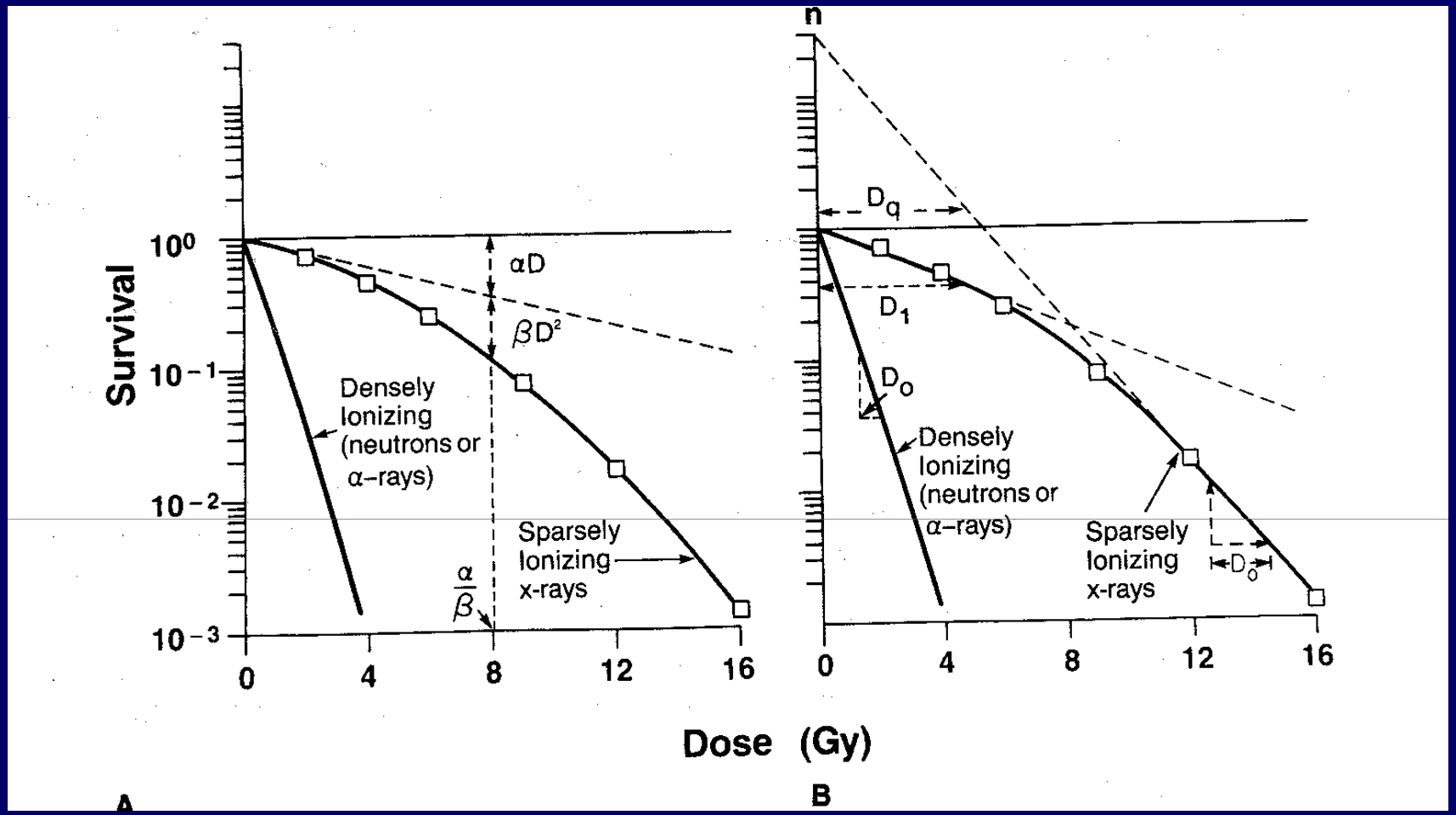
A lineáris-quadratikus megközelítés és előnyei



$E=\alpha D + \beta D^2$

$E=n\,(\alpha d + \beta d^2)$

A lineáris – quadratikus modell

- $E = \alpha D + \beta D^2$
- $E = n(\alpha d + \beta d^2) = (\alpha D + \beta dD)$

- $1/D = (\alpha/E) + (\beta/E)d$ A
- $1/n = (\alpha/E)d + (\beta/E)d^2$ B
- $D = (E/\alpha) / \{1 + d / (\alpha/\beta)\}$ C

$$\frac{D_2}{D_1} = \frac{d_1 + (\alpha/\beta)}{d_2 + (\alpha/\beta)}$$ E

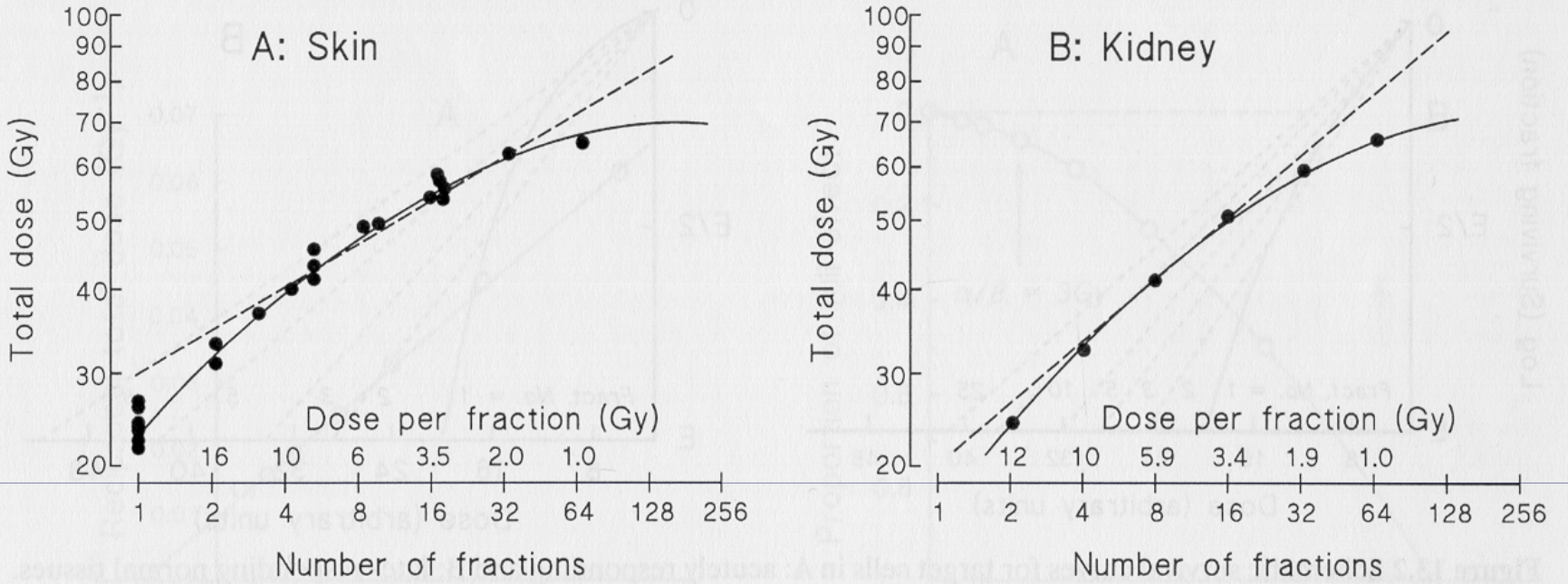


Figure 13.1 Relationship between *total dose* to achieve an isoeffect and *number of fractions*. **A**: acute reactions in mouse skin (Douglas and Fowler, 1976). **B**: late injury in mouse kidney (Stewart *et al*, 1984). Note that the relationship for kidney is steeper than that for skin. The broken lines are NSD formulae fitted to the central part of each data set. The solid lines show the LQ model, from which the guide to the dose per fraction has been calculated. Reproduced with permission.

$$D = \frac{k}{1+d/(\alpha/\beta)}$$

$$D = NSD \times N^{m} \times T^{0.11}$$

m = 0,24 v. 0,35

Sejtbiológiai alapok

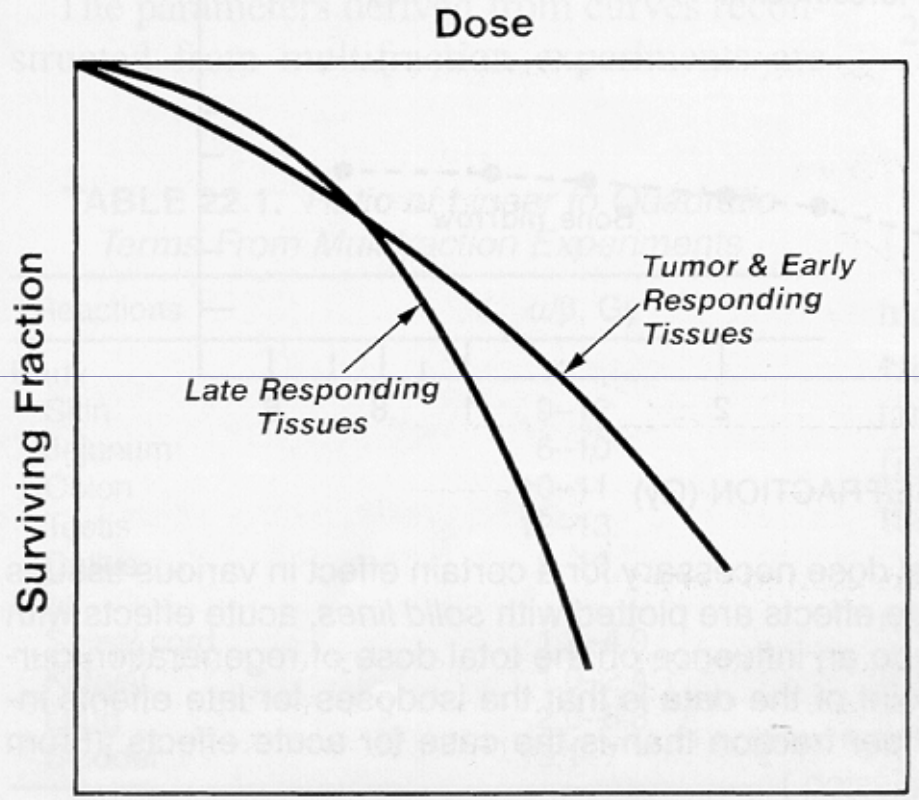


Figure 22.6. The dose–response relationship for late-responding tissues is more curved than for early-responding tissues. In the linear-quadratic formulation this translates into a larger α/β for early than for late effects. The ratio α/β is the dose at which the linear (α) and the quadratic (β) components of cell killing are equal: that is, $\alpha D = \beta D_2$. (Based on the concepts of Withers.)

Az LQ modell sejttúlélési alapja

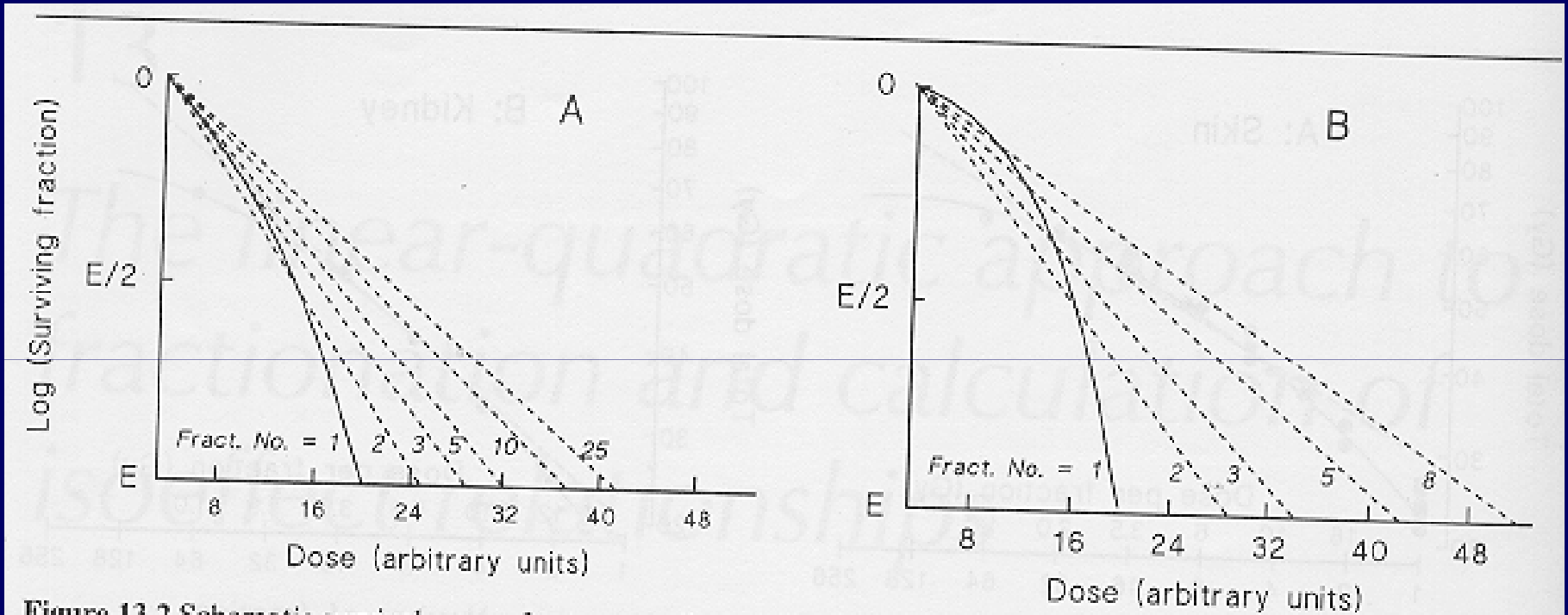


Figure 13.2 Schematic survival curves for target cells in **A**: acutely responding and **B**: late- responding normal tissues. The abscissa is radiation dose on an arbitrary scale. From Thames and Hendry (1987), with permission.

α/β arány meghatározása

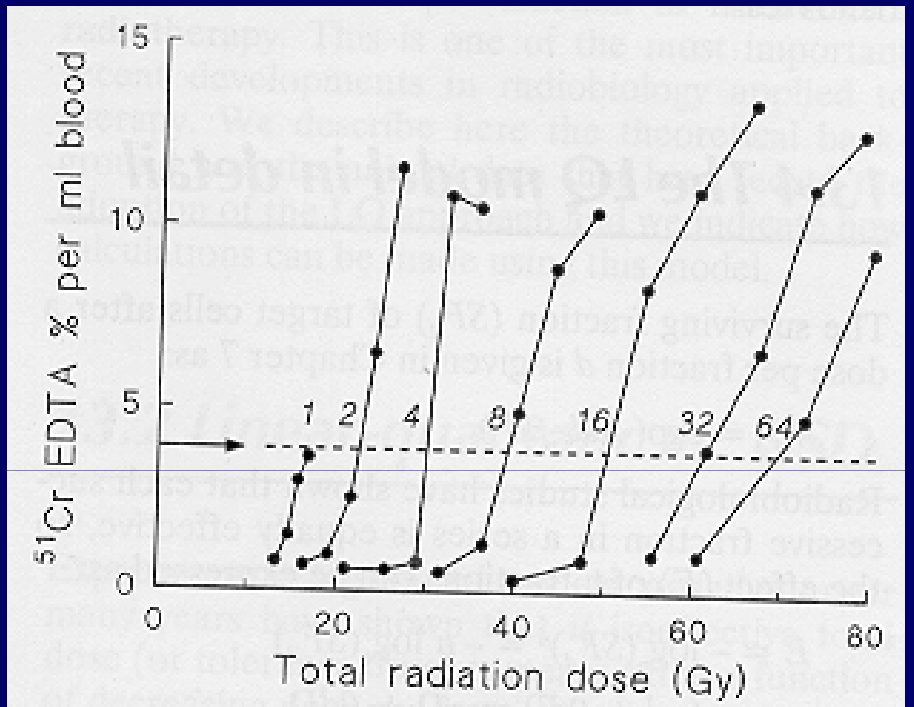


Figure 13.3 Dose–response curves for late damage to the mouse kidney with fractionated radiation exposure. Damage is indicated by EDTA clearance, curves determined for 1 to 64 dose fractions, illustrating the sparing effect of increased fractionation. From Stewart *et al* (1984), with permission.

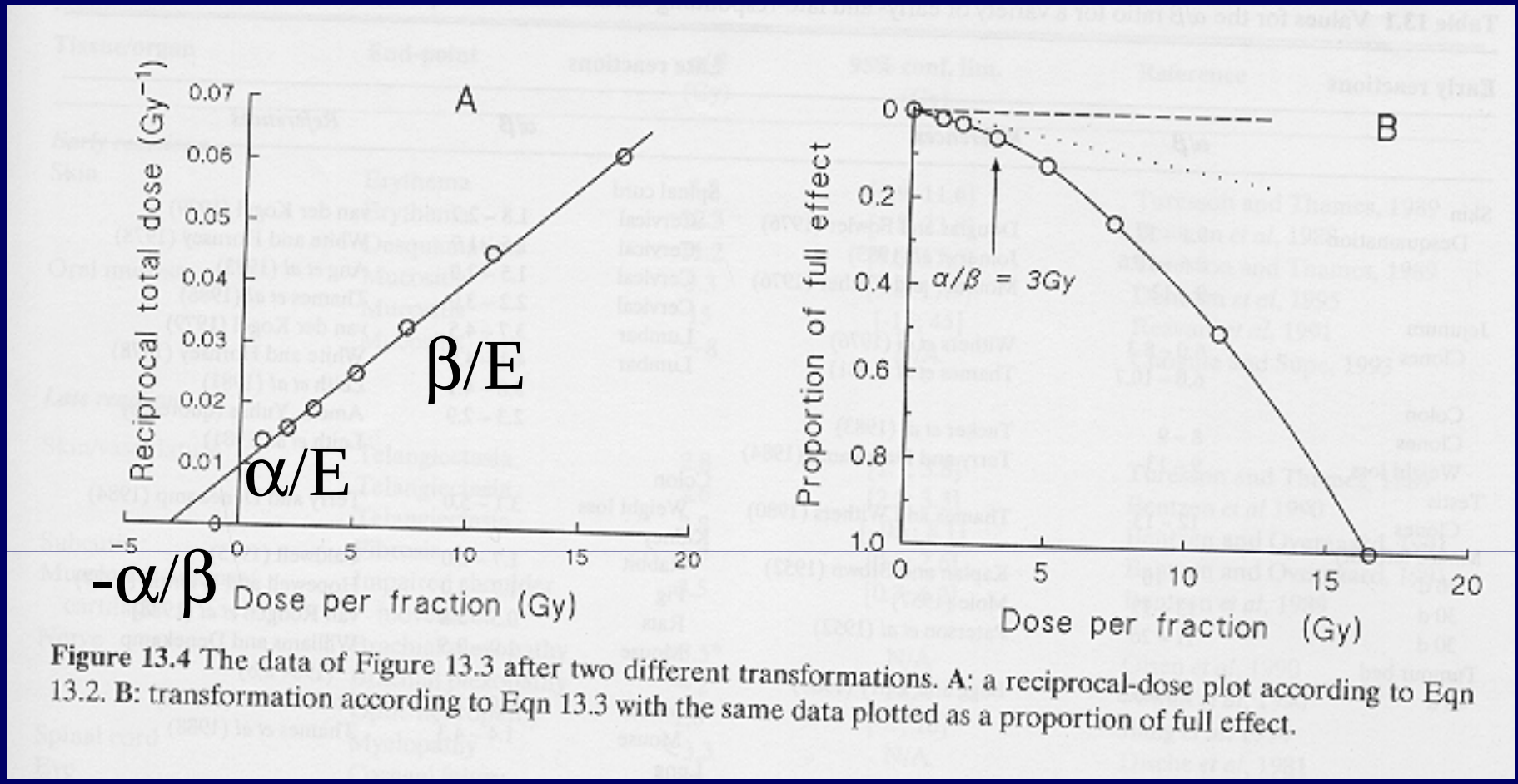


Figure 13.4 The data of Figure 13.3 after two different transformations. **A**: a reciprocal-dose plot according to Eqn 13.2. **B**: transformation according to Eqn 13.3 with the same data plotted as a proportion of full effect.

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

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

Normál szövetek α/β értéke kísérleti állatokban

Table 13.1 Values for the α/β ratio for a variety of early- and late-responding normal tissues in experimental animals

Early reactions	α/β	References
Skin		
Desquamation	9.1 – 12.5	Douglas and Fowler (1976)
	8.6 – 10.6	Joiner *et al* (1983)
	9 – 12	Moulder and Fischer (1976)
Jejunum		
Clones	6.0 – 8.3	Withers *et al* (1976)
	6.6 – 10.7	Thames *et al* (1981)
Colon		
Clones	8 – 9	Tucker *et al* (1983)
Weight loss	9 – 13	Terry and Denekamp (1984)
Testis		
Clones	12 – 13	Thames and Withers (1980)
Mouse lethality		
30 d	7 – 10	Kaplan and Brown (1952)
30 d	13 – 17	Mole (1957)
30 d	11 – 26	Paterson *et al* (1952)
Tumour bed		
45 d	5.6 – 6.8	Begg and Terry (1984)

Late reactions	α/β	References
Spinal cord		
Cervical	1.8 – 2.7	van der Kogel (1979)
Cervical	1.6 – 1.9	White and Hornsey (1978)
Cervical	1.5 – 2.0	Ang *et al* (1983)
Cervical	2.2 – 3.0	Thames *et al* (1988)
Lumbar	3.7 – 4.5	van der Kogel (1979)
Lumbar	4.1 – 4.9	White and Hornsey (1978)
	3.8 – 4.1	Leith *et al* (1981)
	2.3 – 2.9	Amols, Yuhas (quoted by Leith *et al*, 1981)
Colon		
Weight loss	3.1 – 5.0	Terry and Denekamp (1984)
Kidney		
Rabbit	1.7 – 2.0	Caldwell (1975)
Pig	1.7 – 2.0	Hopewell and Wiernik (1977)
Rats	0.5 – 3.8	van Rongen *et al* (1988)
Mouse	1.0 – 3.5	Williams and Denekamp (1984 a,b)
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* (1984b)

α/β values are in grays.
From Fowler (1989); for references, see the original.

Daganatok α/β értéke

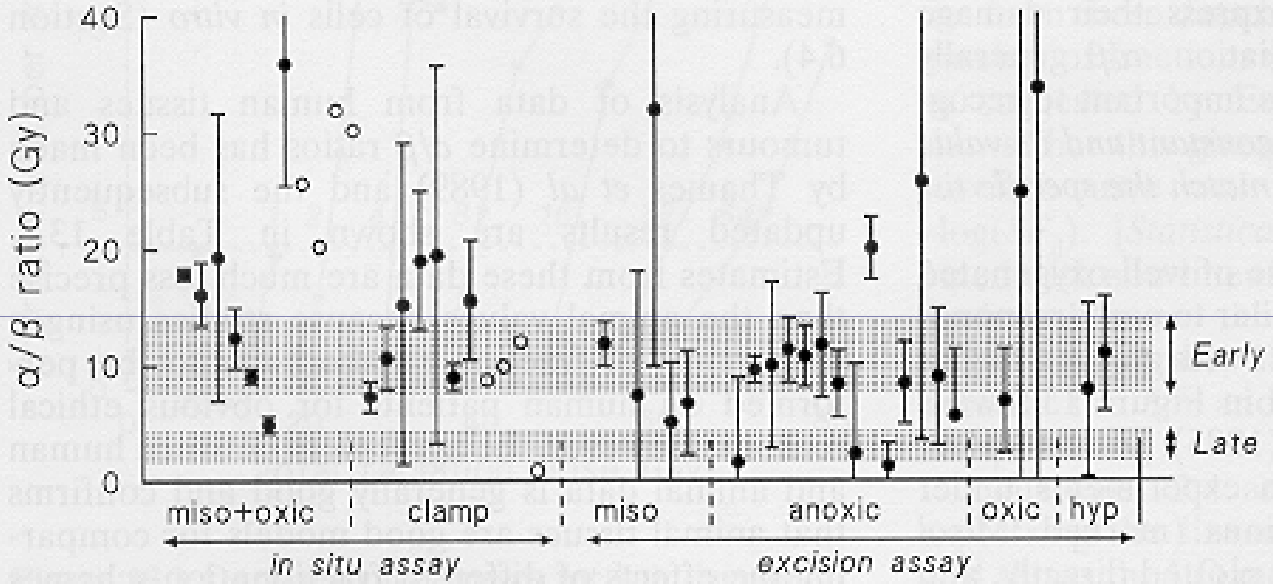


Figure 13.5 Values of α/β for experimental tumours, determined under a variety of conditions of oxygenation (see text). The stippled areas indicate the range of values for early- and late-responding normal tissues. From Williams *et al* (1985), with permission.

α/β értékek emberben

Table 13.2 α/β ratios for human normal tissues and tumours

Tissue/organ	End-point	α/β (Gy)	95% conf. lim. (Gy)	Reference
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
	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
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	±0.7	Deore *et al*, 1993
Lung	Pneumonitis	3.3	±1.5	van Dyk *et al*, 1989
	Fibrosis (radiological)	3.1	[-0.2; 8.5]	Dubray *et al*, 1995
Head and neck	Various late effects	3.5	±1.2	Rezvani *et al*, 1991
Supraglottic larynx	Various late effects	3.8	[0.8; 14]	Maciejewski *et al*, 1986
Oral cavity + oroph.	Various late effects	0.8	[–0.6;2.5]	Maciejewski *et al*, 1990
Tumours				
Head and neck				
Larynx		14.5*	±4.9	Rezvani *et al*, 1993
Vocal cord		~13	wide	Robertson *et al*, 1993
Oropharynx		~16*	N/A	Horiot *et al*, 1992
Buccal mucosa		6.6	[2.9; infinity]	Maciejewski *et al*, 1989
Tonsil		7.2	[3.6; infinity]	Maciejewski *et al*,1989
Nasopharynx		16	[–11; 43]	Lee *et al*, 1995
Skin		8.5*	[4.5; 11.3]	Trott *et al*, 1984
Melanoma		0.6	[–1.1; 2.5]	Bentzen *et al*, 1989
Liposarcoma		0.4	[–1.4; 5.4]	Thames and Suit 1986

* Reanalysis of original published data.
Compiled by Bentzen and Thames (unpublished). See also Thames *et al* (1990).

A biológiailag hatásos dózis

(Biologically Effective Dose – BED) (Fowler, 1989)

$D = (E/\alpha) / \{1 + d / (\alpha/\beta)\}$ C

$E/\alpha = D \{1 + d/(\alpha/\beta)\} = BED$ Gy

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

Ekvivalens dózis 2 Gy frakciókra

(Withers et al. 1983)

Izoeffektív dózis számítások

Extrapolált tolerancia dózis (ETD)

$BED = ETD$

Total effect (TE)

$TE = E/\beta = D\,(\alpha/\beta + d)$ Gy^2

$TE = \alpha/\beta \times BED$

Practical Calculations – Example 1

Background: Head and neck cancer. The planned treatment is 70 Gy in 35 fractions (abbreviated 70 Gy/35 fx). Due to a dosimetric error the first six fractions were given with 4 Gy/fx instead of 2 Gy/fx. The accumulated dose is thus 24 Gy in 6 fx. Treatment will be continued using 2 Gy/fx.

Question: How many fractions of 2 Gy should be given to maintain an equal probability of late fibrosis?

Assumption: α/β for late fibrosis = 3.5 Gy

$BED = D \{1 + d/(\alpha/\beta)\}$

Solution to Example 1:

1.	$BED = 70 \times (1 + 2/3.5) = 110$	calculate *BED*
2.	$PE_1 = 24 \times (1 + 4/3.5) = 51.4$	*PE* of first six fractions
3.	$PE_2 = BED - PE_1 = 58.6$	remaining *PE*
4.	$PE_2 = D_2 \times (1 + 2/3.5) = 58.6$	D_2 at 2 Gy per fraction
5.	$D_2 = 58.6/1.57 = 37.3$	remaining total dose
6.	At 2 Gy/fx: 37.3 / 2 = 18 or 19 fractions	remaining number of fractions

Practical Calculations – Example 2

Background: Melanoma, elective radiotherapy of nodal area. The planned treatment is five fractions of 6 Gy (2 fx/week). After the first fraction it was discovered that by mistake a single dose of 12 Gy had been given. It was decided to complete the treatment with the same total number of five fractions.

Question: What fraction size should be used for the remaining four treatments? Is there a risk of radiation damage to the spinal cord?

Assumptions: α/β for late fibrosis = 3.5 Gy; α/β for damage to the spinal cord = 2 Gy.

BED = D {1 +d/(α /β)}

Solution A to Example 2, Late fibrosis:

1.	$BED = 30 \times (1 + 6/3.5) = 81.4$	*BED* of planned treatment
2.	$PE_1 = 12 \times (1 + 12/3.5) = 53.1$	partial *BED* for first fraction
3.	$PE_2 = 81.4 - 53.1 = 28.3$	partial *BED* for remaining 4 fx
4.	$PE_2 = D_2 \times [1 + D_2/(4 \times 3.5)]$	
5.	$28.3 = D_2 + D_2^2/14$	filling in the known values
6.	$0.0714\, D_2^2 + D_2 - 28.3 = 0$	quadratic equation:
		$D = \left\{-b + \sqrt{b^2 - 4ac}\right\} / 2a$
7.	$D_2 = 14$ Gy; $d_2 = 3.5$ Gy	

Solution B to Example 2, Spinal cord tolerance:

1.	$BED_{ref} = 50 \times (1 + 2/2) = 100$	reference *BED* for the cord; 2 Gy/fx
2.	$BED_{plan} = 30 \times (1 + 6/2) = 120$	planned treatment: 5 × 6 Gy
3.	$BED_{plan} / BED_{ref} = 1.2$	cord tolerance exceeded by 20%
4.	$100 = D_{max} \times (1 + 6/2)$	D_{max} (cord) for 6-Gy fractions
		maximum four fractions of 6 Gy
5.	$D_{max} = 100/4 = 25$ Gy	

Double trouble

Az inkomplet (nem – teljes) repair hatása

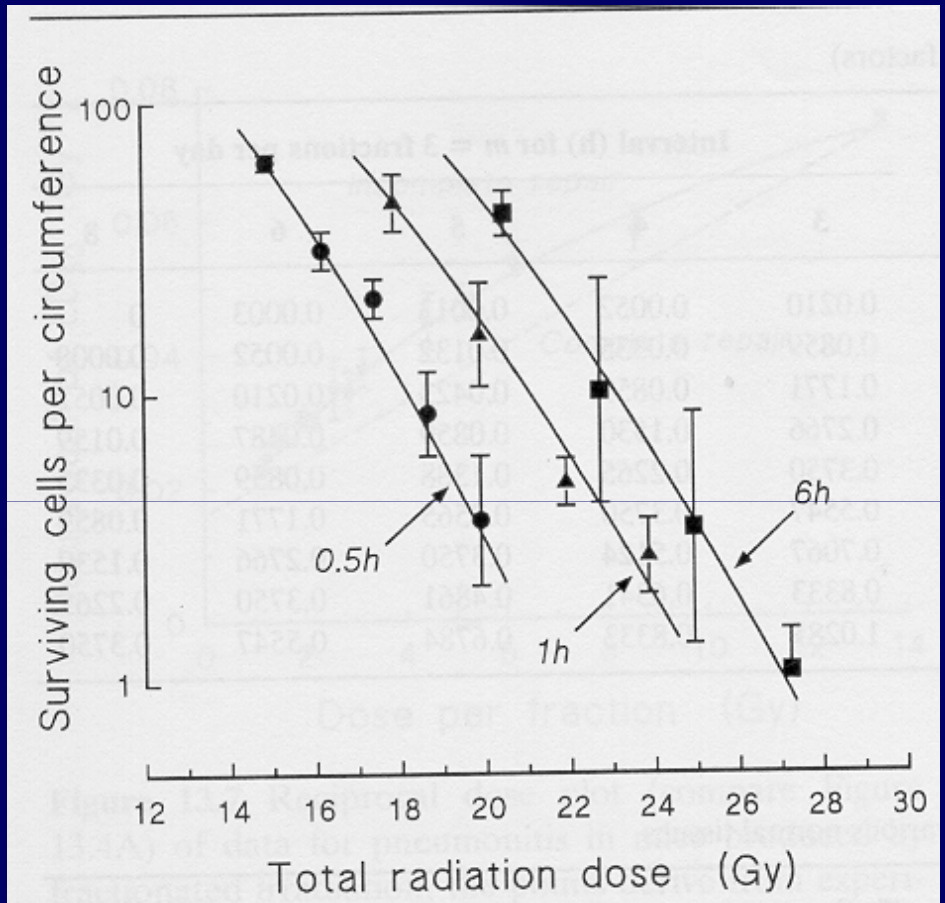


Figure 13.6 Effect of inter-fraction interval on intestinal radiation damage in mice. The total dose required in five fractions for a given level of effect is less for short intervals, illustrating incomplete repair between fractions. From Thames, Withers and Peters (1984), with permission.

$T_{1/2}$ = repair félidő

$T_{1/2}$ = repair félidő

H_m = inkomplet repair faktor (frakcionált besugárzás)

$$BED = D \{1 + d/(\alpha/\beta) + H_m d/(\alpha/\beta)\}$$

(Thames 1985)

Table 13.3 Incomplete repair factors: fractionated irradiation (H_m factors)

Repair half-time (h)	Interval (h) for $m = 2$ fractions per day					Interval (h) for $m = 3$ fractions per day				
	3	4	5	6	8	3	4	5	6	8
0.5	0.0156	0.0039	0.0010	0.0002	0	0.0210	0.0052	0.0013	0.0003	0
0.75	0.0625	0.0248	0.0098	0.0039	0.0006	0.0859	0.0335	0.0132	0.0052	0.0008
1.0	0.1250	0.0625	0.0312	0.0156	0.0039	0.1771	0.0859	0.0423	0.0210	0.0052
1.25	0.1895	0.1088	0.0625	0.0359	0.0118	0.2766	0.1530	0.0859	0.0487	0.0159
1.5	0.2500	0.1575	0.0992	0.0625	0.0248	0.3750	0.2265	0.1388	0.0859	0.0335
2.0	0.3536	0.2500	0.1768	0.1250	0.0625	0.5547	0.3750	0.2565	0.1771	0.0859
2.5	0.4353	0.3299	0.2500	0.1895	0.1088	0.7067	0.5124	0.3750	0.2766	0.1530
3.0	0.5000	0.3969	0.3150	0.2500	0.1575	0.8333	0.6341	0.4861	0.3750	0.2265
4.0	0.5946	0.5000	0.4204	0.3536	0.2500	1.0285	0.8333	0.6784	0.5547	0.3750

From Thames and Hendry (1987), with permission.

Table 13.4 Half-times for recovery from radiation damage ($T_{½}$) in various normal tissues

Tissue	Species	Dose delivery*	$T_{½}$ (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)
Oral mucosa	Human	F	2.0–4.0	Bentzen *et al* (1996)
	Human	FLDR	0.3–0.5	Denham *et al* (1995)
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)
	Human	F	0.35–1.2	Turesson and Thames (1989)
	Human	F	? + <1***	Nyman and Turesson (1995)
Skin (late injury)	Human	F	0.4 + 3.5**	Turesson and Thames (1989)
	Human	F	? + ?***	Nyman and Turesson (1995)
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	1.8	Pop *et al* (1997)
	Human	F	? + >5***	Dische and Saunders (1989)
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)

* F = acute dose fractions, FLDR = fractionated low dose rate, CLDR = continuous low dose rate.
** Two components of repair with different half-times.
*** Evidence for two components of repair with different half-times, but values uncertain.

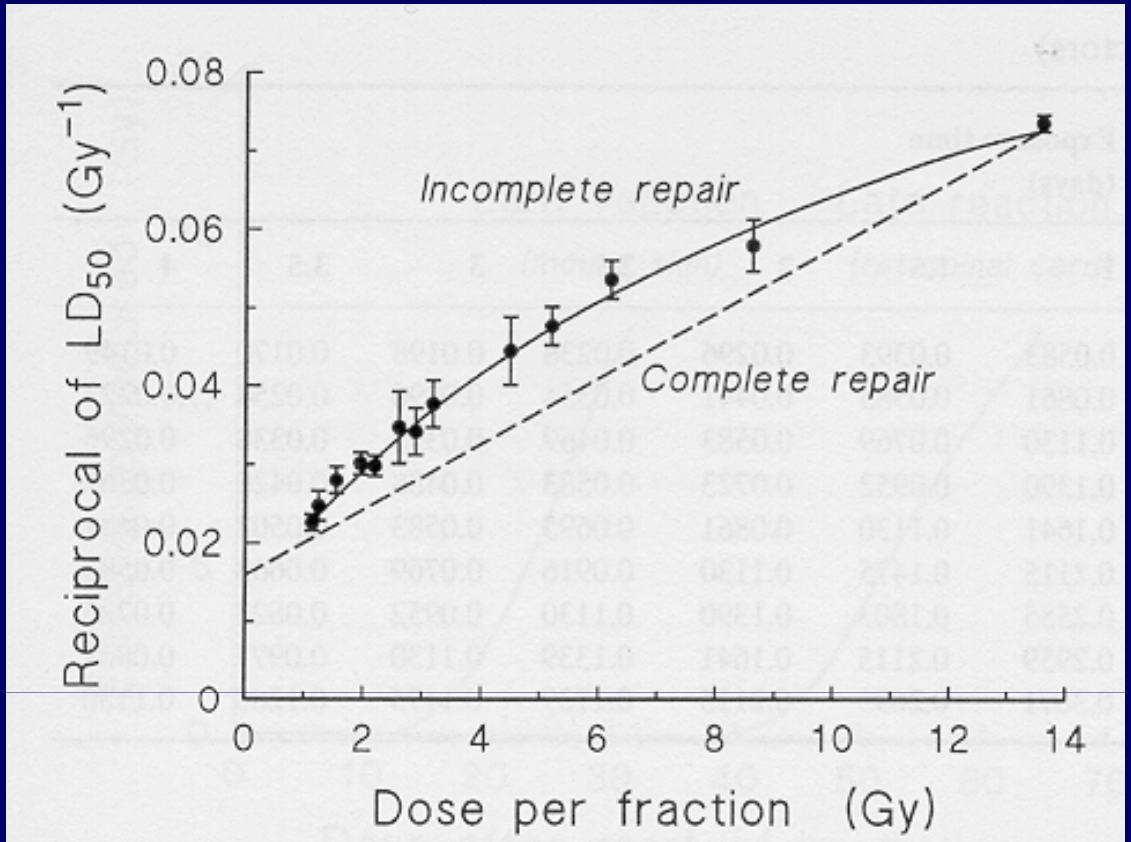


Figure 13.7 Reciprocal dose plot (compare Figure 13.4A) of data for pneumonitis in mice produced by fractionated irradiation; the points derive from experiments with different dose per fraction (and therefore different fraction numbers), always with 3 h between doses. The upward bend in the data illustrates lack of sparing due to incomplete repair. From Thames, Withers and Peters (1984), with permission.

Inkomplet repair faktor (g) folyamatos besugárzás esetén

$$BED = D \{1 + Dg/(\alpha/\beta)\}$$

Table 13.5 Incomplete repair factors: continuous irradiation (*g* factors)

Repair half-time (h)	Exposure time (h)						Exposure time (days)						
	1	2	3	4	8	12	1	1.5	2	2.5	3	3.5	4
0.5	0.6622	0.4774	0.3671	0.2959	0.1641	0.1130	0.0583	0.0393	0.0296	0.0238	0.0198	0.0170	0.0149
0.75	0.7517	0.5888	0.4774	0.3983	0.2339	0.1641	0.0861	0.0583	0.0441	0.0354	0.0296	0.0254	0.0223
1	0.8040	0.6622	0.5571	0.4774	0.2959	0.2115	0.1130	0.0769	0.0583	0.0469	0.0393	0.0338	0.0296
1.25	0.8382	0.7137	0.6165	0.5394	0.3504	0.2555	0.1390	0.0952	0.0723	0.0583	0.0488	0.0420	0.0369
1.5	0.8622	0.7517	0.6622	0.5888	0.3983	0.2959	0.1641	0.1130	0.0861	0.0695	0.0583	0.0502	0.0441
2	0.8938	0.8040	0.7276	0.6622	0.4774	0.3671	0.2115	0.1475	0.1130	0.0916	0.0769	0.0663	0.0583
2.5	0.9136	0.8382	0.7720	0.7137	0.5394	0.4269	0.2555	0.1803	0.1390	0.1130	0.0952	0.0822	0.0723
3	0.9272	0.8622	0.8040	0.7517	0.5888	0.4774	0.2959	0.2115	0.1641	0.1339	0.1130	0.0977	0.0861
4	0.9447	0.8938	0.8471	0.8040	0.6622	0.5571	0.3671	0.2693	0.2115	0.1739	0.1475	0.1280	0.1130

From Thames and Hendry (1987), with permission.

Az időtényező

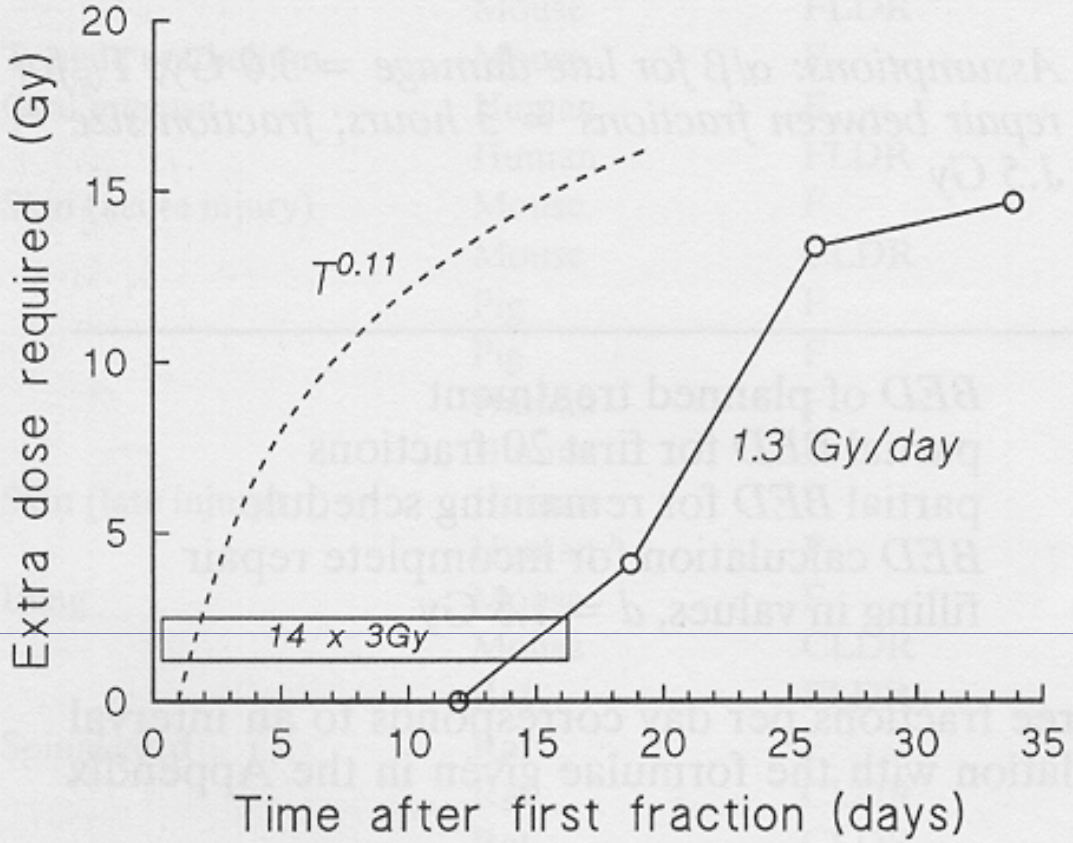


Figure 13.8 Extra dose required to counteract proliferation in mouse skin. Test doses of radiation were given at various intervals after a priming treatment with fractionated radiation. Proliferation begins about 12 days after the start of irradiation and is then equivalent to an extra dose of approximately 1.3 Gy/day. The broken line shows the prediction of the NSD equation. Adapted from Denekamp (1973), with permission.

Az LQ modell nem használ időfaktort. Az NSD igen.

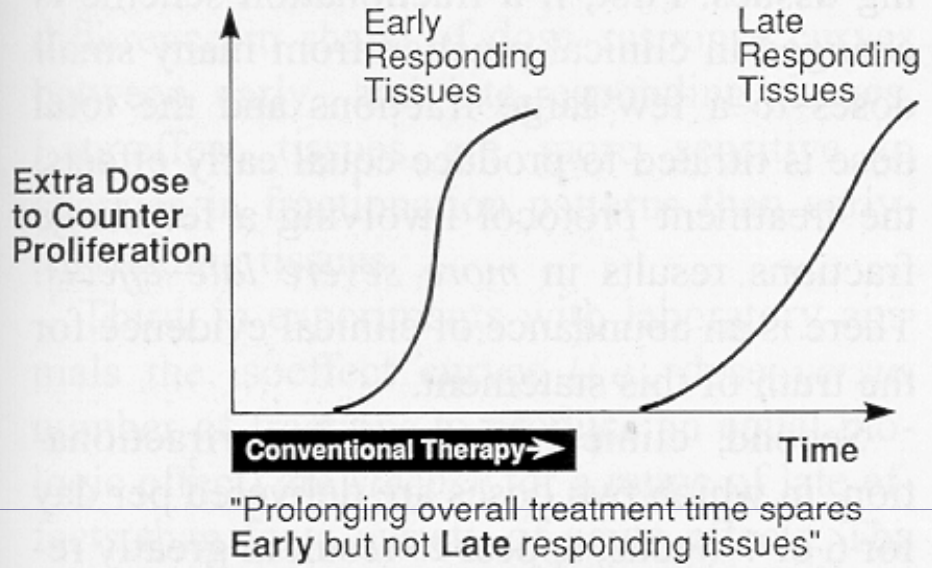


Figure 22.5. Highly speculative illustration attempting to extrapolate the experimental data for early- and late-responding tissue in rats and mice to principles that can be applied in clinical radiotherapy. The extra dose required to counter proliferation in early-responding tissues begins to increase after a few weeks into a fractionated regimen, certainly during the time course of conventional therapy. By contrast, conventional protocols are never sufficiently long to include the proliferation of late-responding tissues.

Szünet a kezelés alatt

- a betegek 1/3-ában
- beteggel kapcsolatos okok
- betegtől független okok

- változatlan kezelés
- frakció-dózis növelése
- változatlan idő alatt, változatlan frakció-számmal
- napi több frakcióval

Overal treatment time

Suwinski et al. (2003) Int. J. Radiat Oncol Biol Phys 56: 399-412

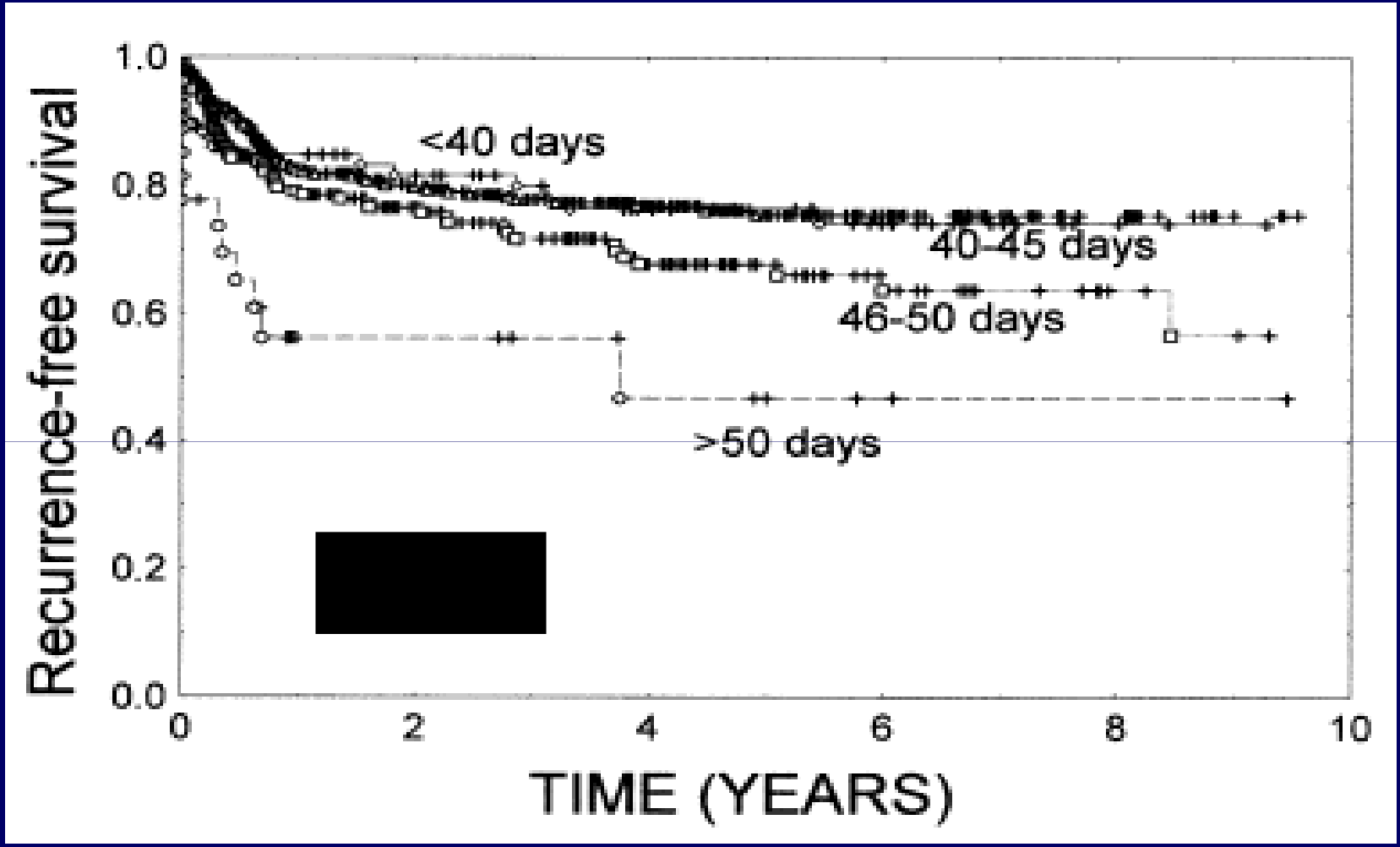


Fig. 2. Locoregional recurrence-free survival according to the overall radiation treatment time (OTT), the average dose intensity of radiation treatment (DI), and total duration of treatment gaps

Gaps during treatment

Suwinski et al. (2003) Int. J. Radiat Oncol Biol Phys 56: 399-412

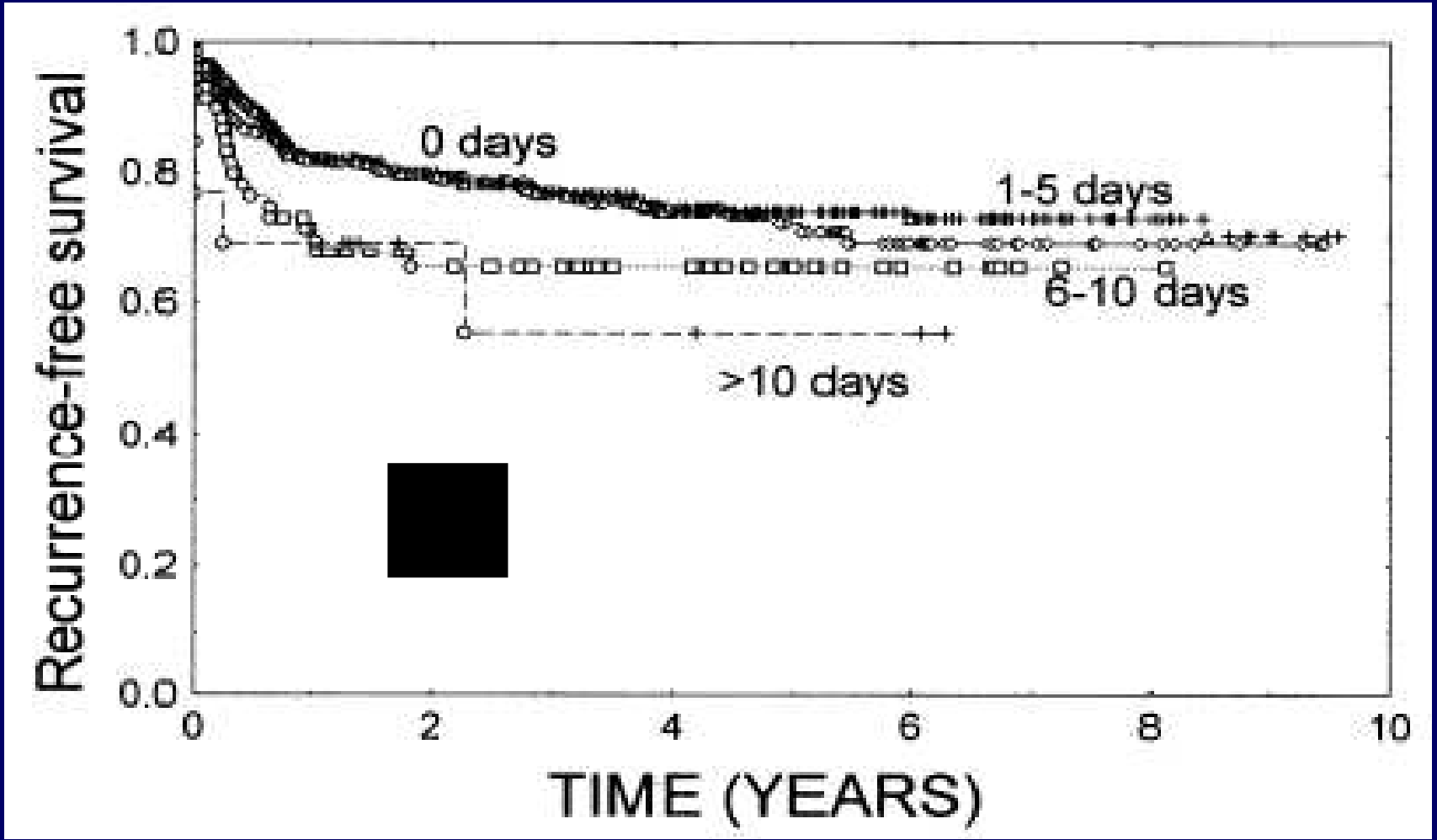


Fig. 2. Locoregional recurrence-free survival according to the overall radiation treatment time (OTT), the average dose intensity of radiation treatment (DI), and total duration of treatment gaps

Overal treatment time

Suwinski et al. (2003) Int. J. Radiat Oncol Biol Phys 56: 399-412

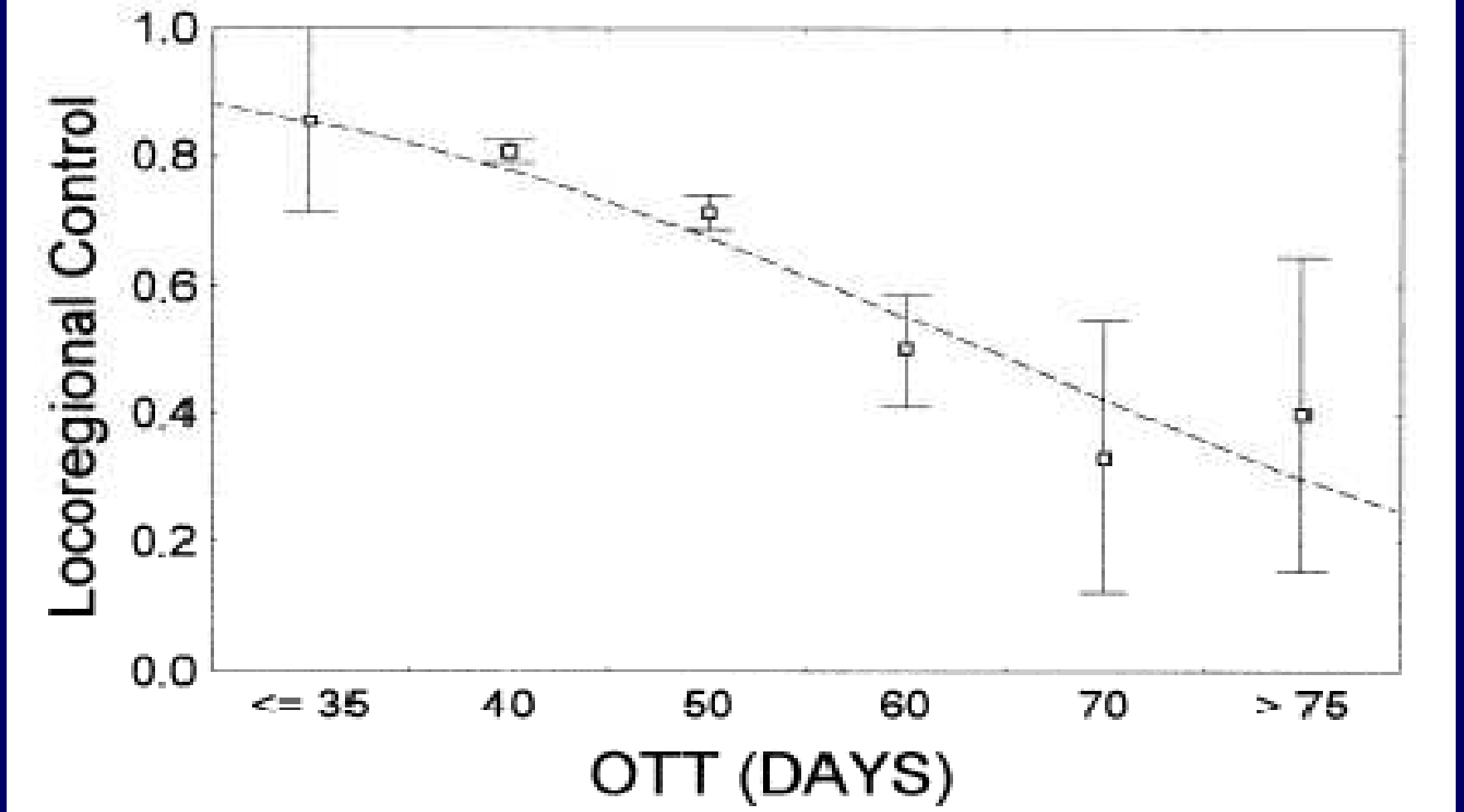


Fig. 3. Locoregional tumor control probability (TCP), according to overall radiation treatment time (OTT) (a) and dose intensity of radiation treatment (DI) (b). The data were restricted to 843 patients who were given total radiation dose in the range of 50–70 Gy.

Interval after surgery

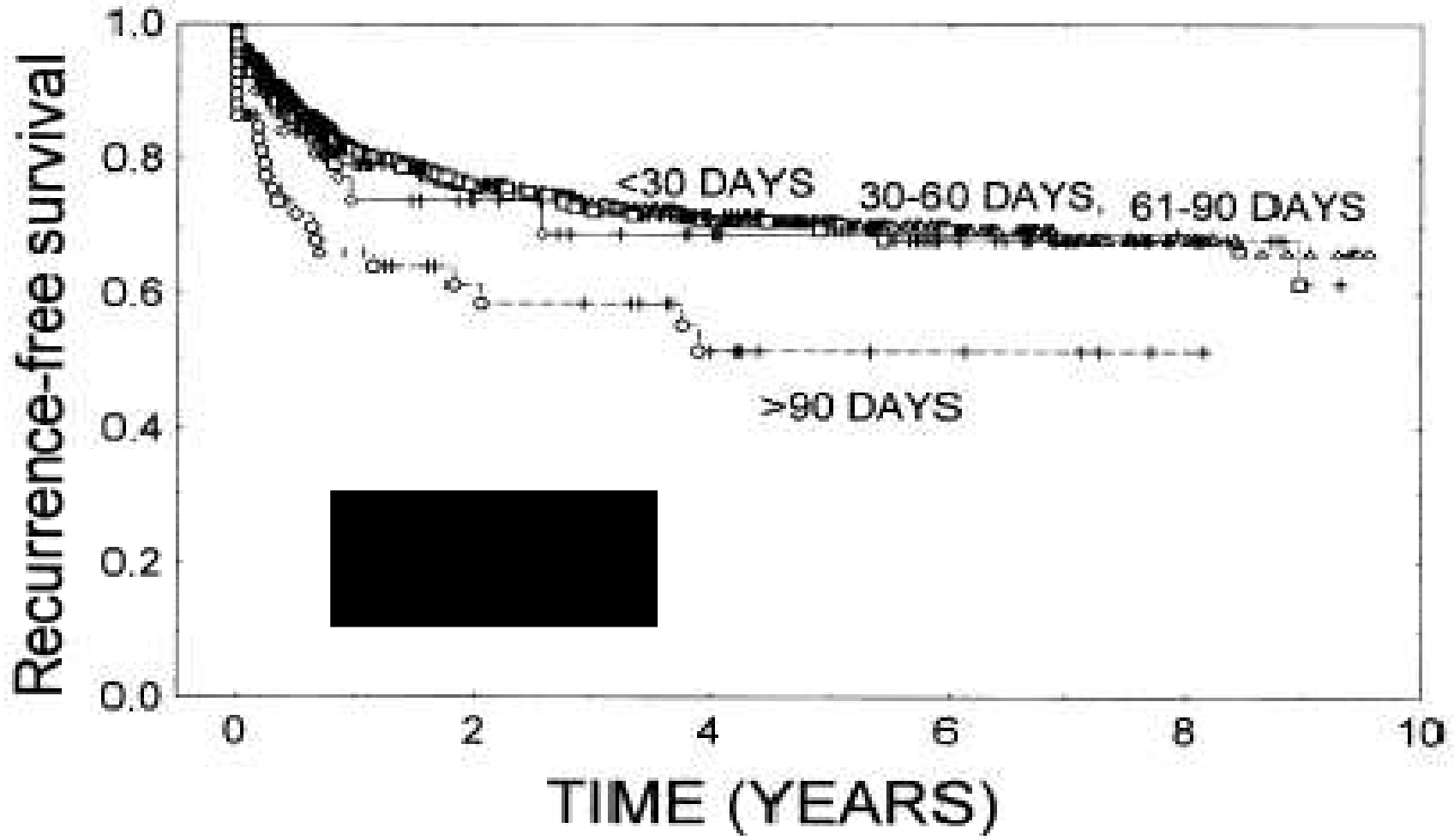


Fig. 4. Locoregional recurrence-free survival according to the duration of the interval surgery-radiotherapy (T_{SPRT}).

Suwinski et al. (2003) Int. J. Radiat Oncol Biol Phys 56: 399-412

Az LQ modell megbízhatósága

Konklúzió

- Az LQ modell kielégítően jellemzi az izoeffektív dózisok és a frakció dózisok viszonyát
- Az α /β arány jól jellemzi a frakcionálásra adott válasz-reakciókat
- A BED formula jól használható izoeffektív dózisok számítására
- Rövid frakciók közti időtartam esetén figyelembe kell venni a $T_{1/2}$ időt