A frakcionált sugárterápia alapjai

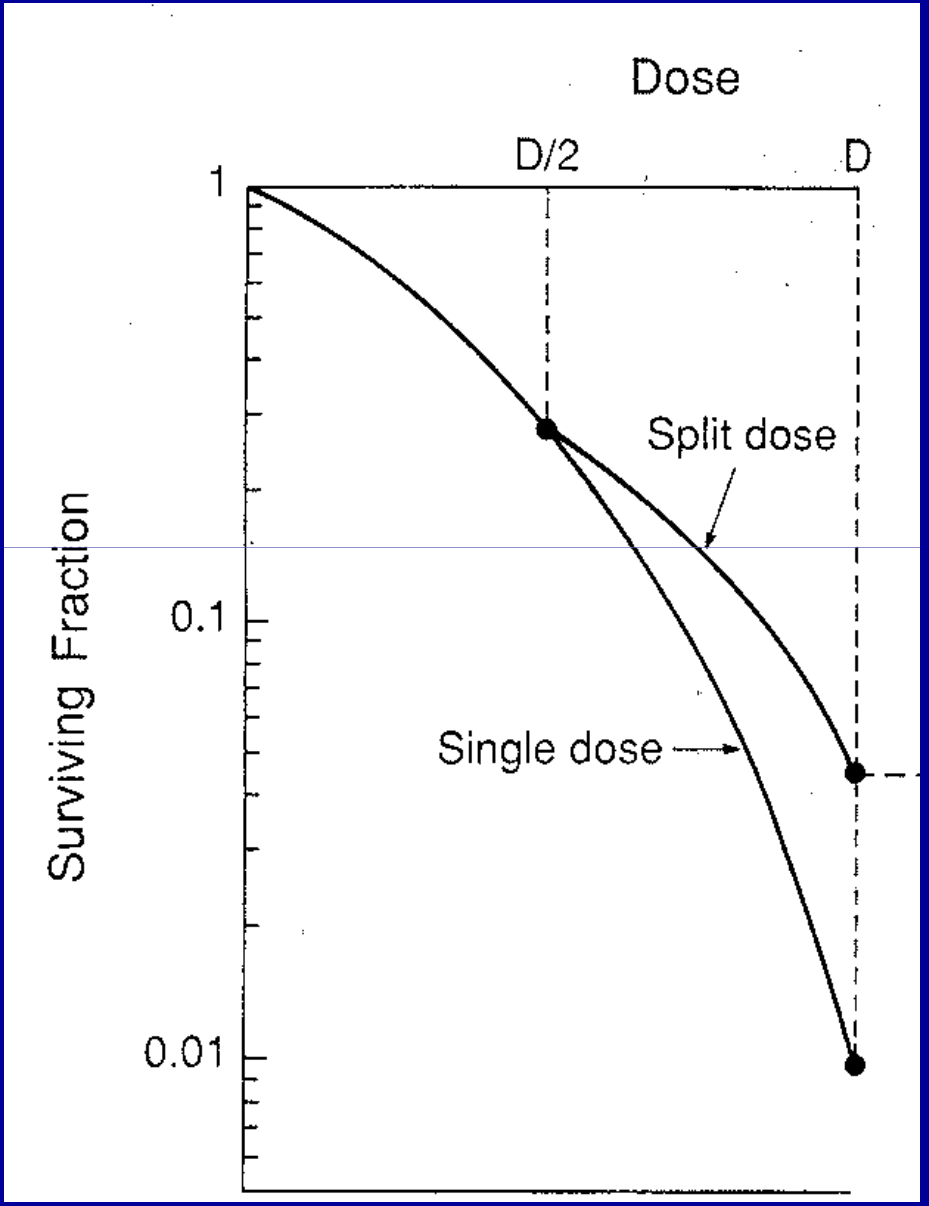
Figure 22.1. Conventional multifraction radiotherapy was based on experiments performed in Paris in the 1920s and 1930s. Rams could not be sterilized with a single dose of x-rays without extensive skin damage, whereas if the radiation were delivered in daily fractions over a period of time, sterilization was possible without skin damage. The testes were regarded as a model of a growing tumor and skin as dose-limiting normal tissue.

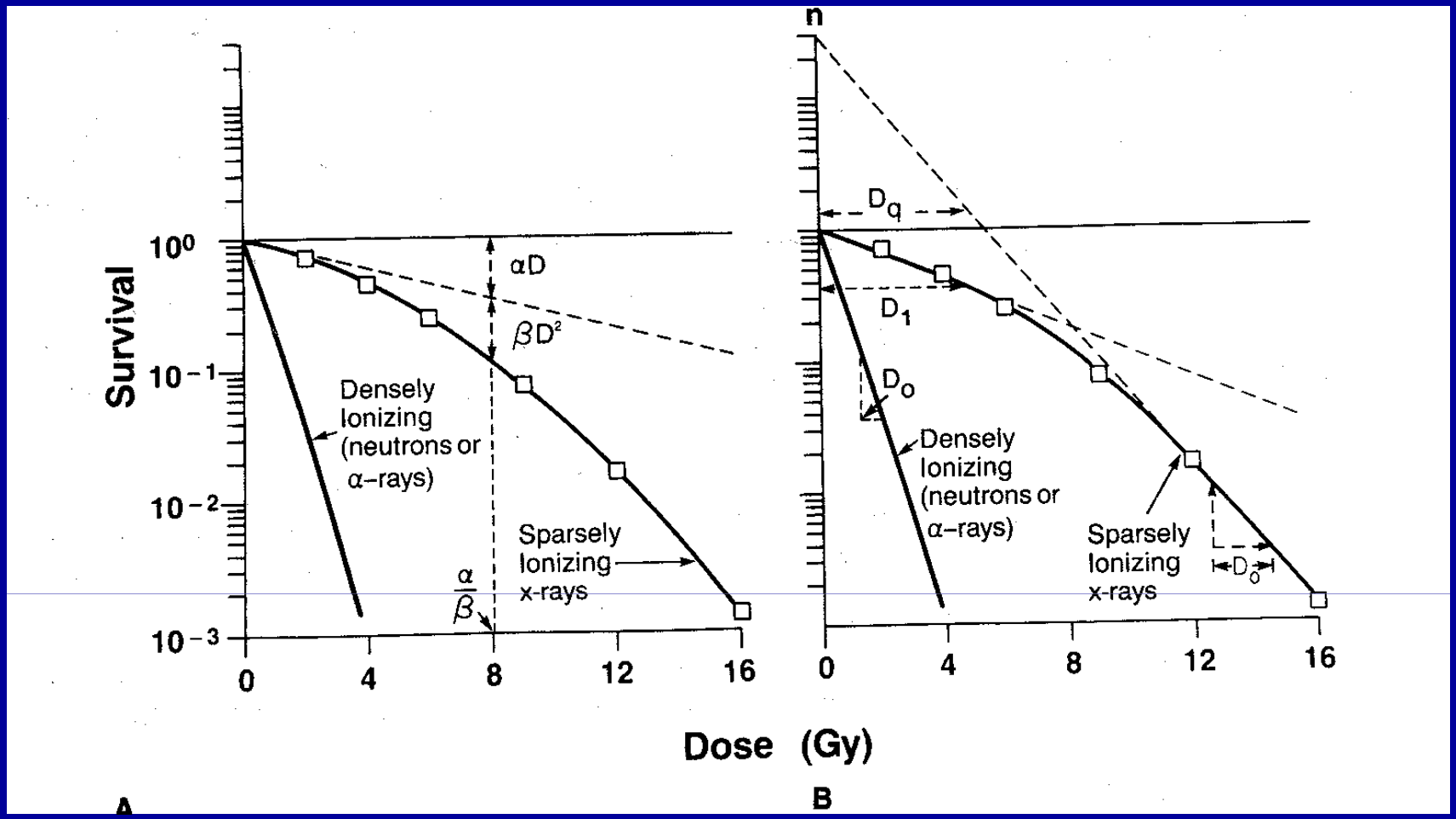
A sugárkárosodások típusai

- Letális károsodás: nem javítható, a sejt halálához vezet.
- Szubletális károsodás: kijavítható, hacsak rövid időn belül újabb szubletális károsodás nem éri a sejtet.
- Potenciálisan letális károsodás: olyan letális károsodás, amely bizonyos körülmények között kijavítható.

Szubletális károsodások

Frakcionált besugárzás hatása





n – extrapolációs szám; D_q – kvázi küszöbdózis; D_0 – 0,37-re csökkenti a túlélést. $Log_e n=D_q/D_0$

$E=\alpha D+\beta D^2$; Ha az α és β egyenlő arányban járul hozzá a hatáshoz

$\alpha D=\beta D^2$, $D=\alpha/\beta$; $BED=nd[1+d/\alpha/\beta]$

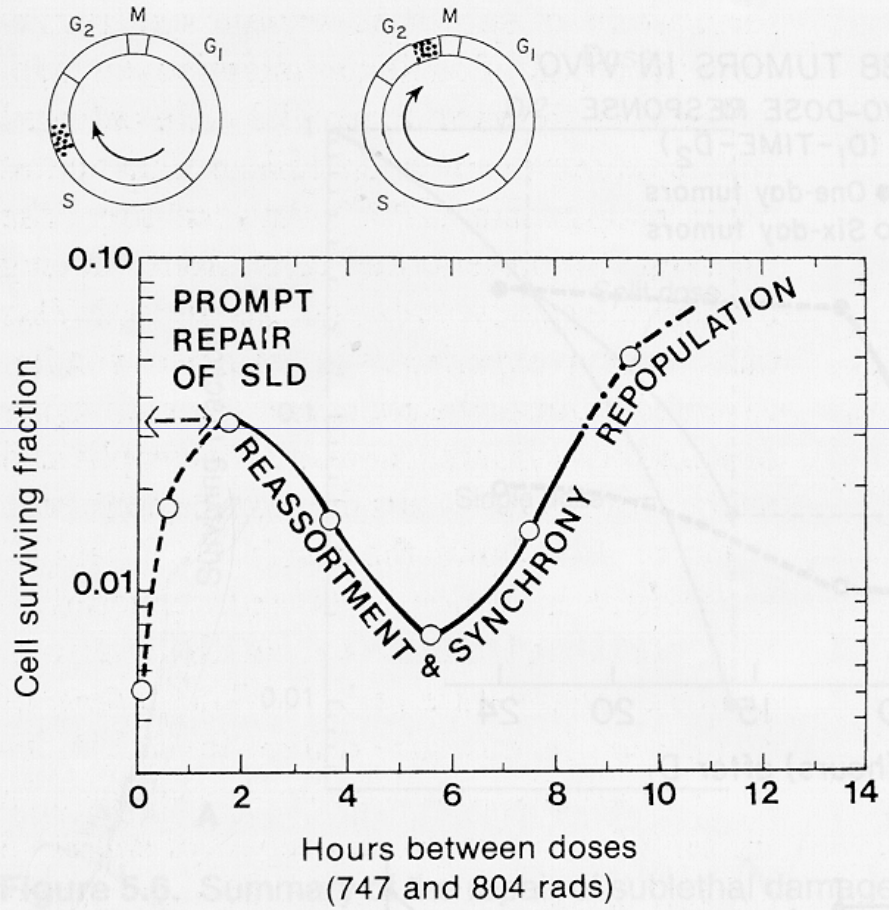


Figure 5.4. Survival of Chinese hamster cells exposed to two fractions of x-rays and incubated at 37°C for various time intervals between the two doses. The survivors of the first dose are predominantly in a resistant phase of the cycle (late S). If the interval between doses is about 6 hours, these resistant cells have moved to the G2-M phase, which is sensitive. (Adapted from Elkind MM, Sutton-Gilbert H, Moses WB, Alescio T, Swain RB: Radiation response of mammalian cells in culture: V. Temperature dependence of the repair of x-ray damage in surviving cells (aerobic and hypoxic). Radiat Res 25:359–376, 1965, with permission.)

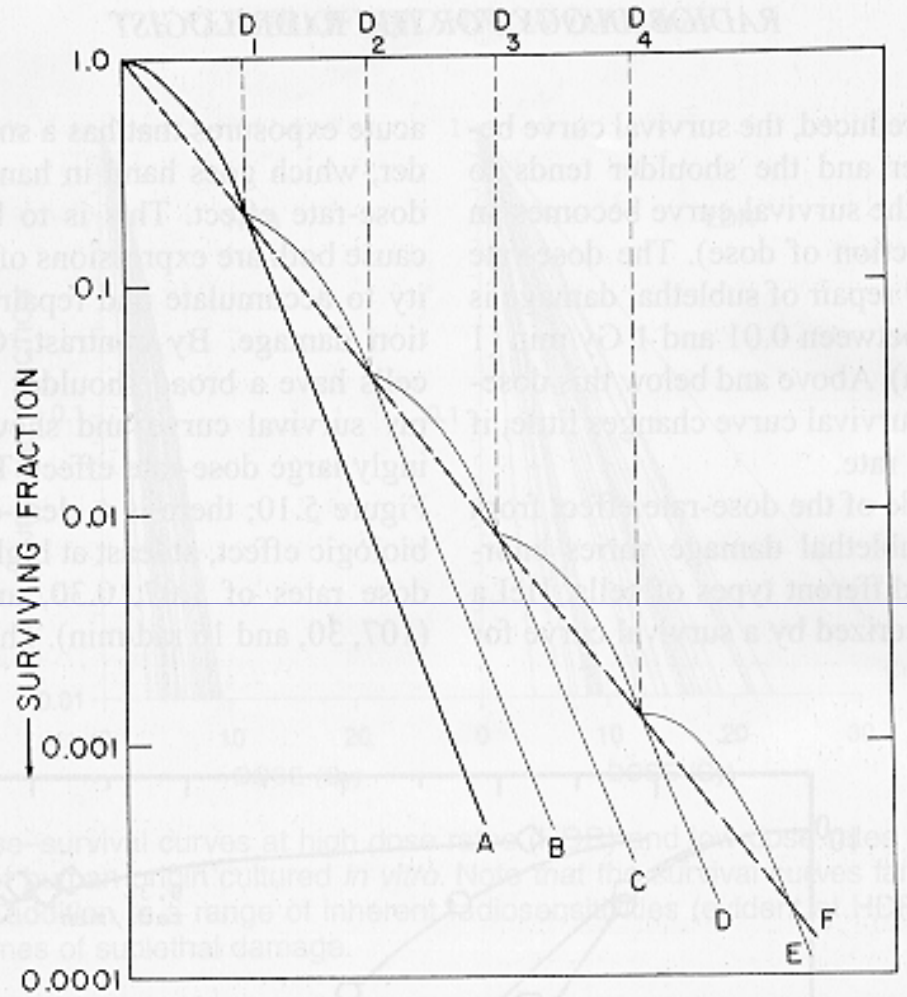


Figure 5.8. Idealized fractionation experiment. Curve A is the survival curve for single acute exposures of x-rays. Curve F is obtained if each dose is given as a series of small fractions of size D_1 with an interval between fractions sufficient for repair of sublethal damage to take place. Multiple small fractions approximate to a continuous exposure to a low dose rate. (From Elkind MM, Whitmore GF: Radiobiology of Cultured Mammalian Cells. New York, Gordon and Breach, 1967, with permission.)

A Strandqvist görbe

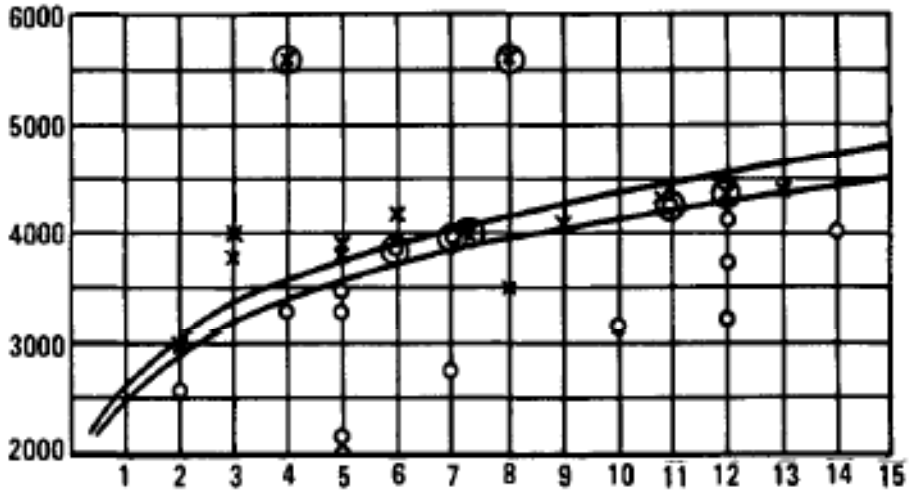


Fig. 2. Recurrences and complications at the Radiumhemmet, 1933–1937 (from Strandqvist (1944) and Fletcher (1980)). Total dose (Gesamtdosis) as a function of overall time in days after the first treatment day for recurrences within 1 year (circles) and complications (x's). (a) Curve lying above recurrences; (b) Curve lying below complications; (c) Boundary zone between the curves of (a) and (b) which separates recurrences and complications with the least possible admixture (reproduced with permission of Lea and Febiger and the author).

1944

A Strandqvist görbe

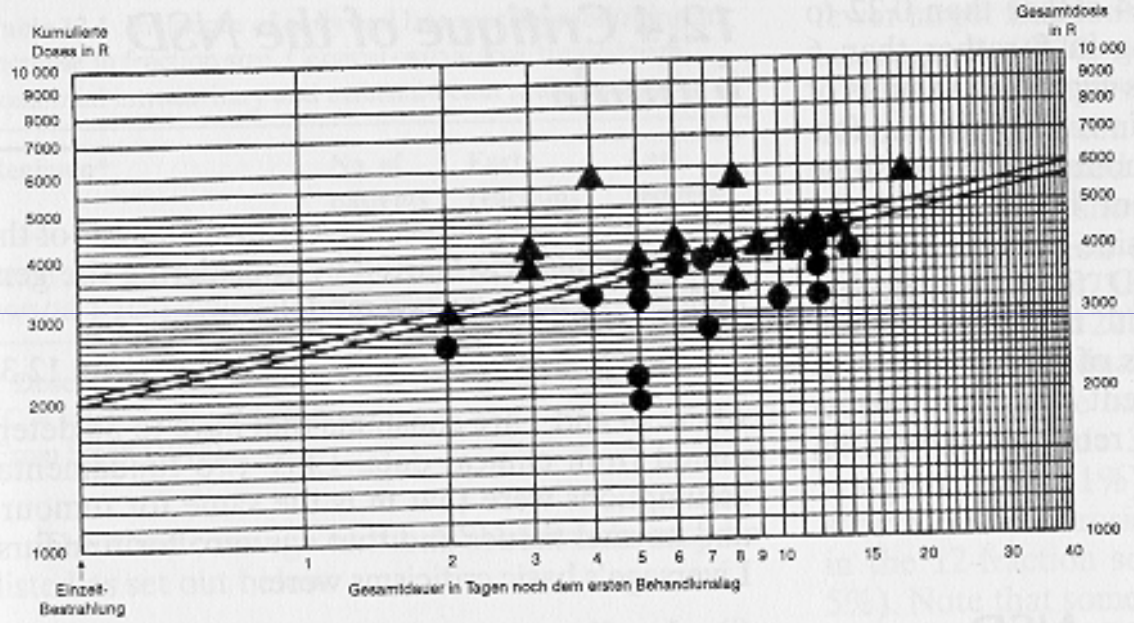


Figure 12.1 The classic data of Strandqvist (1944) on the radiotherapy of skin tumours. The ordinate shows the total radiation dose in roentgens (exposure units); the abscissa gives the overall treatment time in days after the first treatment (Einzeit-Bestrahlung = single dose). Both axes are logarithmic. The circles show recurrences and the triangles show skin complications. Adapted, with permission.

$D=kT^{0.22}$

- 0.22 – a recovery exponens, a görbe meredeksége

1949, Cohen, recovery exponens 0.33

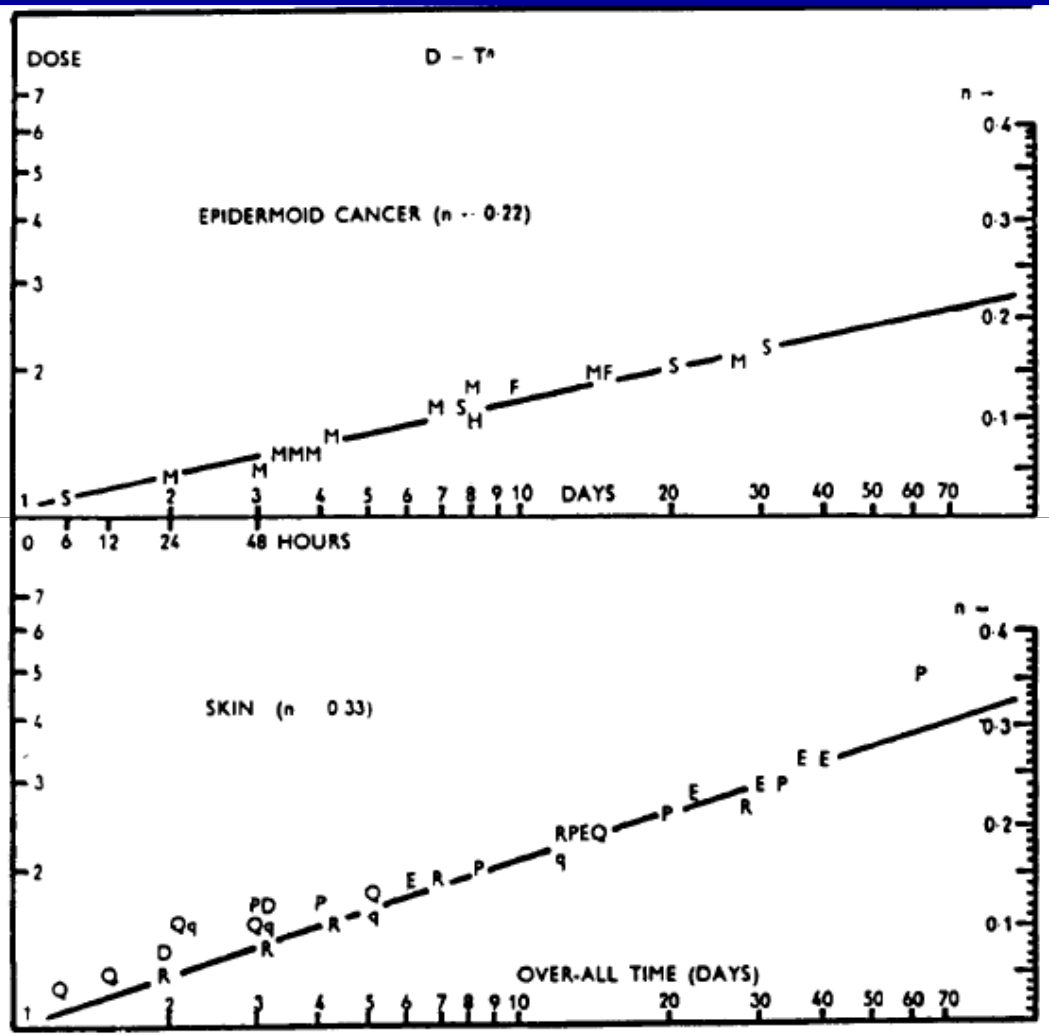


Fig. 4. Determination of the recovery exponent for skin and skin cancer (from Cohen 1949). Symbols refer to authors listed in Table 1 of Cohen (1949); M = McWhirter (1935); R = Reisner (1933); S = Strandqvist (1944). Note that Strandqvist's convention was followed for the tumors with the result that the recovery exponent was 0.22, while a time of 1 day was assigned for a single treatment for skin reactions (recovery exponent = 0.33). When these are plotted with the same convention for single doses, parallel lines cannot be ruled out (reproduced with permission of The British Institute of Radiology and the author).

1969

Az Ellis (Dose, time and fractionation: a clinical hypothesis) formula

- A bőr gyógyulása a kötőszöveti stromától függ
- A csont és az agy kivételével a stroma azonos
- A daganat stroma megegyezik az egészségessel

$$D = NSD \times N^{0.22} \times T^{0.11}$$

A nominális standard dózis (NSD)

A kezelési időtartam nem lényeges a tumor kontroll szempontjából

Cohen 1971

Cell population kinetics (CPK) modell

- A normál reakciók egy kritikus sejtpopuláció kimerítésén alapulnak.

- Szünet beiktatása csökkenti a mellékhatásokat???

Liversage 1971

$$D = k \times N^{m} \times T^{\tau}$$

- A Strandqvist egyenes valójában görbe
- A recovery exponensek kitevője artefakt
- Az m és τ más minden tumorra

- Az Ellis formula 20 évig kikezdhetetlen volt

Az időtényező

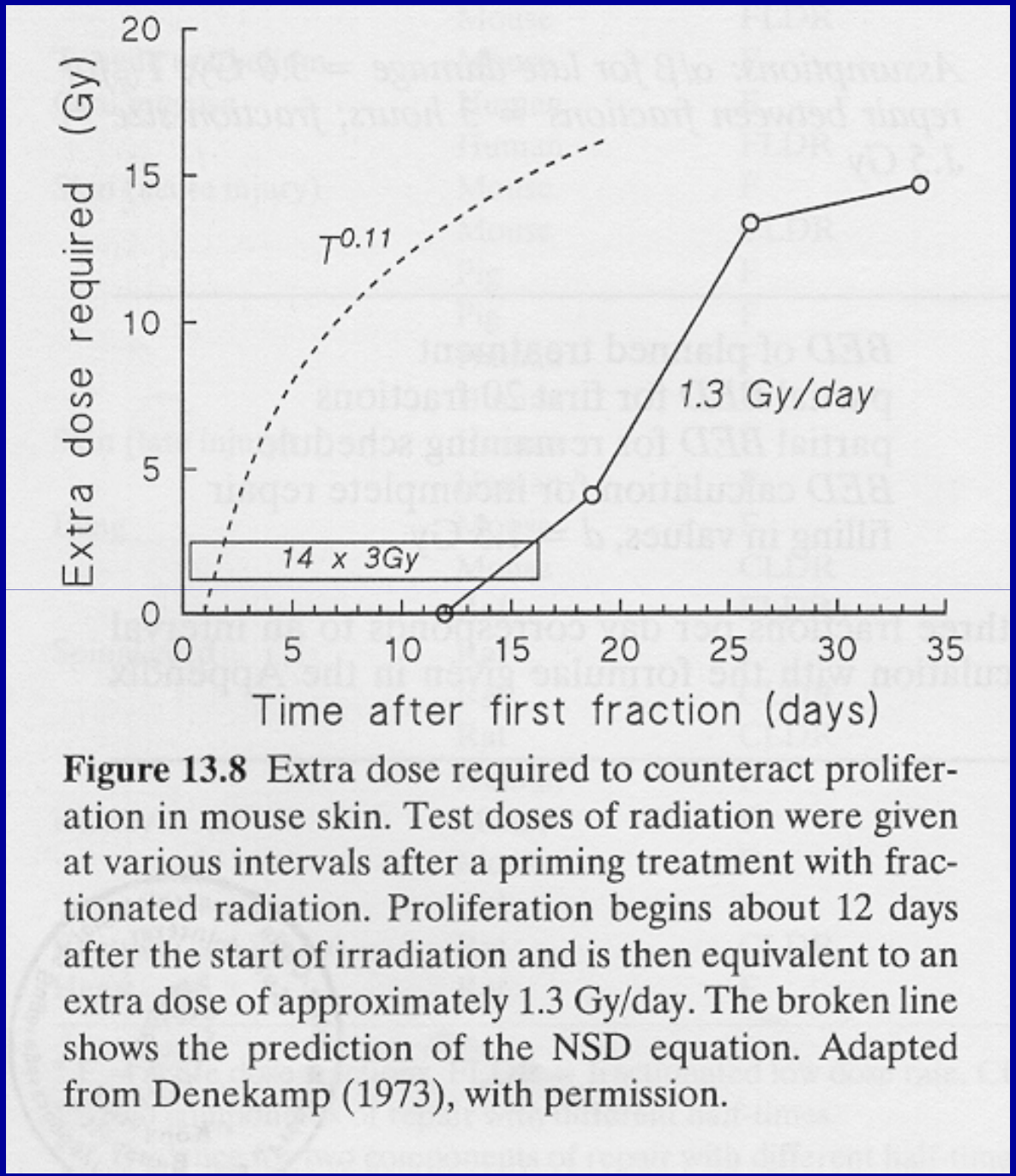


Figure 13.8 Extra dose required to counteract proliferation in mouse skin. Test doses of radiation were given at various intervals after a priming treatment with fractionated radiation. Proliferation begins about 12 days after the start of irradiation and is then equivalent to an extra dose of approximately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

A kezelési idő nem számít a késői mellékhatásoknál

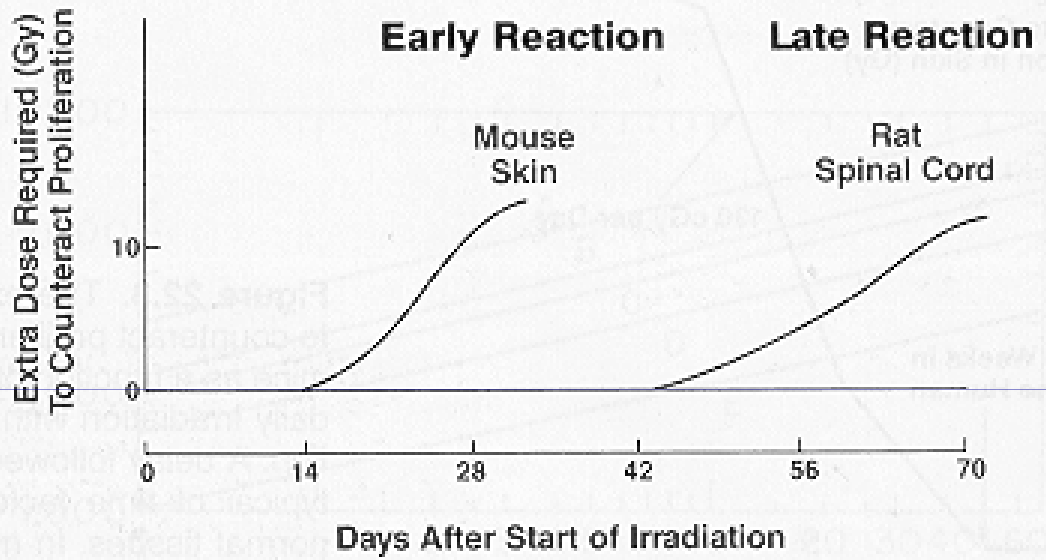


Figure 22.4. The extra dose required to counteract proliferation only as a function of time after starting daily irradiation in rodents. The left curve represents a typical early reaction; the right curve represents a typical late reaction. The delays are much longer in humans. (Adapted from Fowler JF: Radiother Oncol 1:1–22, 1983, with permission.)

Table 12.2 Lack of a time factor for late clinical end-points

End-point	Result	Reference
Telangiectasia	No recovery after a '3-week split'	Turesson and Thames (1989)
Late laryngeal oedema	D_{rec} =0.10 ± 0.22 Gy/day	Overgaard *et al* (1988)
Fistula secondary to salvage surgery	D_{rec} = 0.09 Gy/day	Overgaard *et al* (1988)
Rectosigmoid complications	D_{rec} < 0.15 Gy/day	Bentzen *et al* (1992)
Parotid gland function	$D_{rec} \approx$ 0 Gy/day	Leslie and Dische (1991)
Bladder	Reduction of treatment time to 4 weeks gave no increase in bladder toxicity	Moonen (1994)

* D_{rec} = dose recovered per day, with 1 standard error where available.
From Bentzen and Overgaard (1996); for references, see the original.

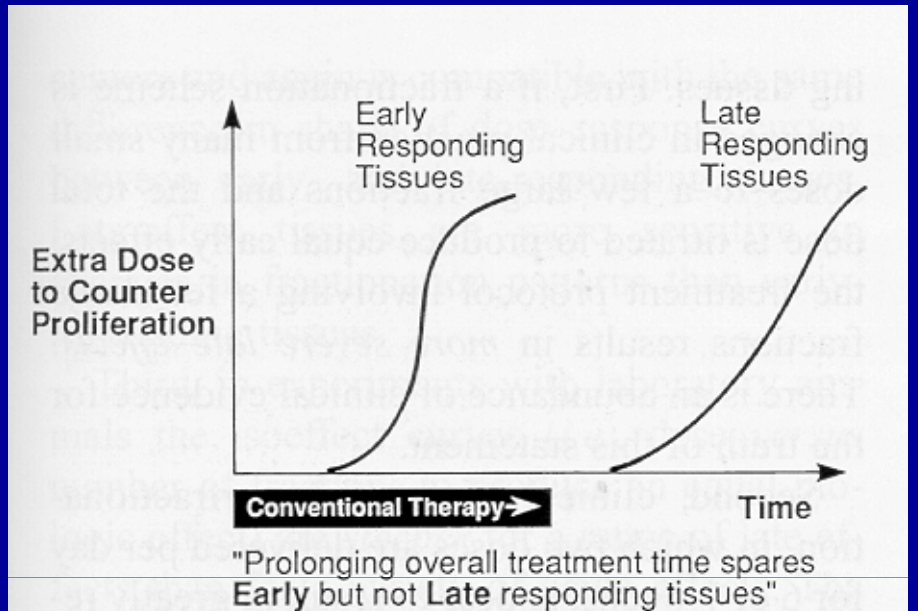


Figure 22.5. Highly speculative illustration attempting to extrapolate the experimental data for early- and late-responding tissue in rats and mice to principles that can be applied in clinical radiotherapy. The extra dose required to counter proliferation in early-responding tissues begins to increase 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.

Az NSD alábecsüli a késői mellékhatásokat nagy frakció dózisok esetén

Table 12.1 Incidence of early and late reactions following an increase in fraction size. Cervical carcinomas treated with combined intracavitary and external-beam radiotherapy

Regimen*	No. of patients	Early reactions	Late sequelae
40/20/26 + IC +10/5/5	24	8 (33%)	8 (33%)
29/5/28 + IC + 6.7/1/1	24	8 (33%)	20 (83%)

* Dose in Gy/number of fractions/overall time in days.
IC = intracavitary radiotherapy.
From Singh (1978).

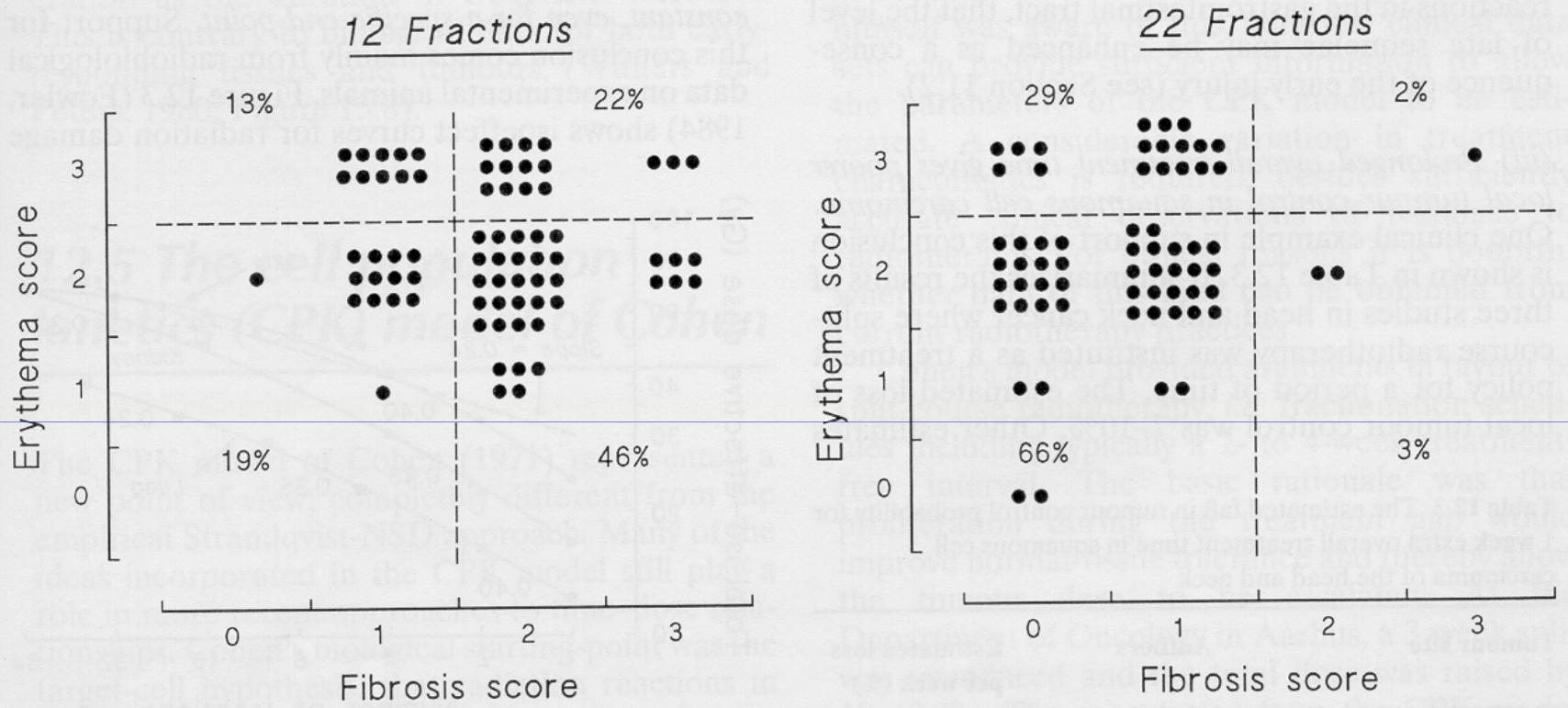


Figure 12.2 Relationship between acute skin reaction (erythema) and late subcutaneous fibrosis in breast cancer patients treated with an equivalent total dose according to the NSD formula but with very different fraction numbers. From M. Overgaard *et al* (1987), with permission.

Hosszú kezelési idő – csökkenő tumor kontroll

Table 12.3 The estimated fall in tumour control probability for 1 week extra overall treatment time in squamous cell carcinoma of the head and neck

Tumour site	Authors	Estimated loss per week (%)
Larynx	Overgaard *et al* (1988)	10
Oropharynx	Bentzen *et al* (1991)	7
Various head and neck cancers	Parsons *et al* (1980)	7

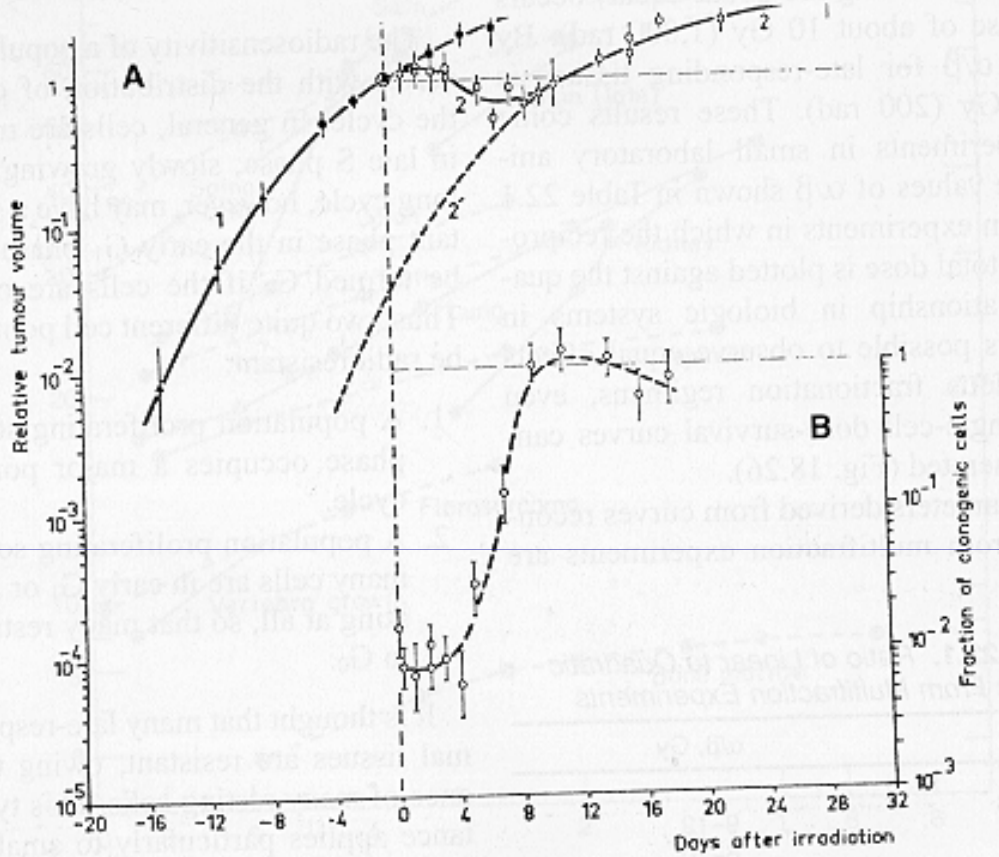


Figure 22.8. Accelerated repopulation. Growth curves of a rat rhabdomyosarcoma showing the shrinkage, growth delay, and subsequent recurrence following treatment with a single dose of 20 Gy (2,000 rad) of x-rays. **A:** Curve 1: Growth curve of unirradiated control tumors. Curve 2: Growth curve of tumors irradiated at time t = 0, showing tumor shrinkage and recurrence. **B:** Variation of the fraction of clonogenic cells as a function of time after irradiation, obtained by removing cells from the tumor and assaying for colony formation in vitro. (From Hermens AF, Barendsen GW: Eur J Cancer 5:173–189, 1969, with permission.)

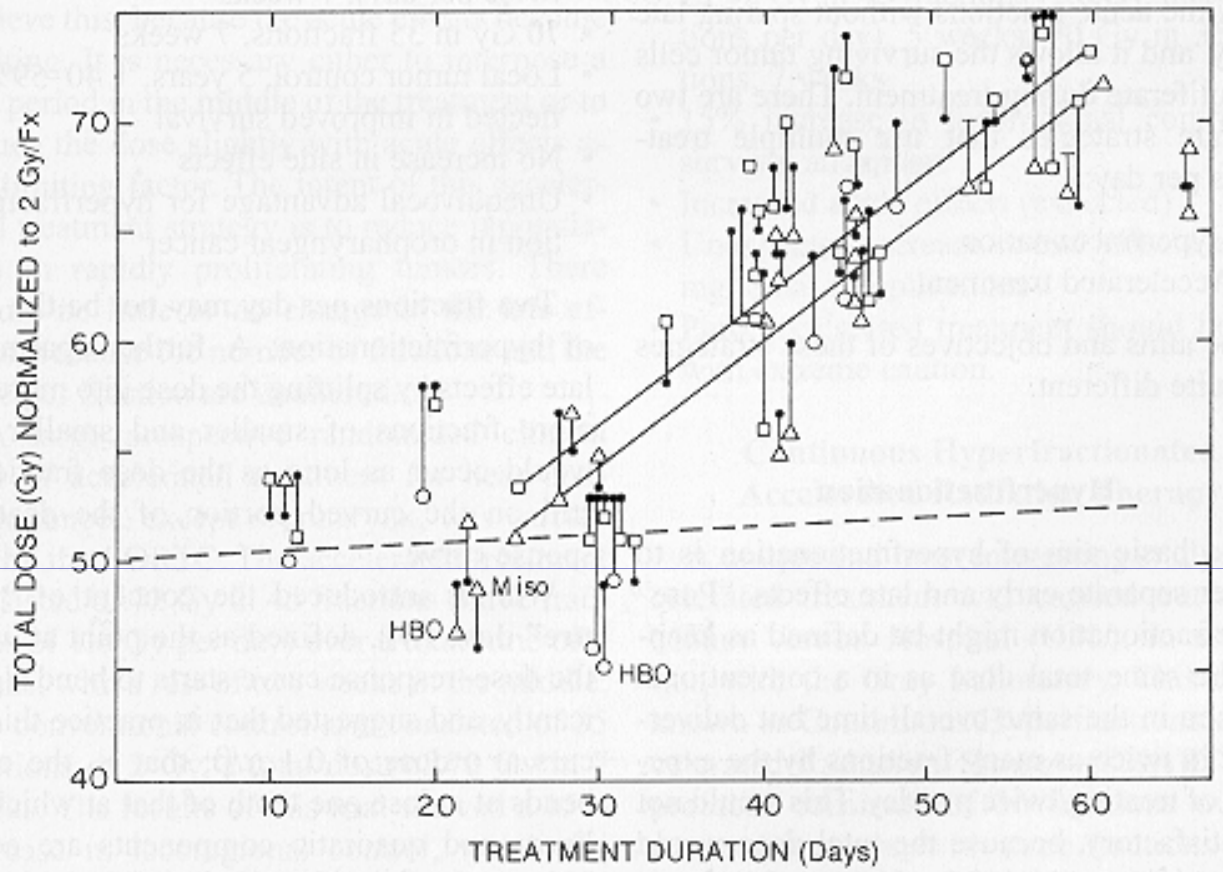


Figure 22.9. Doses to achieve local control in 50% of cases (TCD_{50}), as a function of overall treatment time, for squamous cell tumors of the head and neck. The data points include many published results from the literature, including high-pressure oxygen trials (HBO), and the trial of misonidazole (Miso). The *dashed line* shows the rate of increase in TCD_{50} predicted from a 2-month clonogen doubling rate. (From Withers HR, Taylor JMG, Maciejewski B: The hazard of accelerated tumor clonogen repopulation during radiotherapy. Acta Oncol 27:131–146, 1988, with permission.)

A frakciószám kitevője (m) változó

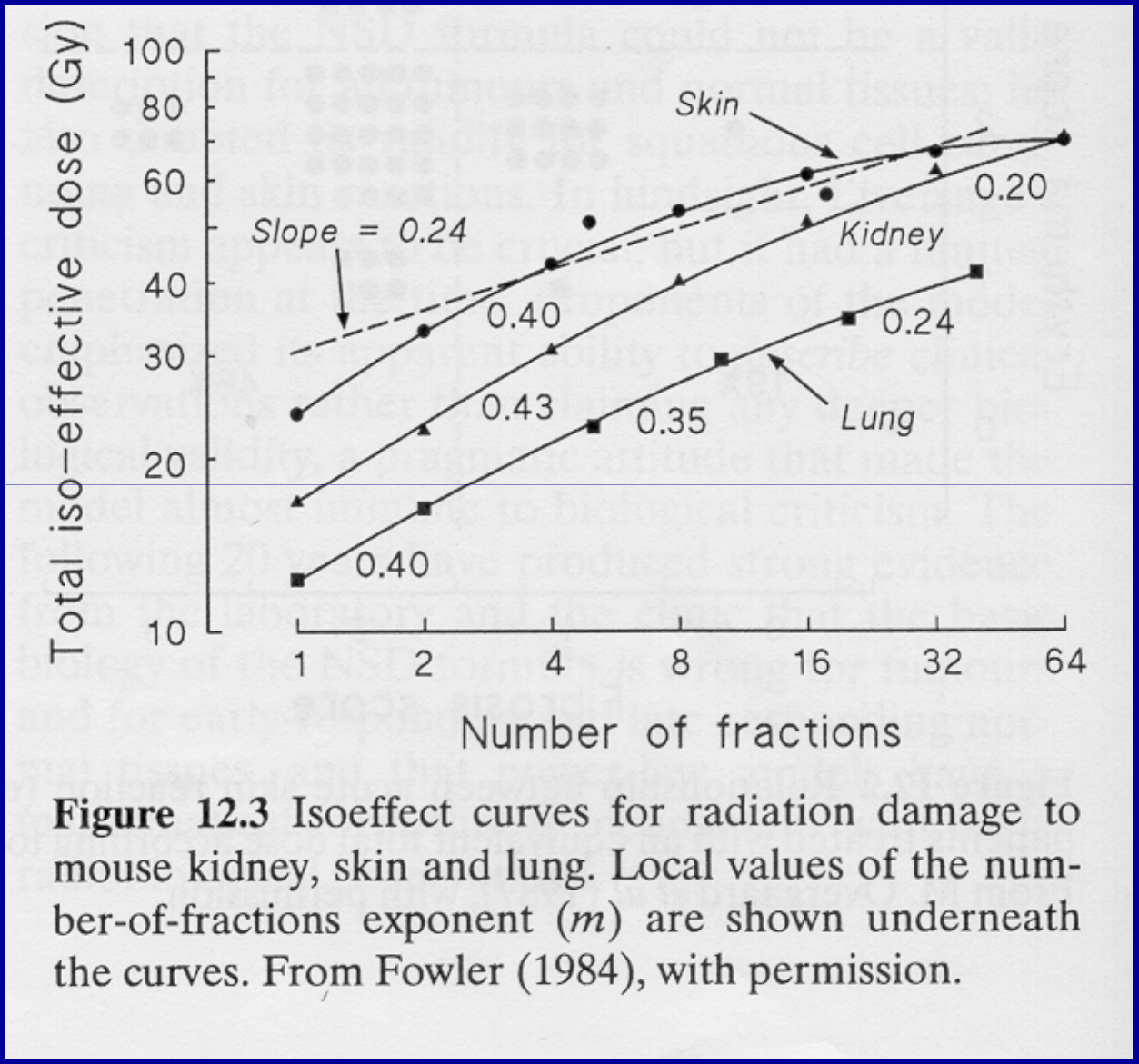


Figure 12.3 Isoeffect curves for radiation damage to mouse kidney, skin and lung. Local values of the number-of-fractions exponent (m) are shown underneath the curves. From Fowler (1984), with permission.

A késői mellékhatások szempontjából a frakció dózis a lényeges

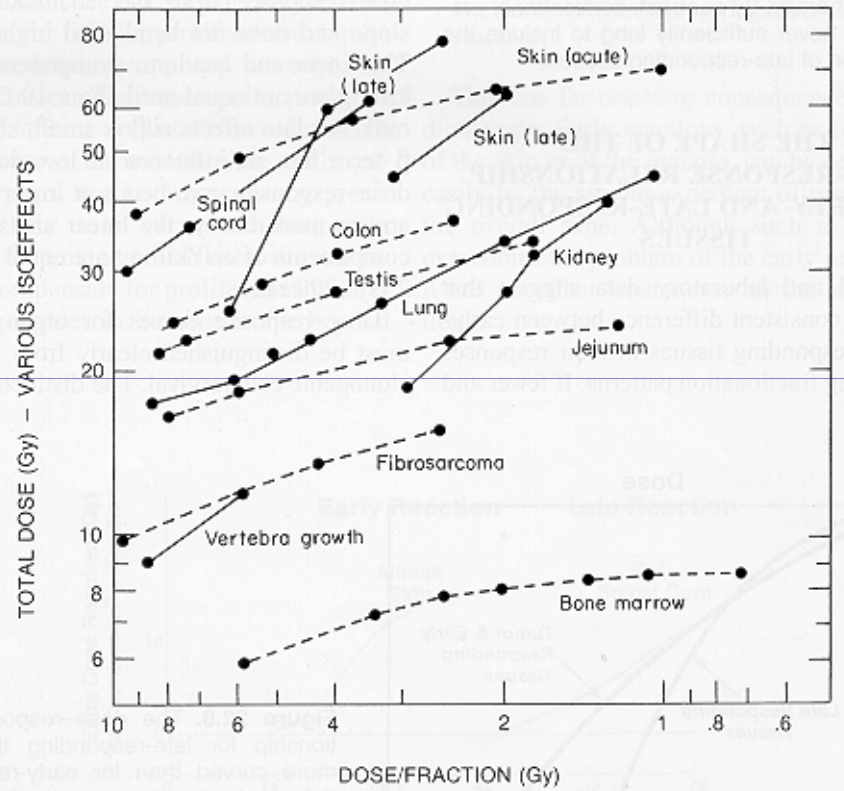


Figure 22.7. Isoeffect curves in which the total dose necessary for a certain effect in various tissues is plotted as a function of dose per fraction. Late effects are plotted with *solid lines*, acute effects with *dashed lines*. The data were selected to exclude an influence on the total dose of regeneration during the multifraction experiments. The main point of the data is that the isodoses for late effects increase more rapidly with a decrease in dose per fraction than is the case for acute effects. (From Withers HR: Cancer 55:2086, 1985, with permission.)

Split course terápia

3 hét szünet + 10-12 Gy

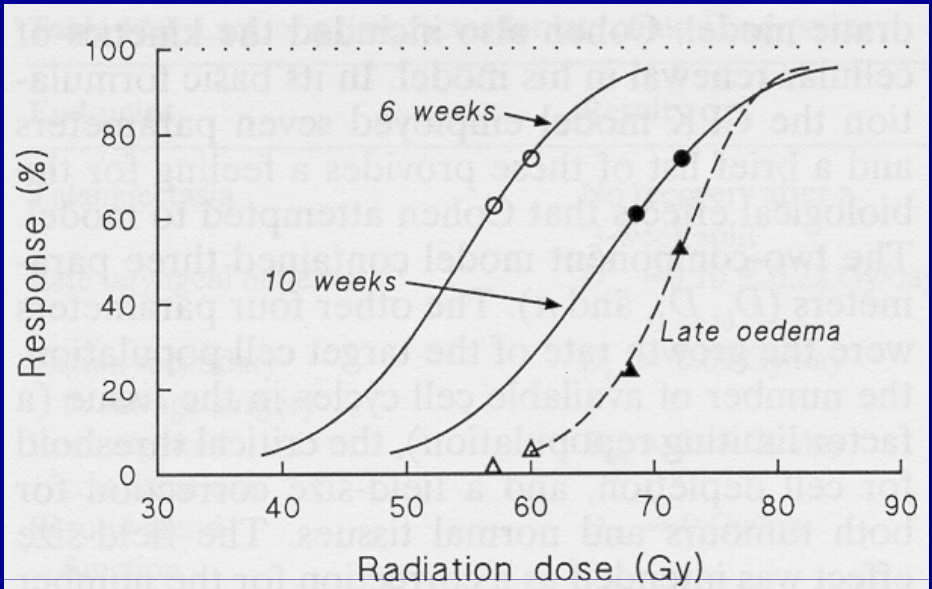


Figure 12.4 The influence of overall treatment time on the dose–response relationship for local control of squamous cell carcinoma of the larynx (circles) and late oedema (triangles). Open symbols show data for continuous-course radiotherapy (nominal duration 6 weeks); closed symbols show data for split-course radiotherapy (nominal duration 10 weeks). Proliferation during the additional 4 weeks shifted the dose–response curve for local control towards higher doses. In contrast, the data for late oedema fit a single dose–response curve independently of treatment time, implying that the split had no effect. Adapted from Overgaard *et al* (1988), with permission.

Konklúzió

- Az NSD alábecsüli a késői mellékhatásokat
- Az NSD nem becsüli jól a frakciószám és a kezelési idő hatását
- Gyorsan osztódó daganatoknál lényeges a kezelési időtartam
- Kezelési időtartam hossza nem befolyásolja a késői mellékhatásokat
- Késői hatások igen érzékenyek a frakció dózisokra
- Minden biológiai folyamatot a modellek nem tudnak figyelembe venni