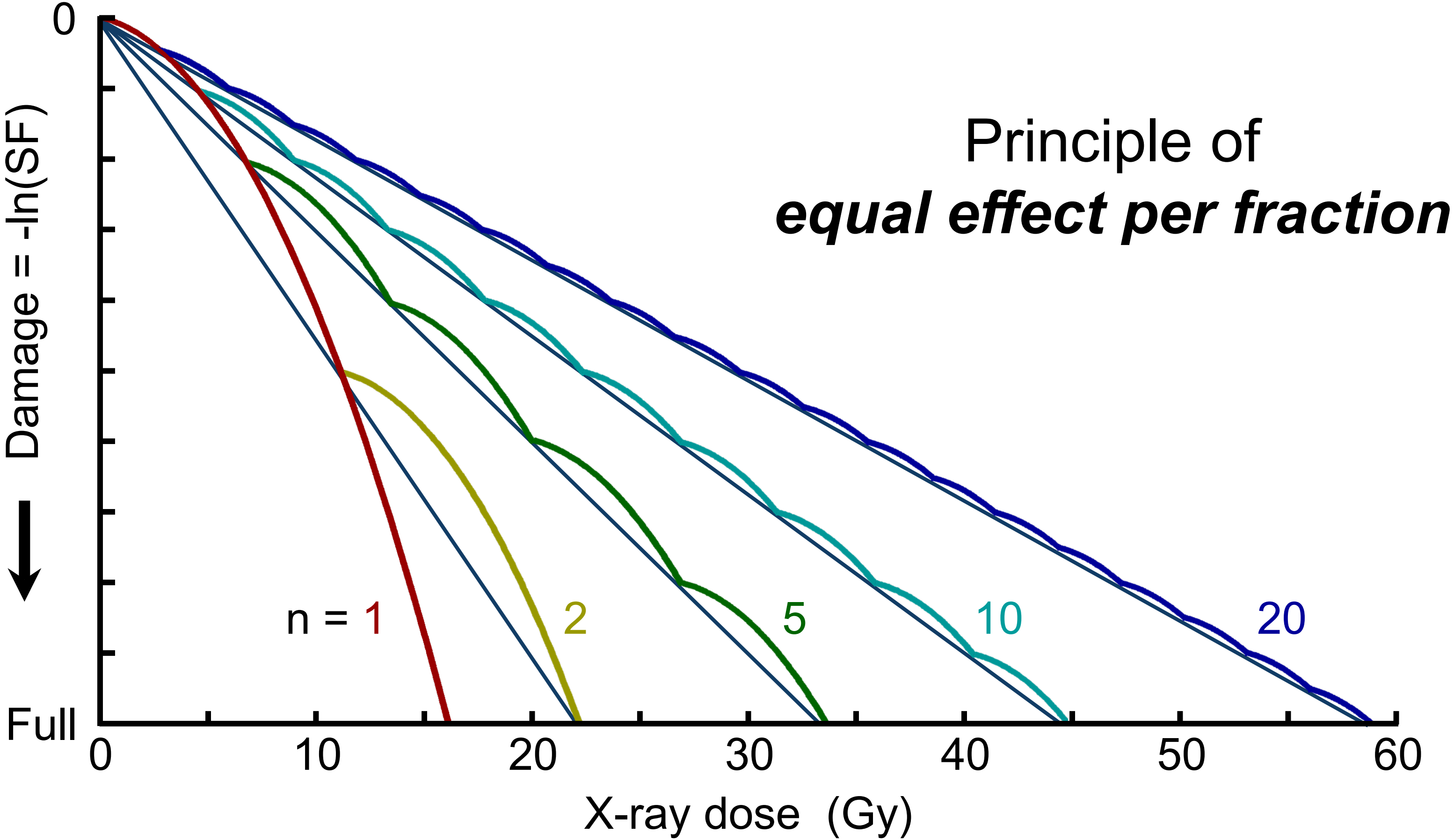



NSD or TDF
LQ
Skin
Total dose (Gy)
100
90
80
70
60
50
40
30
20
Dose per fraction (Gy)
16
10
6
3.5
2.0
1.0
1
2
4
8
16
32
64
Number of fractions
Kidney
Total dose (Gy)
100
90
80
70
60
50
40
30
20
Dose per fraction (Gy)
12
10
5.9
3.4
1.9
1.0
1
2
4
8
16
32
64
128
256
Number of fractions

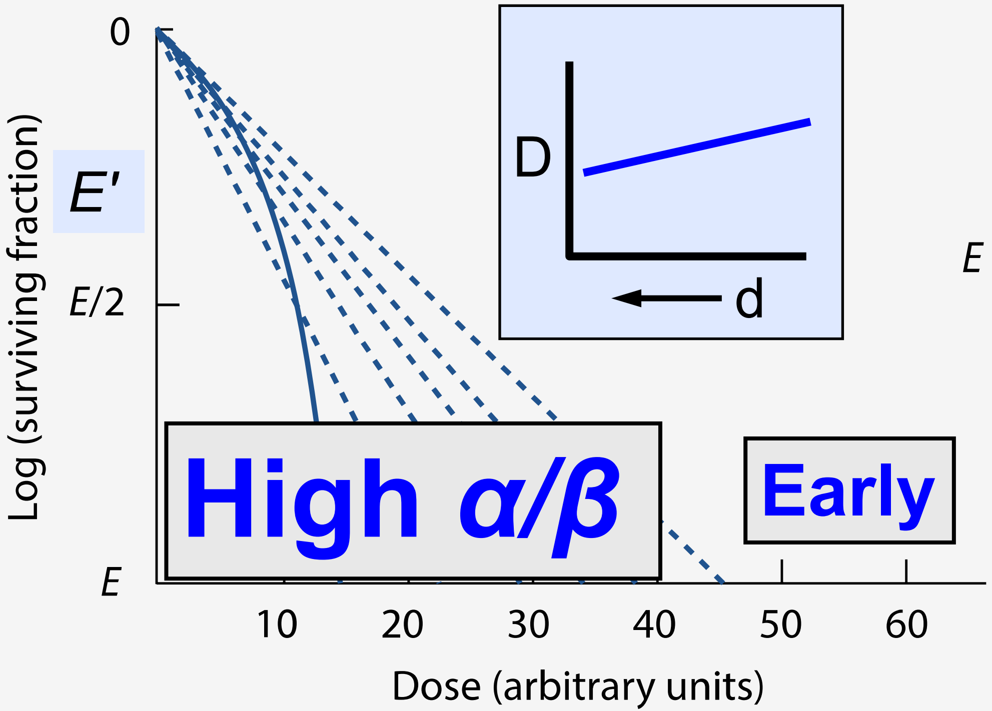


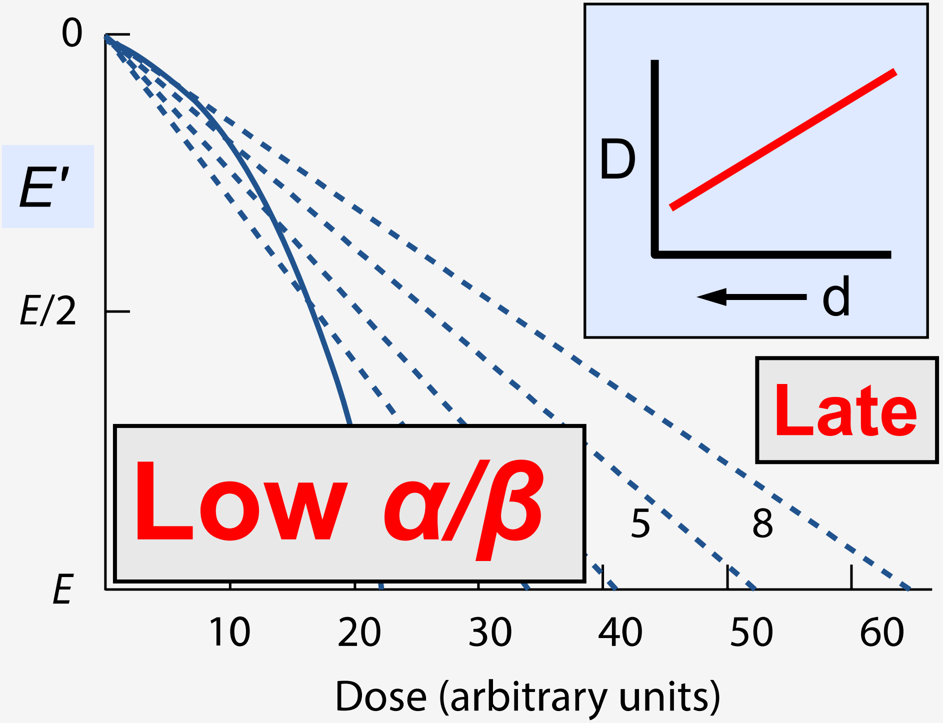
Surviving fraction
1
0.1
0.01
0.001
0
4
8
12
16
Radiation dose (Gy)
αD
βD²
α/β
High α/β
Low α/β

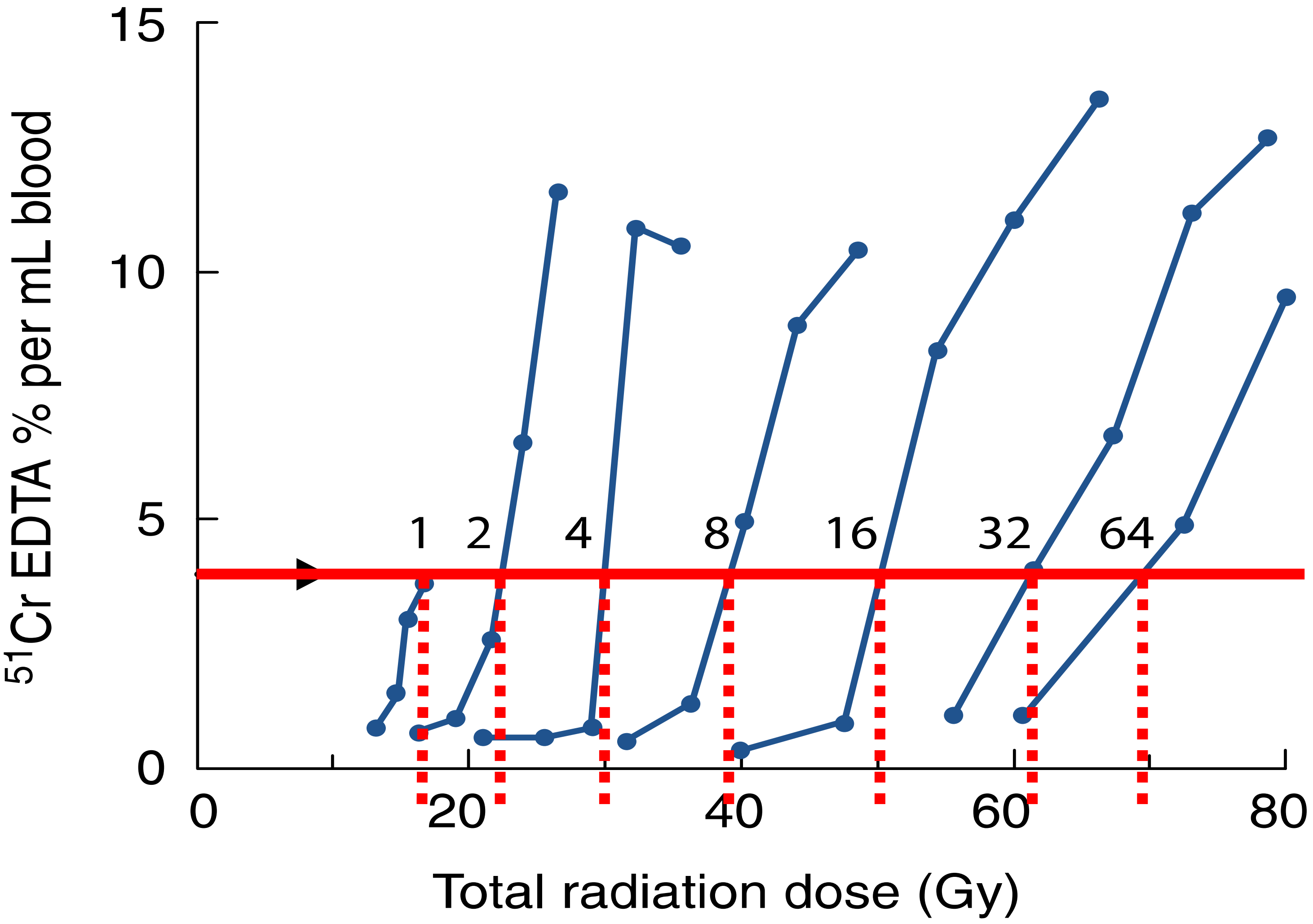
Less effect per gray at low doses per fraction



$$E' = e^{-\alpha D - \beta D^2}$$



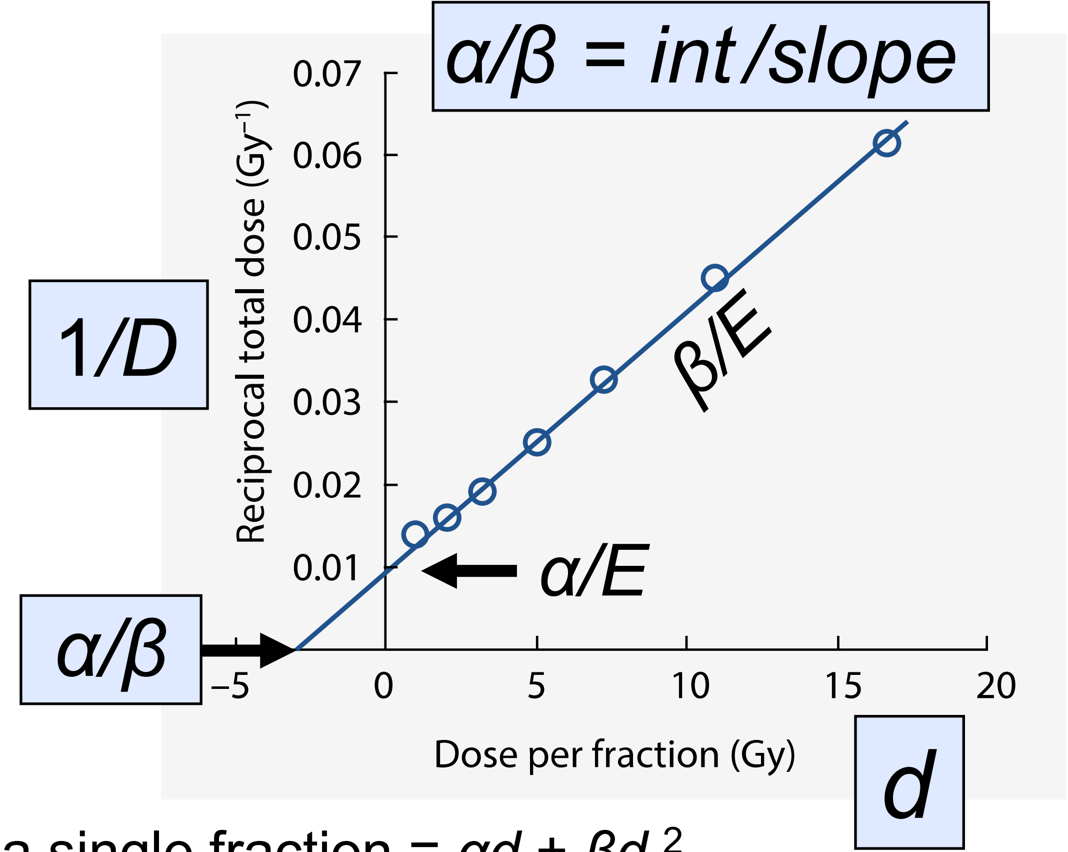




15
10
5
0
51Cr EDTA % per mL blood
1
2
4
8
16
32
64
0
20
40
60
80
Total radiation dose (Gy)

n	*D*	*d*	*1/D*	*1/n*
1	16.5	16.5	.0606	1.0
2	21.9	10.95	.0457	.5
4	29.4	7.35	.0340	.25
8	39.0	4.88	.0256	.125
16	50.3	3.14	.0199	.0625
32	60.9	1.90	.0164	.03125
64	69.3	1.08	.0144	.015625

d	$1/D$
16.5	.0606
10.95	.0457
7.35	.0340
4.88	.0256
3.14	.0199
1.90	.0164
1.08	.0144

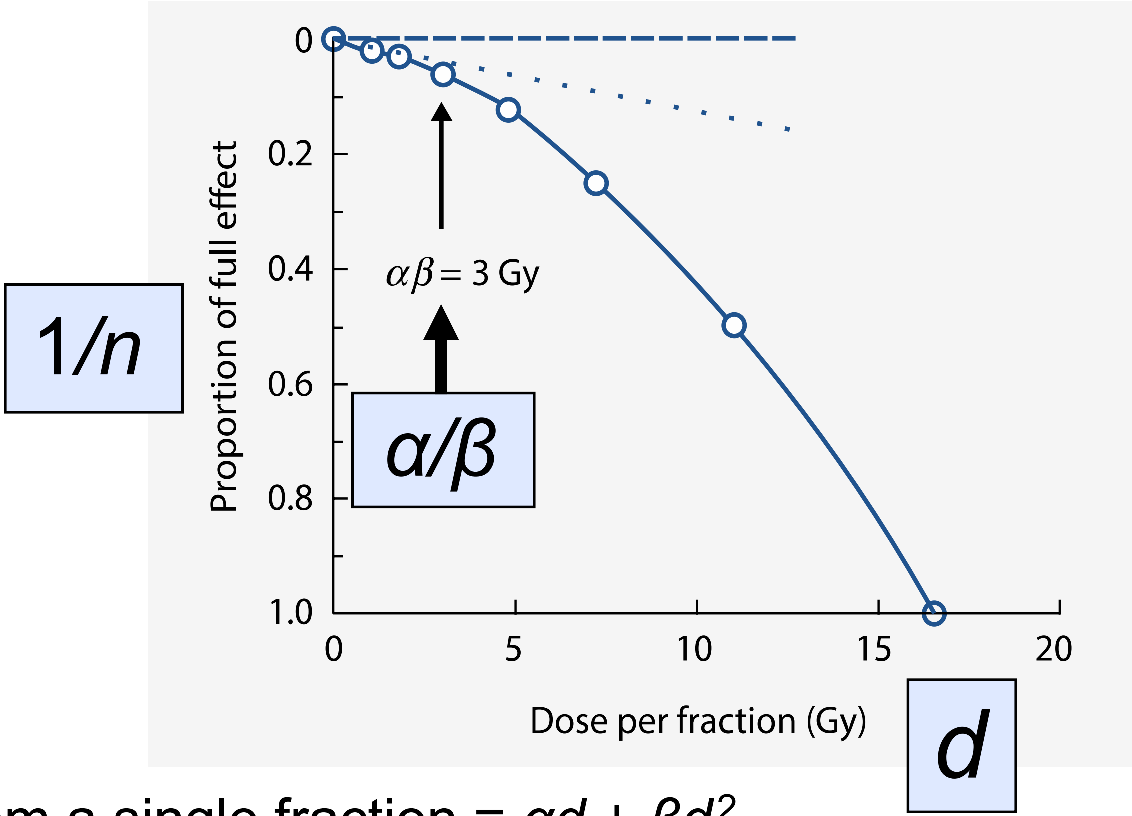


Damage from a single fraction = $\alpha d + \beta d^2$

Total damage from n fractions, $E = n(\alpha d + \beta d^2)$

$E = \alpha D + \beta d D$ $\quad$ $E/D = \alpha + \beta d$ $\quad$ $1/D = (\alpha/E) + (\beta/E)d$

d	*1/n*
16.5	1.0
10.95	.5
7.35	.25
4.88	.125
3.14	.0625
1.90	.03125
1.08	.015625



Damage from a single fraction = $\alpha d + \beta d^2$

Total damage from n fractions, $E = n(\alpha d + \beta d^2)$

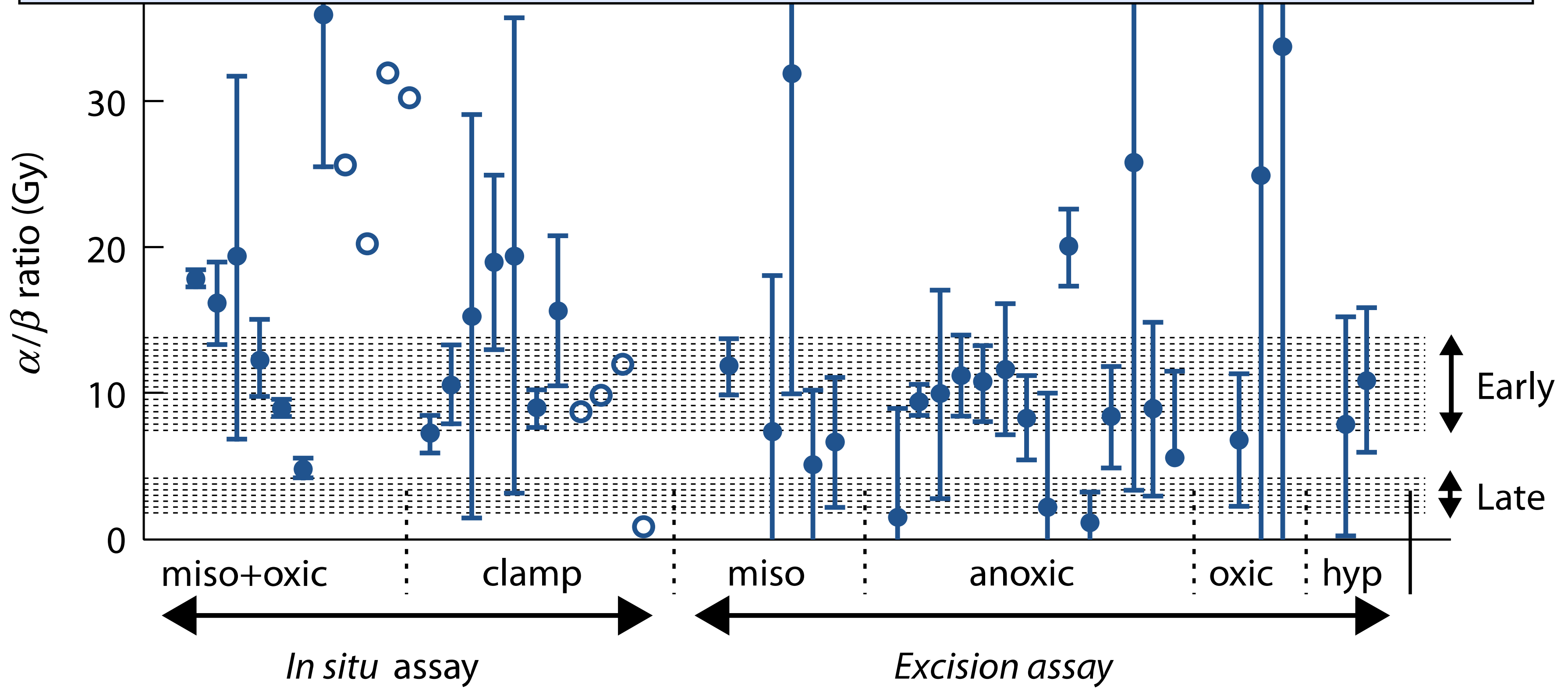
$E/n = \alpha d + \beta d^2$ $\quad\quad$ $1/n = (\alpha/E)d + (\beta/E)d^2$

α/β for early and late responding animal normal tissues

Early reactions			Late reactions		
	α/β	10.6 Gy		α/β	3.0 Gy
Skin			Spinal cord		
Desquamation	9.1 - 12.5	Douglas and Fowler (1976)	Cervical	1.8 - 2.7	van der Kogel (1979)
8.6 - 10.6	Joiner *et al* (1983)		Cervical	1.6 - 1.9	White and Hornsey (1978)
9 - 12	Moulder and Fischer (1976)		Cervical	1.5 - 2.0	Ang *et al* (1983)
Jejunum			Cervical	2.2 - 3.0	Thames *et al* (1988)
Clones	6.0 - 8.3	Withers *et al* (1976)	Lumbar	3.7 - 4.5	van der Kogel (1979)
6.6 - 10.7	Thames *et al* (1981)		Lumbar	4.1 - 4.9	White and Hornsey (1978)
Colon				3.8 - 4.1	Leith *et al* (1981)
Clones	8 - 9	Tucker *et al* (1983)		2.3 - 2.9	Amols, Yuhas (quoted by
Weight loss	9 - 13	Terry and Denekamp (1984)			Leith *et al*, 1981)
Testis			Colon		
Clones	12 - 13	Thames and Withers (1980)	Weight loss	3.1 - 5.0	Terry and Denekamp (1984)
Mouse lethality			Kidney		
30d	7 - 10	Kaplan and Brown (1952)	Rabbit	1.7 - 2.0	Caldwell (1975)
30d	13 - 17	Mole (1957)	Pig	1.7 - 2.0	Hopewell and Wiernik (1977)
30d	11 - 26	Paterson *et al* (1952)	Rats	0.5 - 3.8	van Rongen *et al* (1988)
Tumour bed			Mouse	1.0 - 3.5	Williams and Denekamp
45d	5.6 - 6.8	Begg and Terry (1984)	Mouse	0.9 - 1.8	Stewart *et al* (1984 a)
			Mouse	1.4 - 4.3	Thames *et al* (1988)
		Lung			
			LD_{50}	4.4 - 6.3	Wara *et al* (1973)
			LD_{50}	2.8 - 4.8	Field *et al* (1976)
			LD_{50}	2.0 - 4.2	Travis *et al* (1983)
			Breathing rate	1.9 - 3.1	Parkins and Fowler (1985)
		Bladder			
			Frequency, capacity	5 - 10	Stewart *et al* (1984 b)

Table 9.1, Basic Clinical Radiobiology 5th Ed

α/β for many **experimental** tumors is ~≥ α/β for early-reacting normal tissues



Fractionation in prostate cancer

Int J Radiation Oncology Biol Phys
2011;79:195-201

CLINICAL INVESTIGATION

CONFIRMATION OF A LOW α/β RATIO FOR PROSTATE CANCER TREATED BY EXTERNAL BEAM RADIATION THERAPY ALONE USING A POST-TREATMENT REPEATED-MEASURES MODEL FOR PSA DYNAMICS

Cécile Proust-Lima, Ph.D.,[*†] Jeremy M. G. Taylor, Ph.D.,[‡§] Solène Sécher, Ph.D.,[*†] Howard Sandler, M.D.,[||] Larry Kestin, M.D.,[¶] Tom Pickles, M.D.,[#] Kyoungwha Bae, Ph.D.,[**] Roger Allison, F.R.A.N.Z.C.R.,[††] and Scott Williams, M.D., F.R.A.N.Z.C.R.[‡‡]

*INSER … France;
Departn … cology,
Cedars … k, MI;
#British … ia, PA;
††D … gy,

Mean = 1.55 [CL 0.46 – 4.52]

Results: Adjusted for other factors, total dose of EBRT and sum of squared doses per fraction were associated with long-term rate of change of PSA level ($p = 0.0017$ and $p = 0.0003$, respectively), an increase of each being associated with a lower rate of rise. The α/β ratio was estimated at 1.55 Gy (95% confidence band, 0.46–4.52 Gy). This estimate was robust to adjustment of the linear mixed model.

Fractionation in prostate cancer

1.55 (0.46–4.52) Gy   5093 patients   Proust-Lima C
PSA evolution median follow up 4.7 years   d/f < **2.8 Gy**
6 institutional datasets, no risk-group dependence
Int J Radiat … 01

1.48 Gy

1.4 (0.9–2.2 … R
Biochem rel … /f < **6.7 Gy**
7 institutiona … dence
Int J Radiat Oncol Biol Phys 2012;82:e17-e24

1.86 (0.7–5.1) Gy   274 patients   Leborgne F
Biochem disease free survival at 5 years   d/f < **3.15 Gy**
Single institution, no risk-group dependence
Int J Radiat Oncol Biol Phys 2012;82:1200-7

Fractionation in breast cancer

The UK Standardisation of Breast Radiotherapy (START) trials of radiotherapy hypofractionation for treatment of early breast cancer: 10-year follow-up results of two randomised controlled trials

Lancet Oncol 2013; 14: 1086–94

Joanne S Haviland, J Roger Owen, John A Dewar, Rajiv K Agrawal, Jane Barrett, Peter J Barrett-Lee, H Jane Dobbs, Penelope Hopwood, Pat A Lawton, Brian J Magee, Judith Mills, Sandra Simmons, Mark A Sydenham, Karen Venables, Judith M Bliss, John R Yarnold*, on behalf of the START Trialists' Group†*

Summary

Background 5 … at lower total doses of radi… the historical standard regi… prespecified analysis, we r… s.

Interpretation Long-term follow-up confirms that appropriately dosed hypofractionated radiotherapy is safe and effective for patients with early breast cancer. The results support the continued use of 40 Gy in 15 fractions, which has already been adopted by most UK centres as the standard of care for women requiring adjuvant radiotherapy for invasive early breast cancer.

Mean = 3.5 [CL 1.2–5.7]

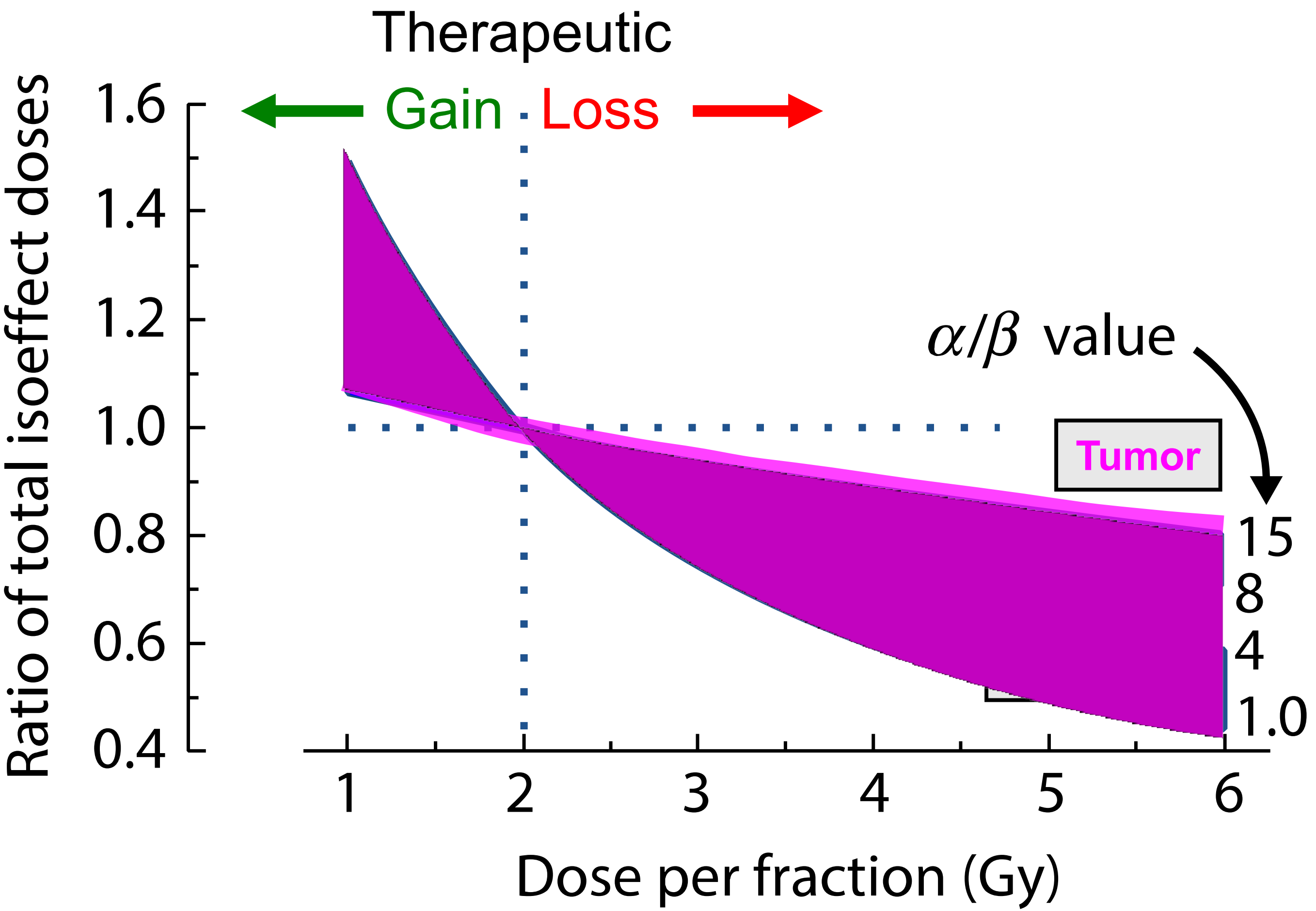
Table 10.1: *α/β* values for **human** normal tissues and tumors

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				t al. (1995)
				t al. (1991)
				nd Supe (1993)
Late reactions				
Skin/vasculature				and Thames (1989)
				t al. (1990)
				nd Overgaard (1991)
				t al. (2013)
Subcutis				nd Overgaard (1991)
Breast				t al. (2013)
				t al. (2013)
				t al. (2013)
Muscle/vasculature/				t al. (1989)
Nerve				l. (1990)
				al. (1990)
				. (1994)
Spinal cord				al. (1981)
Eye				. (1994)
Bowel				l. (1993)
				al. (1999)
Lung				t al. (2000)
				al. (1995)
Head and neck				t al. (1991)
				and Thames (1999)
Supraglottic larynx				ki 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)
Lung (NSCLC, early)		8.2	7.0; 9.4	Studchke and Pöttgen (2010)
Skin		8.5	4.5; 11.3	Trott et al. (1984)
Prostate		2.7	1.6; 3.8	Vogelius and Bentzen (2018)
Breast		3.5	1.2; 5.7	Haviland et al. (2013)
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)

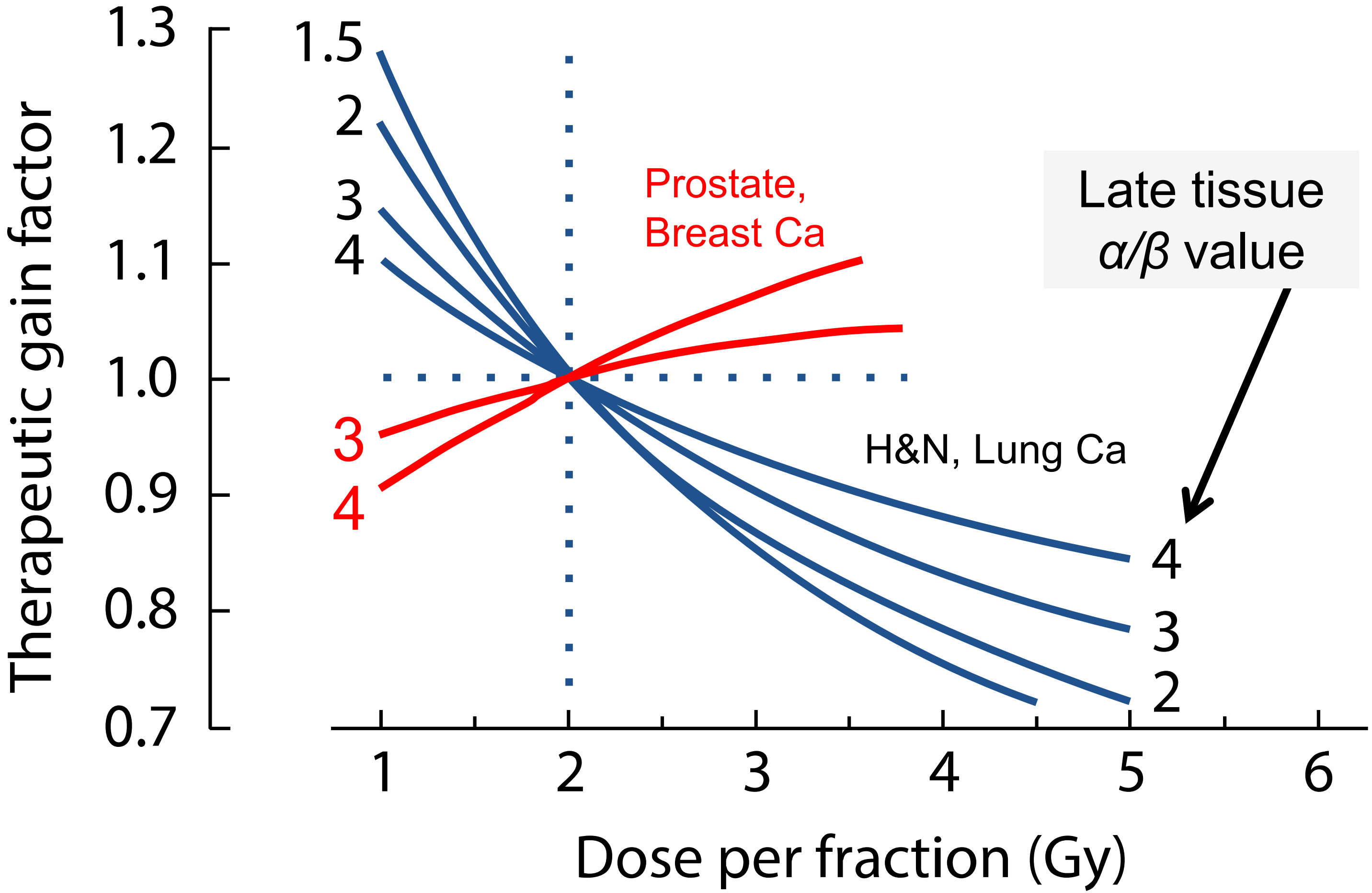
Mean Late 2.9

Mean Early 10.6

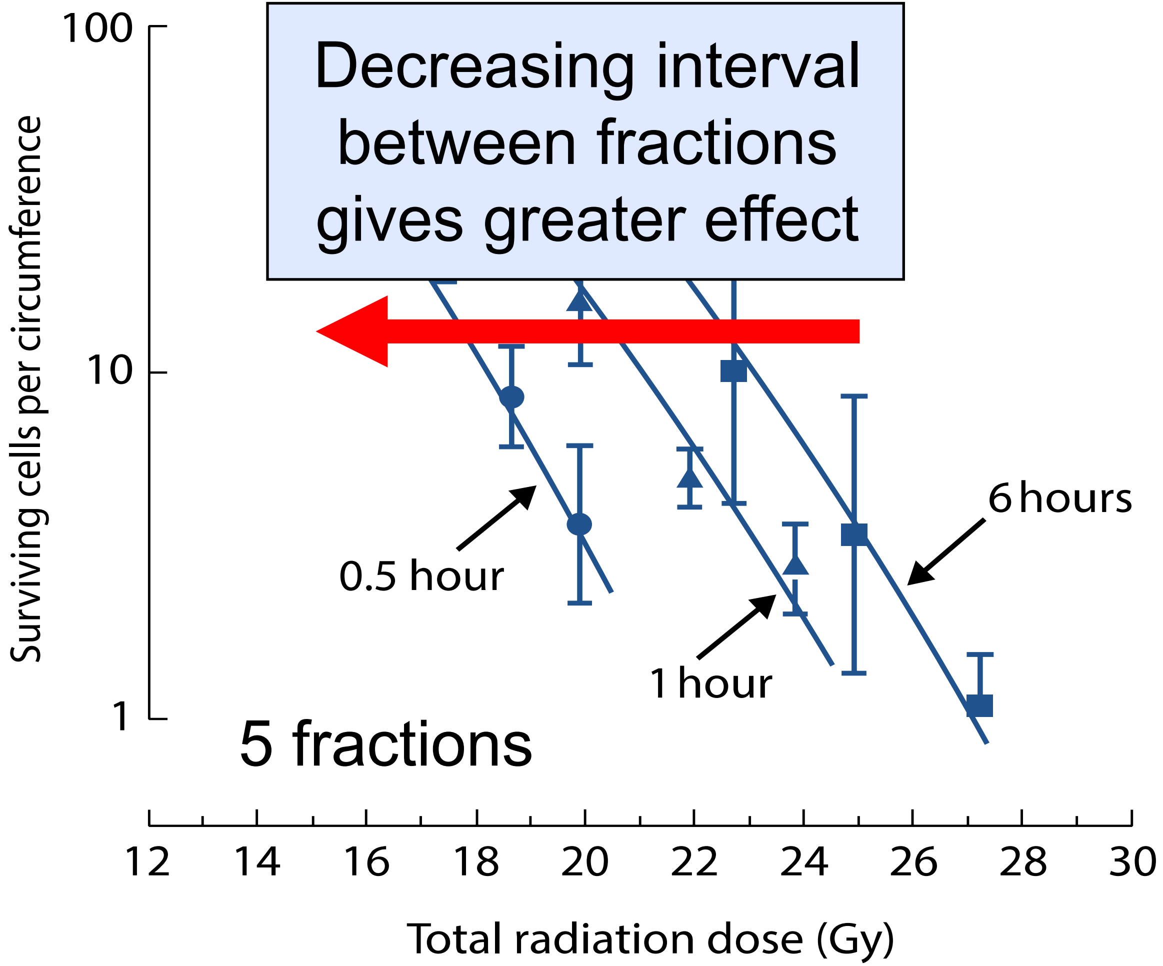
H&N, Lung tumors ***high***,
Breast, Prostate tumors ***low***

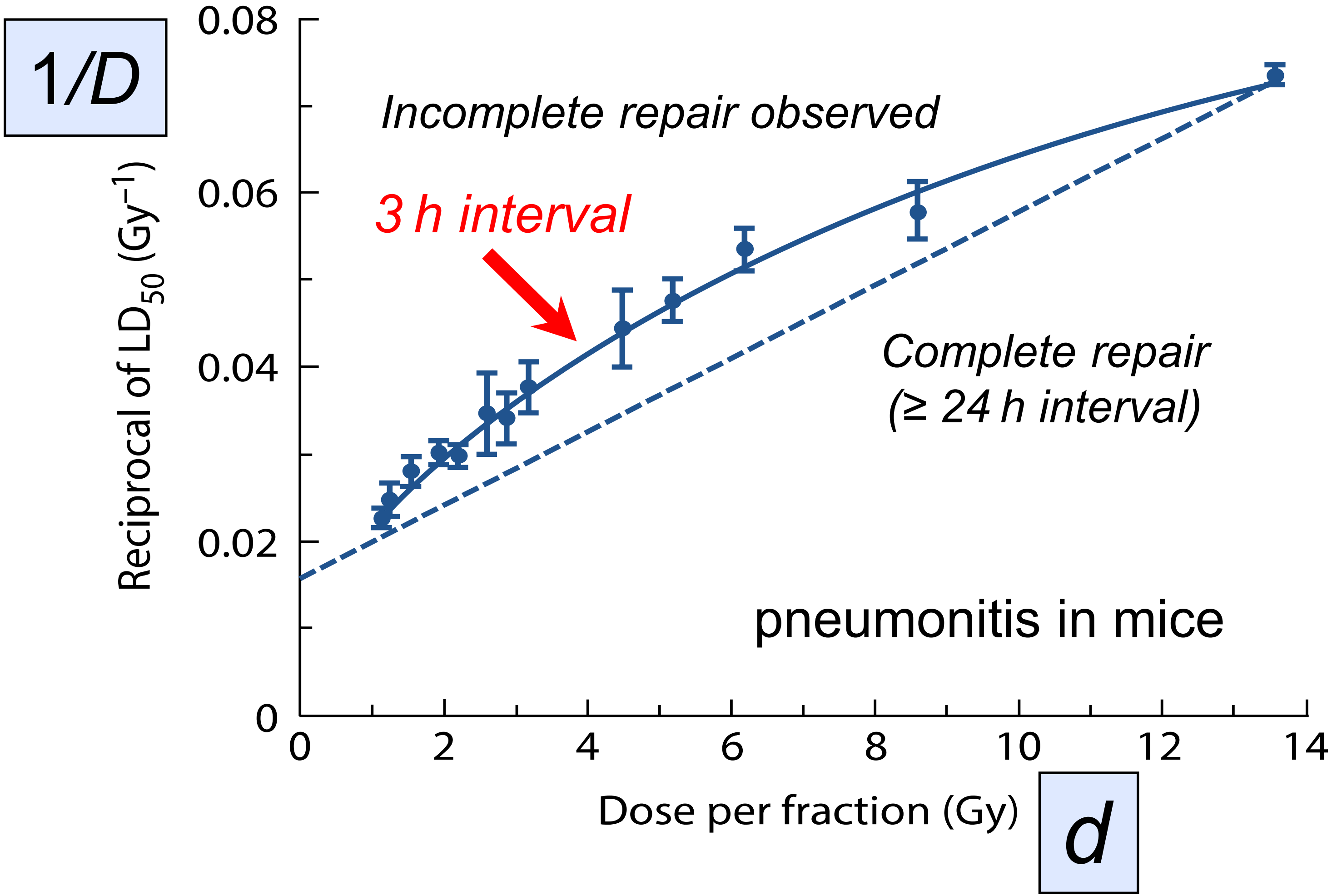


Therapeutic
Gain
Loss
Ratio of total isoeffect doses
1.6
1.4
1.2
1.0
0.8
0.6
0.4
α/β value
Tumor
15
8
4
1.0
1
2
3
4
5
6
Dose per fraction (Gy)



Therapeutic gain factor
1.3
1.2
1.1
1.0
0.9
0.8
0.7
1.5
2
3
4
Prostate,
Breast Ca
3
4
Late tissue
α/β value
H&N, Lung Ca
4
3
2
1
2
3
4
5
6
Dose per fraction (Gy)


Decreasing interval between fractions gives greater effect
100
10
1
Surviving cells per circumference
0.5 hour
1 hour
6 hours
5 fractions
12
14
16
18
20
22
24
26
28
30
Total radiation dose (Gy)


1/D
Incomplete repair observed
3 h interval
Complete repair
(≥ 24 h interval)
pneumonitis in mice
Reciprocal of LD50 (Gy−1)
0.08
0.06
0.04
0.02
0
0
2
4
6
8
10
12
14
Dose per fraction (Gy)
d

Basic LQ equation:

$$-\log_e SF_n = E = n\left(\alpha d + \beta d^2\right) = D\left(\alpha + \beta d\right)$$

LQ equation with incomplete repair:

$$E = D\left(\alpha + \beta d\left(1 + H_m\right)\right)$$

m is the number of fractions per day

H_m varies from:

0 ("full repair") to m-1 ("no repair")

Incomplete repair factors: fractionated irradiation (H_m factors)

Repair half-time (hours)	Interval for m = 2 fractions per day						Interval for m = 3 fractions per day				
	3	4	5	6	8	10	3	4	5	6	8
0.50	0.016	0.004	0.001	0.000	0.000	0.000	0.021	0.005	0.001	0.000	0.000
0.75	0.063	0.025	0.010	0.004	0.001	0.000	0.086	0.034	0.013	0.005	0.001
1.00	0.125	0.063	0.031	0.016	0.004	0.000	0.177	0.086	0.042	0.021	0.005
1.25	0.190	0.109	0.063	0.036	0.012	0.004	0.277	0.153	0.086	0.049	0.016
1.50	0.250	0.158	0.099	0.063	0.025	0.010	0.375	0.227	0.139	0.086	0.034
2.00	0.354	0.250	0.177	0.125	0.063	0.031	0.555	0.375	0.257	0.177	0.086
2.50	0.435	0.330	0.250	0.190	0.109	0.063	0.707	0.512	0.375	0.277	0.153
3.00	0.500	0.397	0.315	0.250	0.158	0.099	0.833	0.634	0.486	0.375	0.227
4.00	0.595	0.500	0.420	0.354	0.250	0.177	1.029	0.833	0.678	0.555	0.375
5.00	0.660	0.574	0.500	0.435	0.330	0.250	1.170	0.986	0.833	0.707	0.512

Table 9.2

Half times for recovery ($T_{1/2}$) in normal tissues

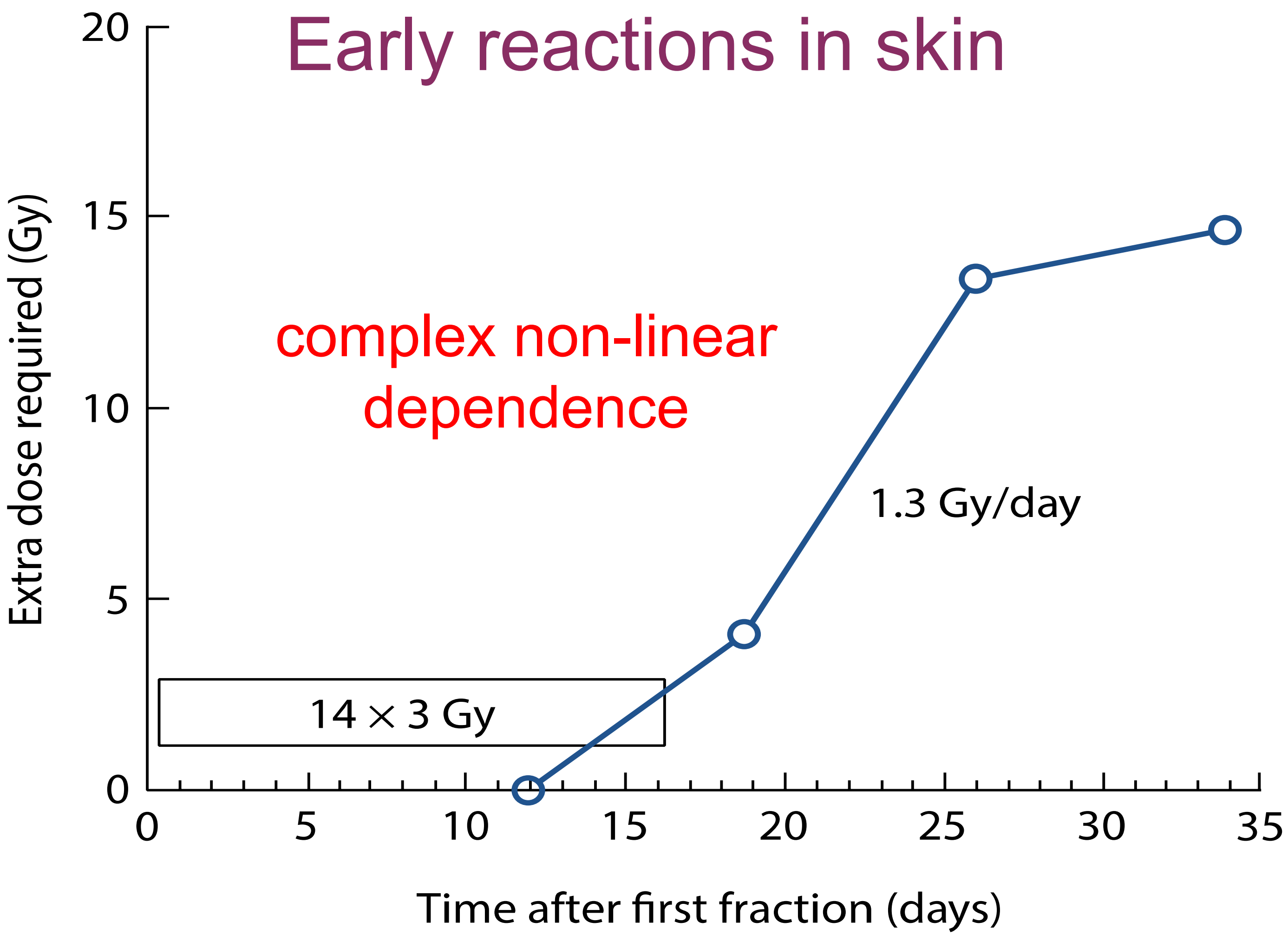
Tissue	Species	Dose delivery#	$T_{1/2}$ (hours)	Source
Haemopoietic	Mouse	CLDR	0.3	Thames *et al.* (1984)
Spermatogonia	Mouse	CLDR	0.3–0.4	Delic *et al.* (1987)
Jejunum	Mouse	F	0.45	Thames *et al.* (1984)
	Mouse	CLDR	0.2–0.7	Dale *et al.* (1988)
Colon (acute injury)	Mouse	F	0.8	Thames *et al.* (1984)
	Rat	F	1.5	Sassy *et al.* (1988)
Lip mucosa	Mouse	F	0.8	Ang *et al.* (1985)
	Mouse	CLDR	0.8	Scalliet *et al.* (1987)
	Mouse	FLDR	0.6	Stüben *et al.* (1991)
Tongue epithelium	Mouse	F	0.75	Dörr *et al.* (1993)
Skin (acute injury)	Mouse	F	1.5	Rojas *et al.* (1991)
	Mouse	CLDR	1.0	Joiner *et al.* (unpublished)
	Pig	F	0.4 + 1.2*	van den Aardweg and Hopewell (1992)
	Pig	F	0.2 + 6.6*	Millar *et al.* (1996)
Lung	Mouse	F	0.4 + 4.0*	van Rongen *et al.* (1993)
	Mouse	CLDR	0.85	Down *et al.* (1986)
	Rat	FLDR	1.0	van Rongen (1989)
Spinal cord	Rat	F	0.7 + 3.8*	Ang *et al.* (1992)
	Rat	CLDR	1.4	Scalliet *et al.* (1989)
	Rat	CLDR	1.43	Pop *et al.* (1996)
Kidney	Mouse	F	1.3	Joiner *et al.* (1993)
	Mouse	F	0.2 + 5.0	Millar *et al.* (1994)
	Rat	F	1.6–2.1	van Rongen *et al.* (1990)
Rectum (late injury)	Rat	CLDR	1.2	Kiszel *et al.* (1985)
Heart	Rat	F	>3	Schultz-Hector *et al.* (1992)

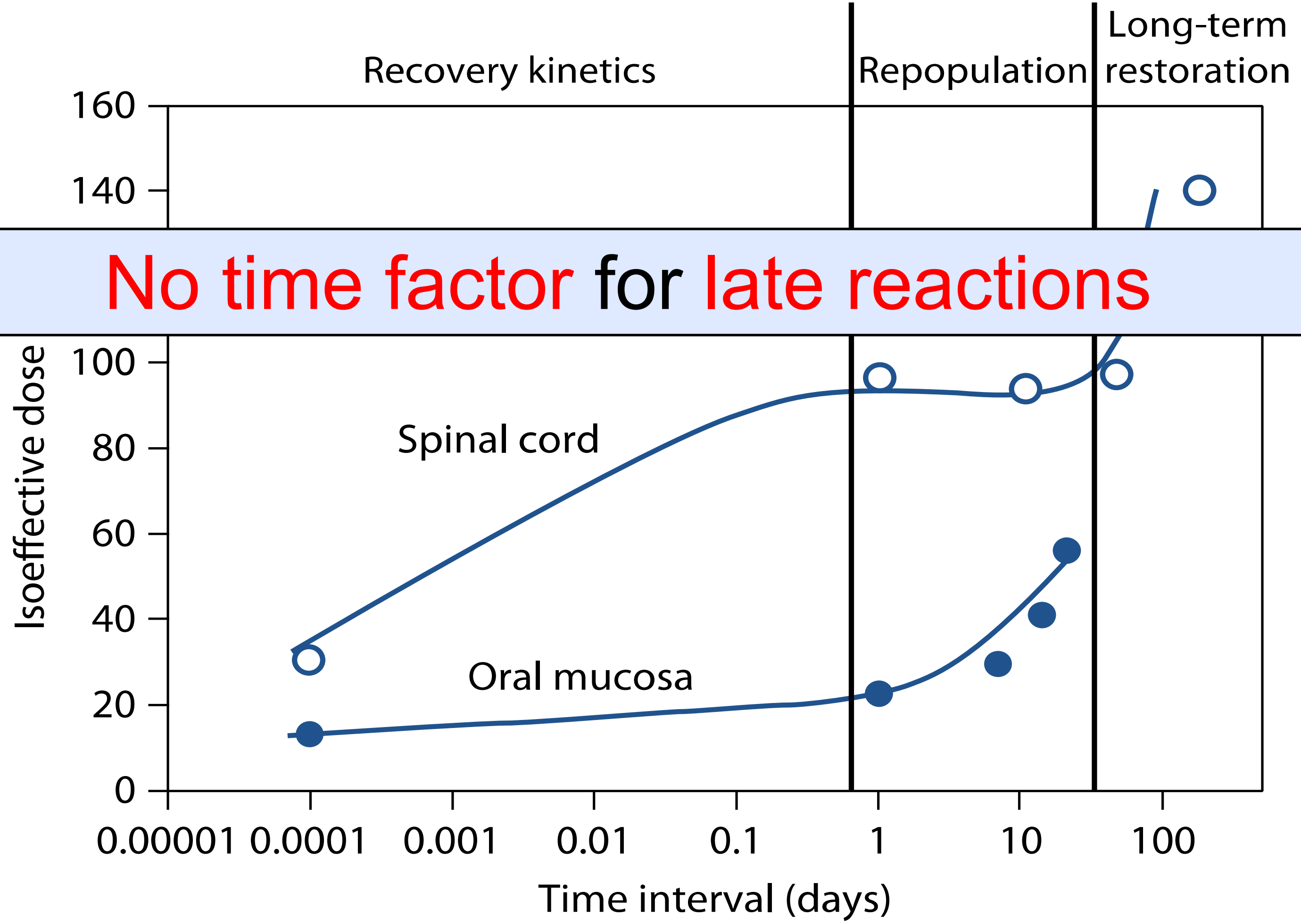
* Two components of repair with different half-times.

continuous low dose rate; F, acute dose fractions; FLDR, fractionated low dose rate.

Tables 9.3, 10.2

Early reactions in skin





No time factor for late reactions

Figure 12.1: Dorr & Kummermehr 1990, Dorr et al 1993, Ruifrok et al 1992, Landuyt et al 1997

Do NOT put proliferation factors in your LQ calculations.

Consider the effect of proliferation separately from changes in dose per fraction and interfraction interval.

EQD2…

Coming up…
Calculations!

EQD2

Bentzen SM et al. *Radiother Oncol* 2012;105:266-8

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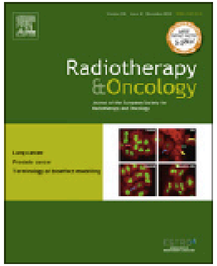

Modeling of bioeffect

Bioeffect modeling and equieffective dose concepts in radiation oncology – Terminology, quantities and units

Søren M. Bentzen [a,*], Wolfgang Dörr [b], Reinhard Gahbauer [c], Roger W. Howell [d], Michael C. Joiner [e], Bleddyn Jones [f], Dan T.L. Jones [g], Albert J. van der Kogel [h], André Wambersie [i], Gordon Whitmore [j]