Radiobiology for Brachytherapy

Alex Rijnders
Europe Hospitals
Brussels, Belgium

EUROPE
EUROPA
CLINIQUES DE L'EUROPE
EUROPA ZIEKENHUIZEN

a.rijnders@europehospitals.be
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Introduction

Brachytherapy is in most cases a very curative treatment

Long term local control rates are in many situations higher than 90%

Because high doses are required (often above 60Gy), the rate of complications can be high

Slides cortacy JJ Mazeron

Introduction

GOALS

- Maximise tumour response +++
- Minimise the effects on normal tissues:
  - Early effects: early responding tissues +
  - Late effects: late responding normal tissues +++
- Increase the therapeutic ratio +++

Temporary Implants

Low Dose Rate:

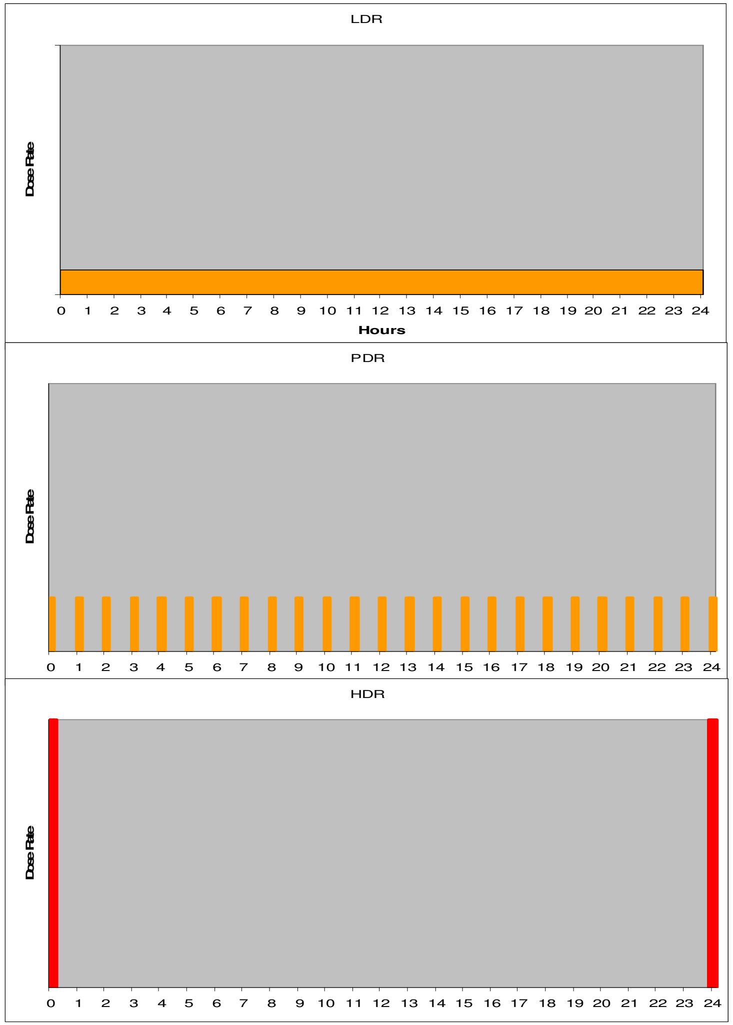
- ❖ Continuous irradiation
- ❖ 0.40 – 2 Gy/h

Pulsed Dose Rate:

- ❖ mimic low dose rate
- ❖ short pulses, same average dose rate

High Dose Rate:

- ❖ >0.2 Gy/min
- ❖ One/a few fractions



LDR

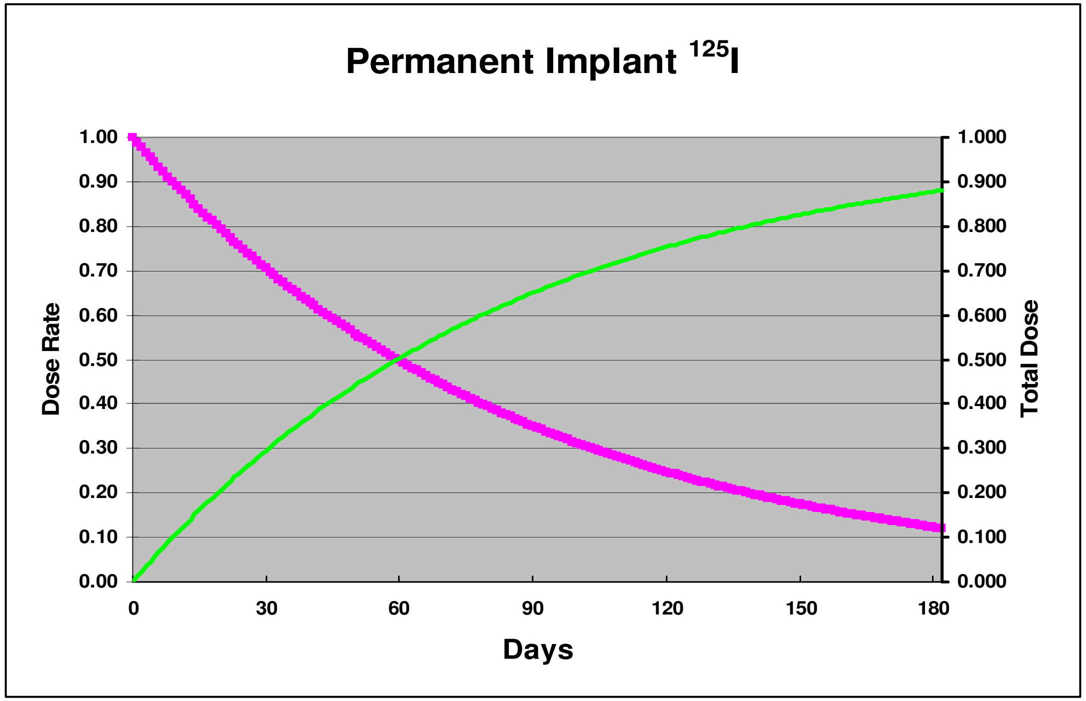
PDR

HDR

Permanent Implants

Radioactive sources remain in the patient and decay

- ❖ Relative short half life
- ❖ Low energy (radiation protection)

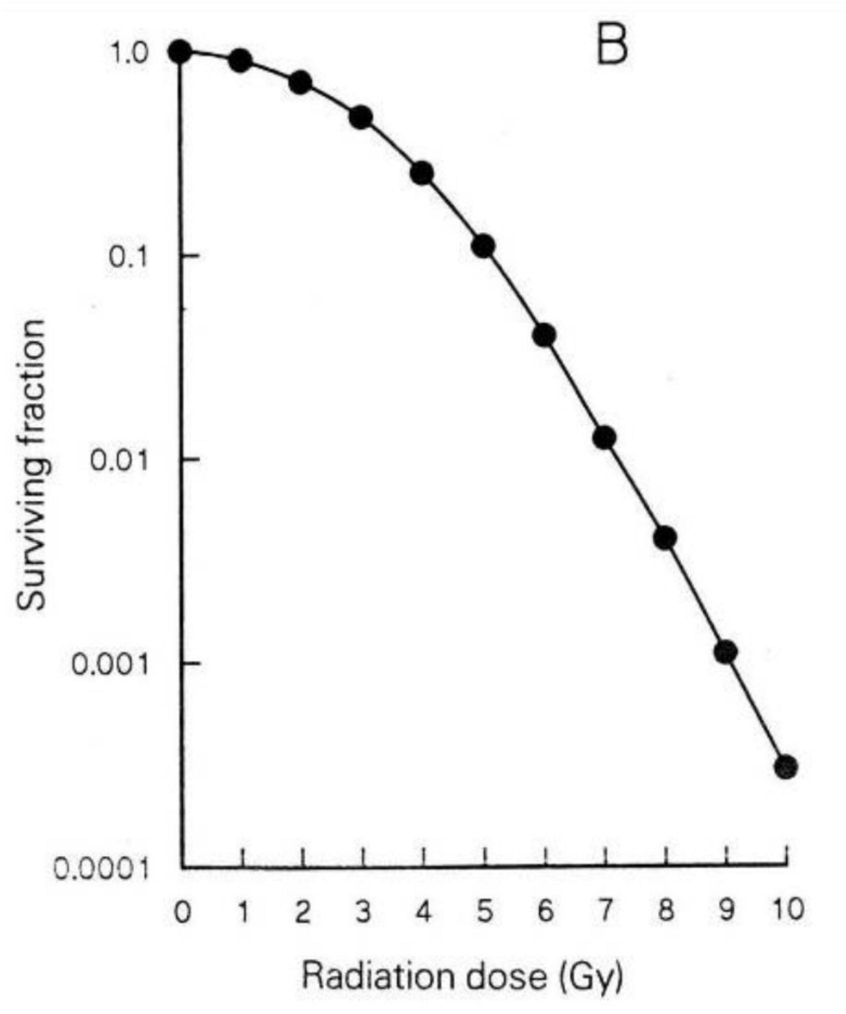


High Dose Rate Brachytherapy

- The radiobiological processes involved in HDR BT are similar to those involved in fractionated external beam radiotherapy
- Indeed, hypofractionated HDR brachytherapy can be considered as hypofractionated external beam radiotherapy (but the treated volume is small +++)

High Dose Rate Brachytherapy

The survival curve (single exposure)



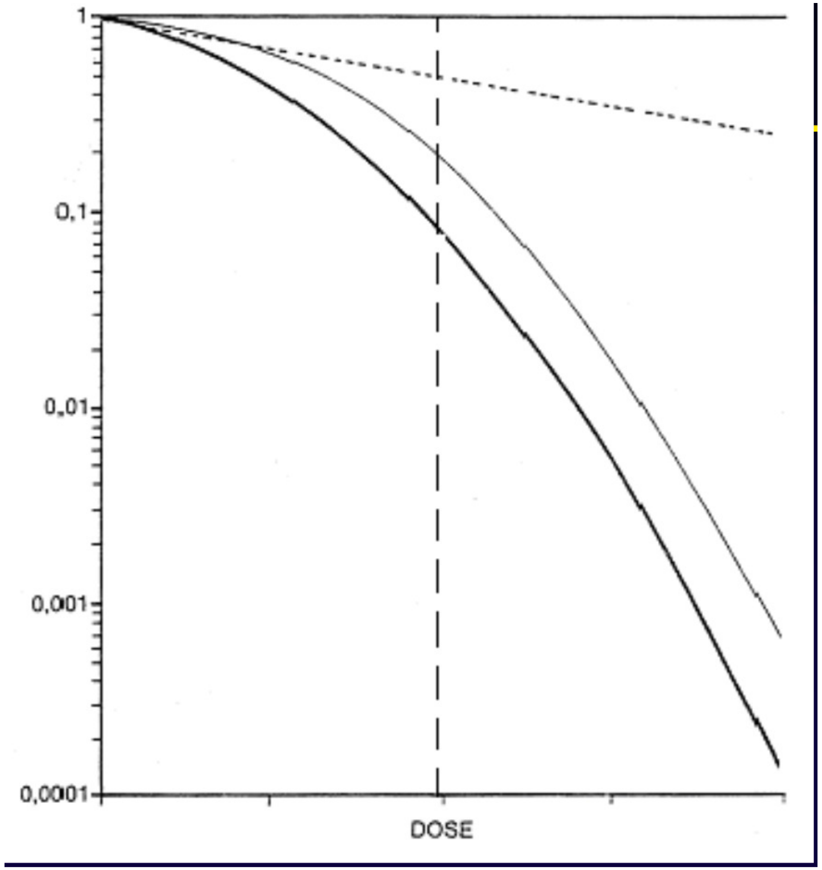
How to quantify the dose-response relation?

For this very brief irradiation, the survival fraction S decreases with increasing dose D, as a result of 2 mechanisms:

- **Lethal (non-reparable) lesions, with S=exp(-αD), represented by the tangent to the survival curve at the origin**
- **Sublethal lesions, non-lethal and potentially reparable, but the accumulation of which can cause cell death, with S=exp(-βD^2)**

Dose-response relation

The combination of these 2 types of cell kill leads to the classical linear-quadratic (LQ) formula



- Linear component
- Quadratic component
- Linear-quadratic

LQ formula

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

With:

D = Total dose

αD = non reparable lesions (linear)

βD^2 = reparable lesions (quadratic)

LQ formula

When linear effects = quadratic effects

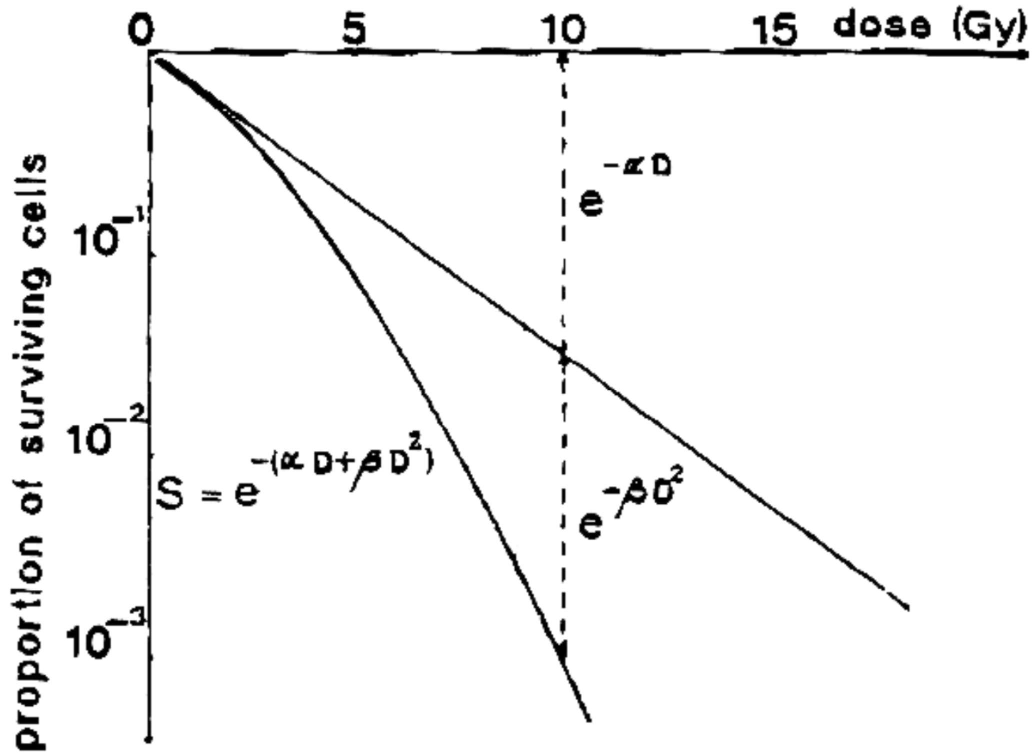
$\beta D^2 = \alpha D$

$\beta D = \alpha$

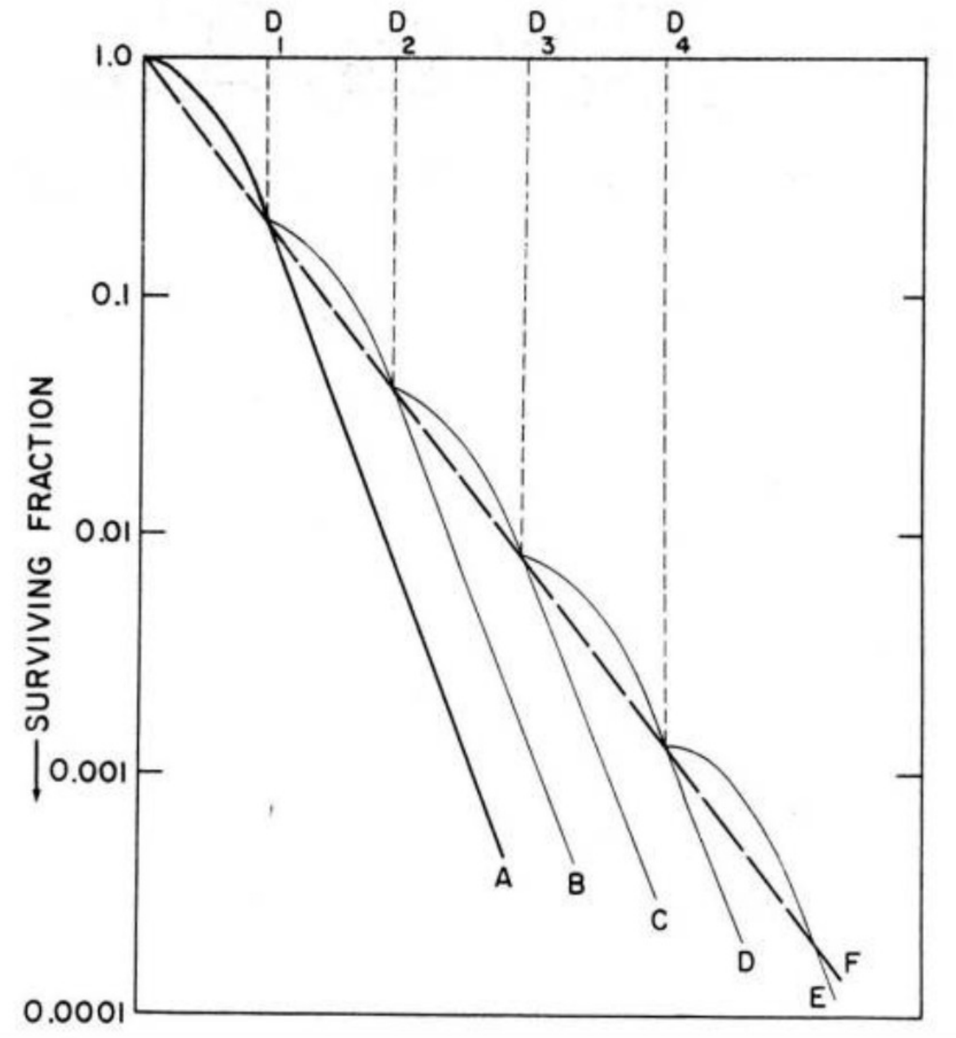
$D = \alpha / \beta$

Thus α / β **=dose**

α / β **in Gy**



Survival curve - multiple exposures

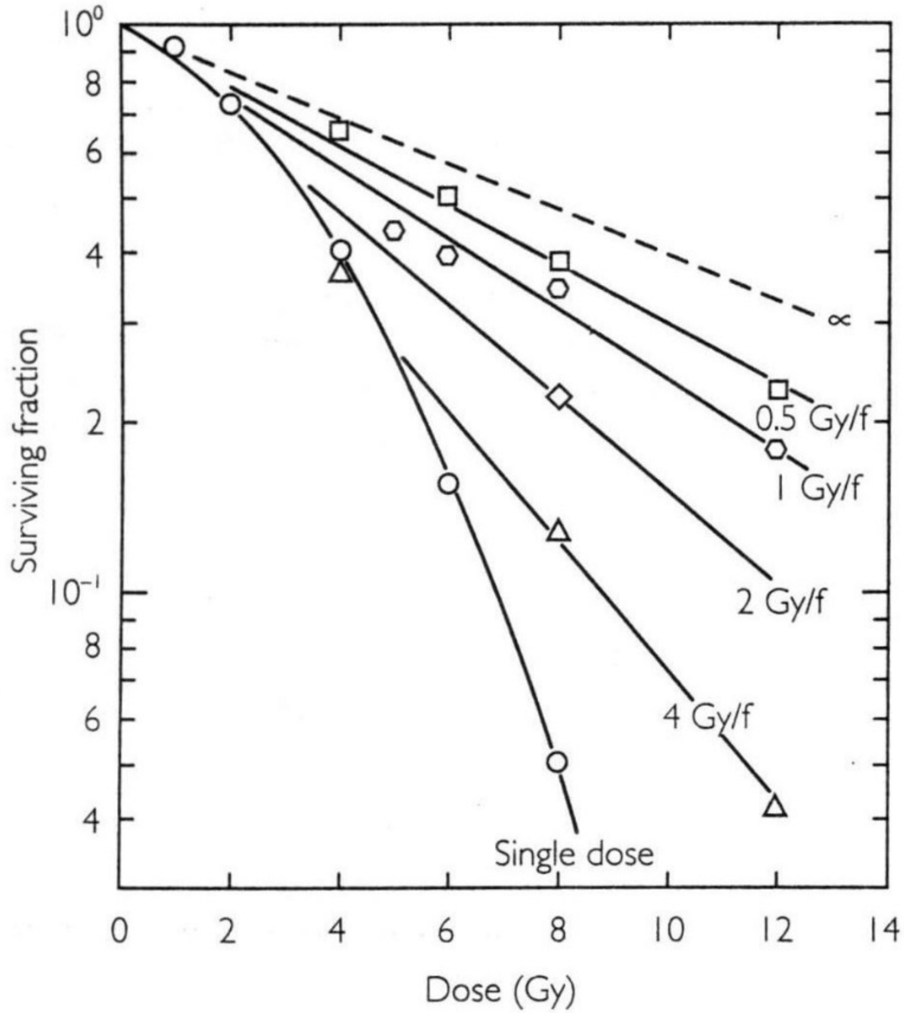


Large α / β means small shoulder, small repair capacity (Carcinoma, early reactions)

Small α / β means large shoulder, better repair capacity (late reactions)

=> Fractionation more effect on late reactions

Survival curve – dose per fraction



Survival curve - multiple exposures

$S = \exp\{-(\alpha d + \beta d^2)\}$ One fraction

Total effect E of n fractions

$E = -\log(S)^n$

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

$E = \alpha D + \beta dD$

With:

D = Total dose

d = dose per fraction

Survival curve - multiple exposures

$S = \exp\{-(\alpha D + \beta D^2)\}$ Single exposure

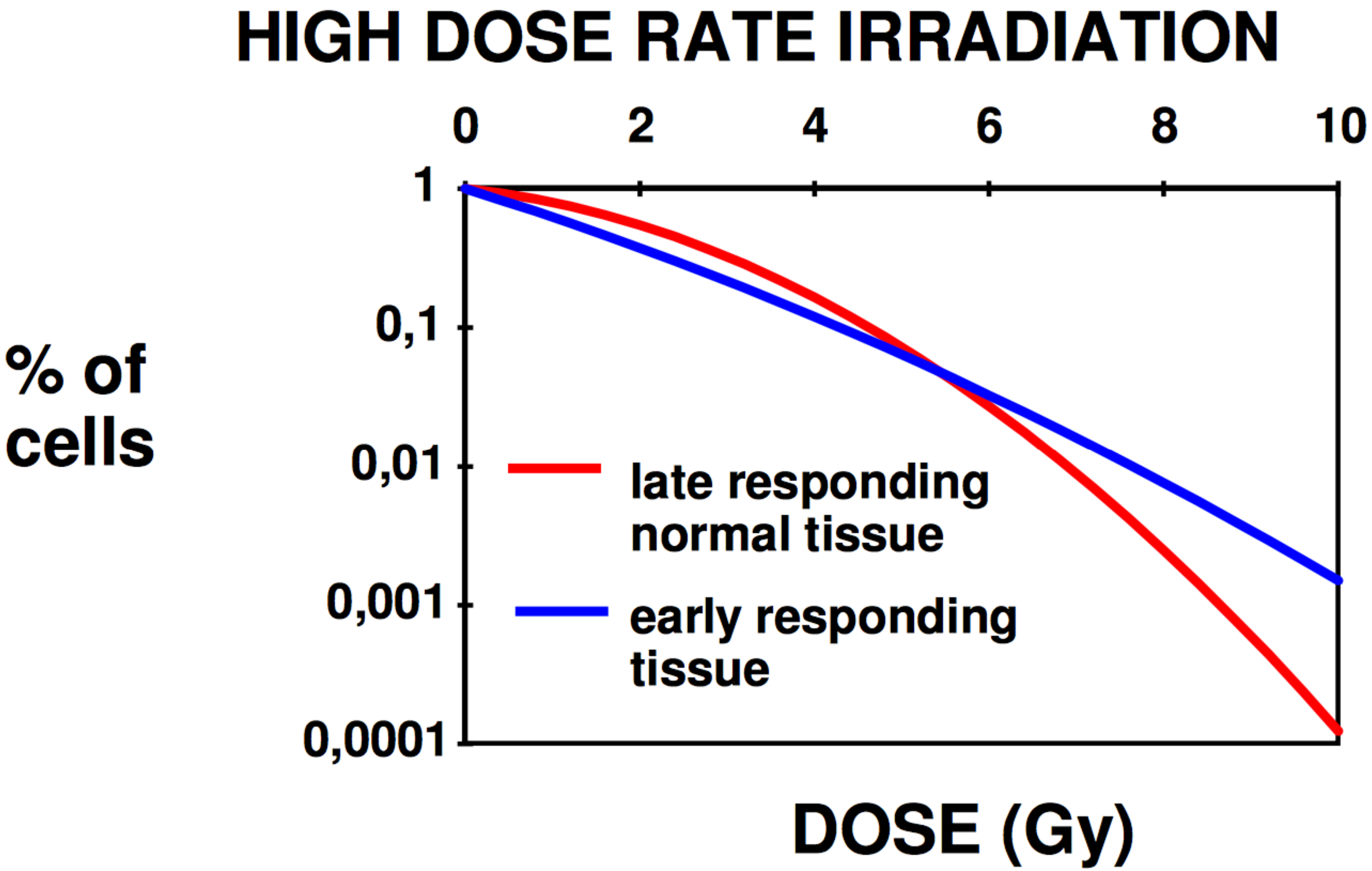
$S = \exp\{-(\alpha D + \beta dD)\}$ Multiple exposures

With:

D = Total dose

d = dose per fraction

Survival curve – tissue type



Survival curve – tissue type

Survival curves for early reacting normal tissue and tumours are less curved than those for late reacting normal tissue.

Early reacting normal tissues and tumours are less sensible to dose per fraction than late reacting normal tissues.

Survival curve – tissue type α / β

$S = \exp\{-(\alpha D + \beta dD)\}$

Early reacting (normal) tissues and squamous cell carcinomas:

α / β **= 10 Gy (7-20 Gy)**

Late reacting (normal) tissues:

α / β **= 3 Gy (0.5-6 Gy)**

J. Dutreix, Radiother. Oncol. 15,25, 1989

Survival curve – tissue type α/β

Breast

Plausible population averaged radiobiological parameters (95% CI) are α/β = 2.88 Gy (0.75-5.01 Gy).

Potential doubling time T(d)=14.4±7.8days.

Analysis for radiation alone data suggested an α/β = 3.89 ± 6.25Gy, verifying the low α/β ratio based on the post-lumpectomy irradiation data

XS. Qi, Radiother. Oncol. 100, 2282, 2011

Practical use: equivalence formula

Treatment 1: $S = \exp\{-(\alpha D + \beta dD)\}$

Treatment 2: $S' = \exp\{-(\alpha D' + \beta d'D')\}$

If S'=S $D' = D(\alpha/\beta + d) / (\alpha/\beta + d')$

With: D and D' = Total dose and

d and d' = dose per fraction

$$D_{eq2} = D(\alpha/\beta + d) / (\alpha/\beta + 2)$$

Exemple: equivalence formula

Calculate biologically equivalent dose (ref 2 Gy/fraction) for 30 Gy in 10 fractions:

$$D_{eq2} = 30 \, (\alpha/\beta + 3) \, / \, (\alpha/\beta + 2)$$

- Tumour / early reactions $\alpha/\beta = 10$ Gy

$$D_{eq2} = 30 * 13 / 12 = 32,5 \text{ Gy}$$

- Late responding normal tissue $\alpha/\beta = 3$ Gy

$$D_{eq2} = 30 * 6 / 5 = 36 \text{ Gy}$$

Exemple: equivalence formula

Calculate biologically equivalent dose (ref 2 Gy/fraction) for 30 Gy in 5 fractions:

$$D_{eq2} = 30\ (\alpha/\beta + 6)\ /\ (\alpha/\beta + 2)$$

- Tumour / early reactions α/β = 10 Gy

$$D_{eq2} = 30 * 16 / 12 = 40\ Gy$$

- Late responding normal tissue α/β = 3 Gy

$$D_{eq2} = 30 * 9 / 5 = 54\ Gy$$

Exemple: equivalence formula

Calculate biologically equivalent dose (ref 2 Gy/fraction) for 30 Gy in <u>3</u> fractions:

$$D_{eq2} = 30\ (\alpha/\beta + 10)\ /\ (\alpha/\beta + 2)$$

- Tumour / early reactions $\alpha/\beta = 10$ Gy

$$D_{eq2} = 30 * 20 / 12 = 50 \text{ Gy}$$

- Late responding normal tissue $\alpha/\beta = 3$ Gy

$$D_{eq2} = 30 * 13 / 5 = 78 \text{ Gy}$$

D_{eq2} for 30 Gy

Early reacting – tumour (carcinoma)

2 Gy/Fraction	3 Gy/fraction	6 Gy/fraction	10 Gy/fraction
3O	32.5	40	50

Late reacting tissue (complications)

2 Gy/Fraction	3 Gy/fraction	6 Gy/fraction	10 Gy/fraction
30	36	54	78

Proliferation – repopulation

Proliferation has little effect in tumours for treatment times < 3-4 weeks, but, past that period accelerated repopulation of fast-growing tumours can be observed.

Dose M to compensate for repopulation:

M = 2 Gy * t / Tpot Tpot=potential doubling time

	Total duration of irradiation (t) in days					
Tpot	5 days	10 days	20 days	30 days	40 days	50 days
2 days	5 Gy	10 Gy	20 Gy	30 Gy	40 Gy	50 Gy
5 days	2 Gy	4 Gy	8 Gy	12 Gy	16 Gy	20 Gy
10 days	1 Gy	2 Gy	4 Gy	6 Gy	8 Gy	10 Gy

Exemple: Repopulation

Calculate the dose M to compensate for repopulation when Tpot = 5 days

- 70 Gy / 1 week (as in brachytherapy)

  M = 3 Gy

- 70 Gy / 7 weeks (as with external radiotherapy

  Tumour : M = 20 Gy

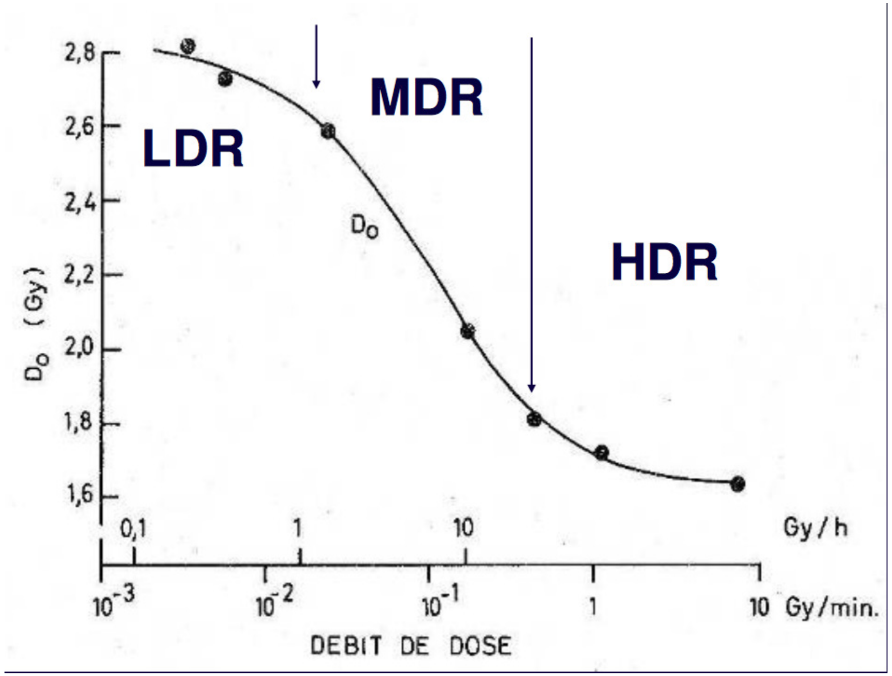
  Late effects : 0 Gy

Conclusions: Radiobiology in HDR

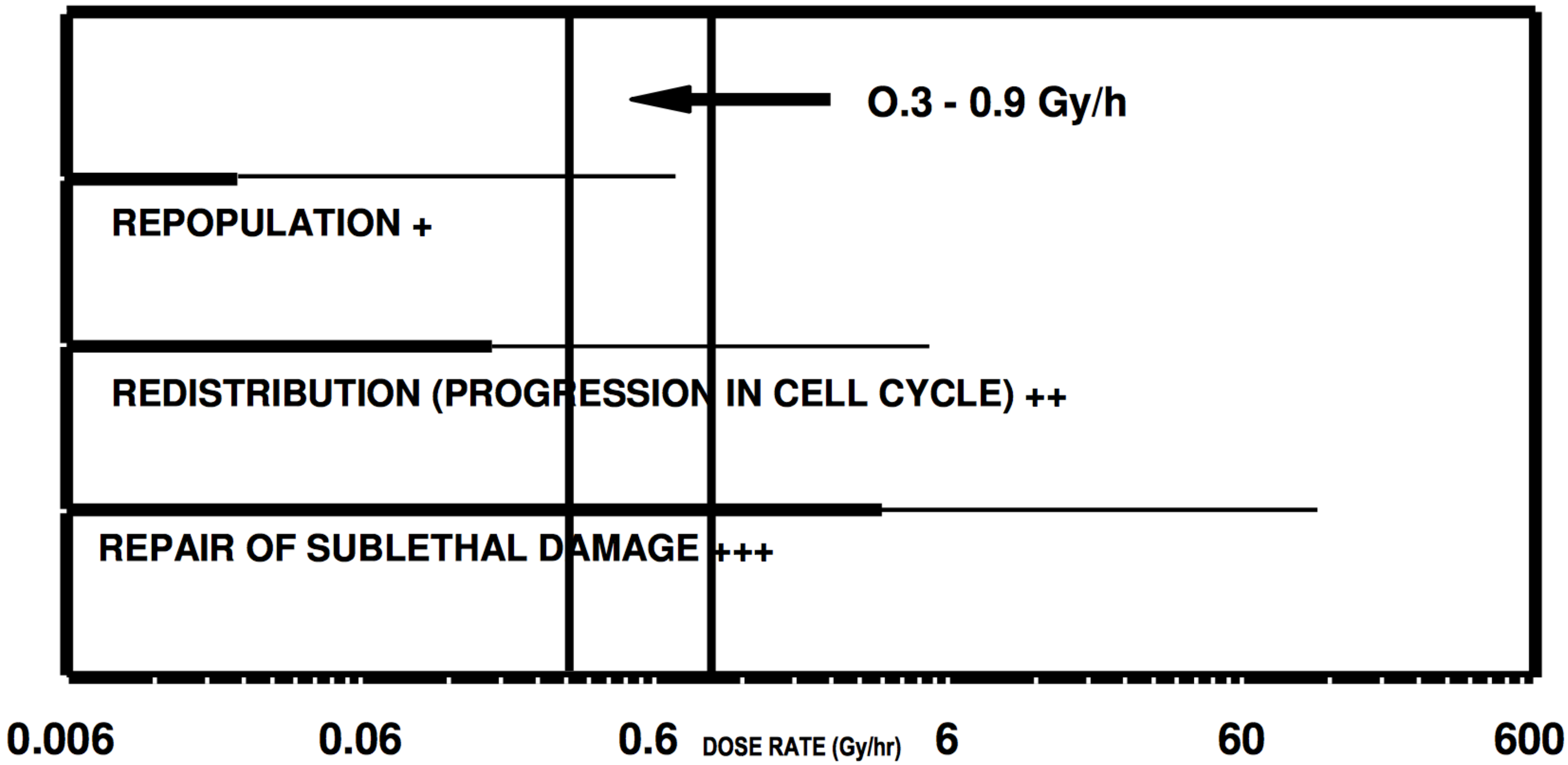
- High dose rate brachytherapy is very similar to fractionated external beam radiation therapy (but the treated volume is smaller)
- Small doses per fraction prevent from severe late effects
- Validity of LQ-model questionable for dose/fraction >10Gy

Dose rates: ICRU recommendation

- **High dose rate (HDR) : > 12 Gy/h**
- **Medium Dose Rate (MDR): 2 - 12 Gy/h**
- **Low Dose Rate (LDR): 0.4 - 2 Gy/h**



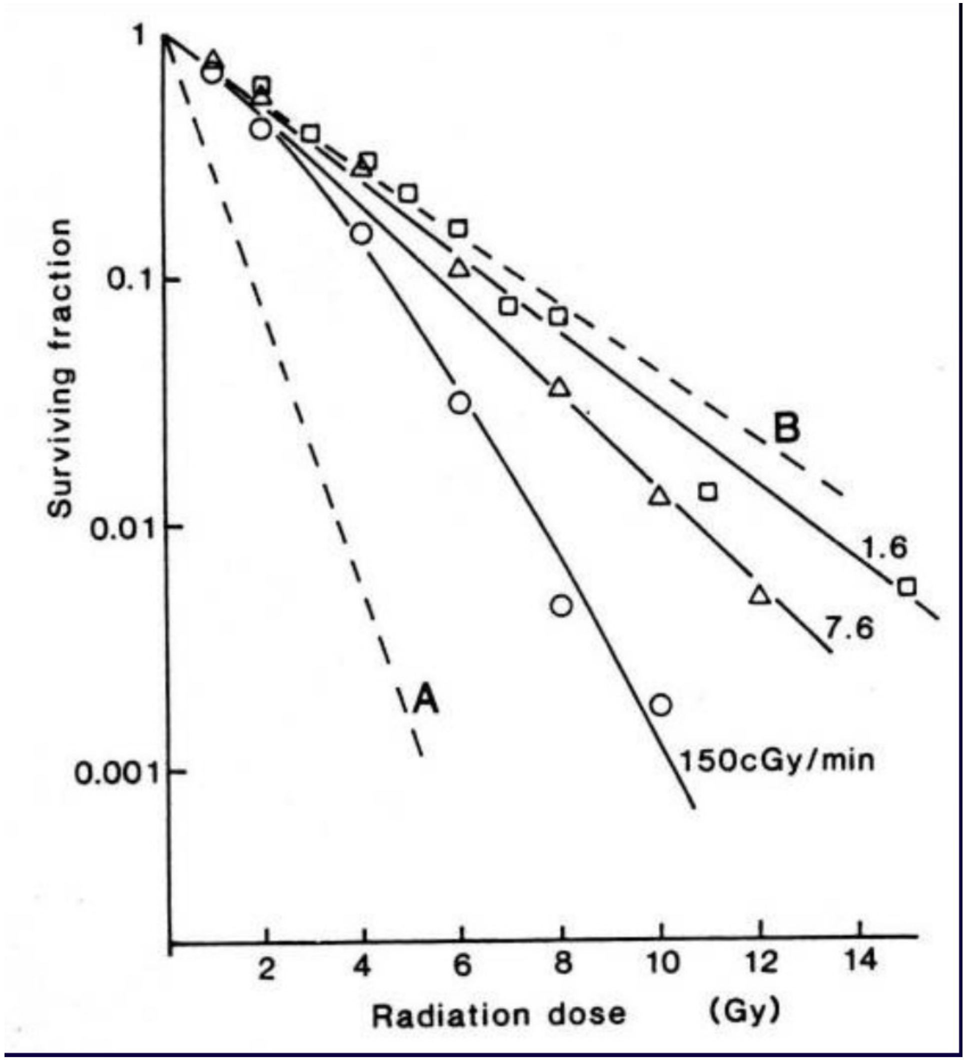
Low Dose Rate



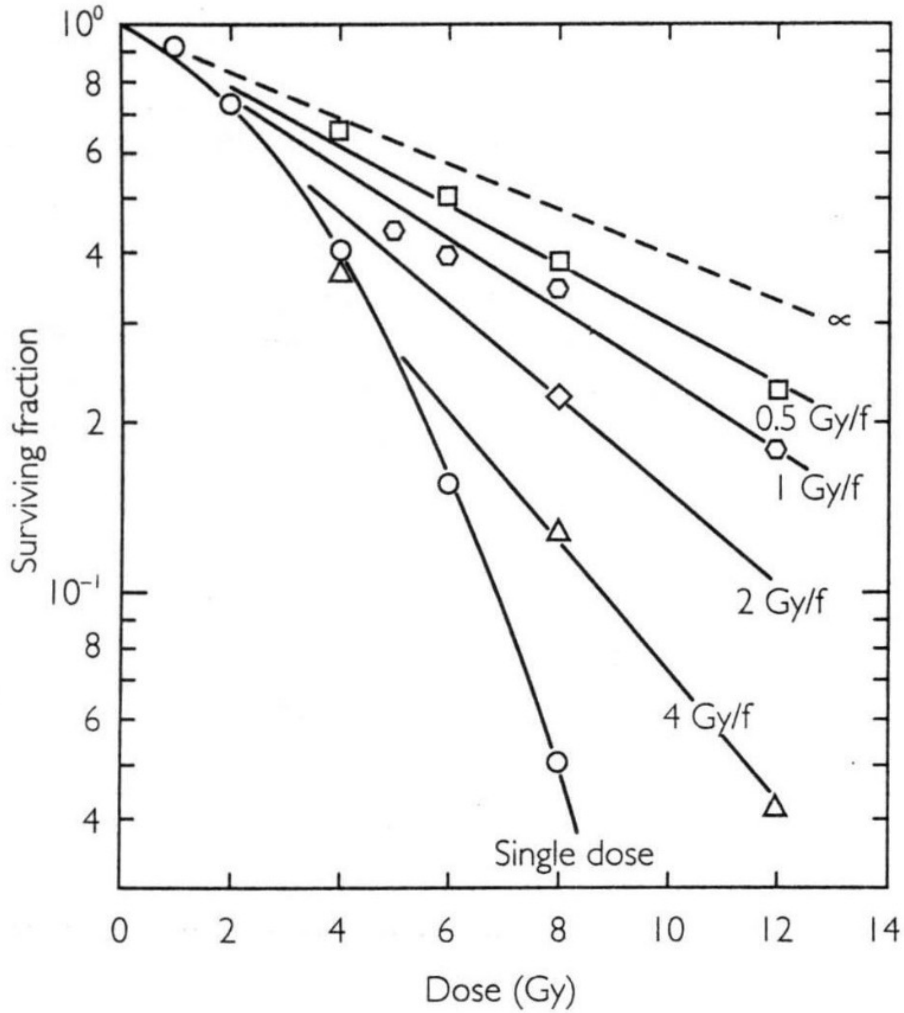
Low Dose Rate BT

- The biological effect of radiation decreases as treatment time increases
- The biological effect of radiation decreases as dose rate increases

Survival curve for LDR: Dose Rate



Survival curve for HDR: dose per fraction



Survival curve : LDR

$$S = \exp\{-(\alpha D + \beta\, dD)\}$$ HDR multiple exposures

$$S = \exp\{-(\alpha D + \beta\ .\ 2.9\ .\ T_{½}\ .\ Dr\ .\ D)\}$$ LDR

With:

D = Total dose

T½ = half time for repair

Dr = Dose rate

Equivalence formula

$D' = D\,(\alpha/\beta + d) / (\alpha/\beta + d')$ HDR

$D' = D\,(\alpha/\beta + 2.9\,T_{1/2}\,Dr) / (\alpha/\beta + 2.9\,T_{1/2}\,Dr')$ LDR

With: D and D' = Total dose

Dr and Dr' = dose rate

$T_{1/2}$ = repair half time

Survival curve: α / β and $T_{1/2}$

Early reacting (normal) tissues and squamous cell carcinomas:

α / β = 10 Gy

$T_{1/2}$ = 1 hr

Late reacting (normal) tissues:

α / β = 3 Gy (0.5-6 Gy)

$T_{1/2}$ = 1.5 hr

J. Dutreix, Radiother. Oncol. 15,25, 1989

Equivalence formula d - Dr

$S = \exp\{-(\alpha D + \beta\, dD)\}$ HDR multiple exposures

$S = \exp\{-(\alpha D + \beta\ .\ 2.9\ .\ T_{½}\ .\ Dr\ .\ D)\}$ LDR

$$\Rightarrow \quad d = 2.9\ .\ T_{½}\ .\ Dr$$

With:

d = dose per fraction

T½ = half time for repair

Dr = Dose rate

Equivalence formula Carcinoma

$T_{½} = 1$ hr

$d = 2.9 \cdot T_{½} \cdot Dr$

-3 Gy / fraction = 1 Gy / hr

-1.8 Gy / fraction = 0.6 Gy / hr

-1.2 Gy / fraction = 0.4 Gy / hr

Equivalence formula Late effects

$T_{½} = 1.5$ hr

$d = 2.9 . T_{½} . Dr$

-4.5 Gy / fraction = 1 Gy / hr

-2.4 Gy / fraction = 0.6 Gy / hr

-1.8 Gy / fraction = 0.4 Gy / hr

Conclusions: Radiobiology in LDR

- There is an effect of dose rate on local outcome in low dose rate brachytherapy
- This effect can be compared to the effect of dose per faction in external beam radiation therapy

Conclusions: Radiobiology in LDR

- Dose adjustments seem in most cases unnecessary in the range 0.3 to 0.9 Gy/hr
- A decrease in dose rate may be beneficial to normal tissue tolerance without significantly affecting local control

Conclusions: Radiobiology in LDR

- **Dose adjustments are mandatory in the range 1 to 2 Gy/hr**
- **There are a few retrospective studies showing that a 10 to 20% reduction in dose should be adequate**