ISOEFFECT CALCULATION IN HDR BRACHYTHERAPY
(BASIC CLINICAL RADIOBIOLOGY)

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TYPES OF BRACHYTHERAPY PROCEDURES
(ICRU REPORT 38)
Clinical work of Brachytherapy since 1950 was to optimise the therapeutic ratio by exploiting the differential response of healthy and malignant tissue to the delivery of the maximal tumoricidal dose in as short time as possible.

B. Pierquin 1992
SINGLE STRAND BREAK (SSB)
REPAIR MECHANISM

Direct (direct ionization)
DNA damage

Indirect (free radical-mediated)
DNA damage

CTACGGTCTT
CGGTCCTCT
DNA helix with 12 nucleotide gap

CTA
GATGCCAGATGATACCC

CTACTATGG
GATGCCAGATGATACCC

CTACGGTCTT
CTACTATGG

hydrogen bonded base pairs

NUCLEASE

DNA HELICASE

DNA POLYMERASE
PLUS DNA LIGASE

Alberts B. Molecular biology of the cell. 1994
DOUBLE STRAND BREAK (DSB) REPAIR MECHANISM

Direct (direct ionization) DNA damage
Indirect (free radical-mediated) DNA damage

Sensor proteins
Rad9-Rad1-Hus1

Upstream kinases
ATR, ATM, Chk2

Mediators/regulators
M/R/N, BRCA1, p53

Effector proteins

Cell-cycle response
Apoptotic response

HR
Rad51 and paralogues, BRCA2, Rad52, Rad54, XRCC2, XRCC3

NHEJ
Ku70, Ku86, DNA-PKcs, Artemis, XRCC4, LigaseIV

Willers H. et al. BJ Cancer 2004
LETHAL DAMAGE
SUBLETHAL DAMAGE

Direct (direct ionization)
DNA damage

Indirect (free radical-mediated)
DNA damage

Viable cells
(no lesions)

Correct repair

Lesions produced by irradiation

Potentially lethal (i.e. repairable) lesions

Lethal lesions (cell death)

Steel G. Basic clinical radiobiology, 2002
- Physical
- Chemical
- Biological

$10^{-18}$ $10^{-12}$ $10^{-6}$ $10^3$ $10^6$ $10^9$

(seconds)

Free-radical reactions
Enzyme reactions
Repair processes
Early effects
Late effects
Carcinogenesis

Excitation
Ionization
Cell proliferation

(hours)

(days)
INSIDE A FRACTION

![Graph showing the relationship between Value (%) and Fraction time (%). The graph compares DOSE, DAMAGE, Log(DAMAGE), REPAIR, and Expon(REPAIR) across different fraction times and values.](image-url)
LINEAR QUADRATIC MODEL
NSD: Nominal standard dose (Ellis, 1969)

TDF: time-dose-fractionation (Orton & Ellis, 1973)

ERD: extrapolated response dose (Barendsen, 1982)

LQ: linear-quadratic (Orton & Cohen, 1988)
Surviving fraction

Extrapolation number

Initial exponential region
(Slope = \frac{1}{D_0})

Terminal exponential region
(Slope = \frac{1}{D_0})

Dose (cGys)
• **α**: Parámetro que expresa la muerte celular por impacto único/daño letal (parte lineal). Valor en Gy⁻¹
• **β**: Parámetro que expresa la muerte celular por impacto doble/daño subletal (parte cuadrática). Valor en Gy⁻²
• **α/β**: proporción entre el daño letal respecto al subletal de un tejido. Valor en Gy.

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**Conventional hypofractionation**  ✴ **Grey zone**  ✴ **Extreme hypofractionation**
Rapid proliferative tissues are less sensitive to changes in fractionation (large doses per fraction or higher dose rate).

Slow proliferative tissues are more sensitive to changes in fractionation (large doses per fraction or lower dose rate).

Early effects

Large $\frac{\alpha}{\beta}$ small change in early effects due to fractionation

Late effects

Small $\frac{\alpha}{\beta}$ large change in late effects due to fractionation
ENDOTHELIAL MEDIATED CELL DAMAGE

The much smaller proportion at 2 Gy than 8 Gy per pulse is showed.

Only the red proportion is altered by $\alpha/\beta$, $T_{1/2}$ and dose per pulse.

Keeping low the dose per pulse guarantees minimal risk of excess damage in late tissues.

Adapted from Fowler 1999
Adapted from Fowler 1999

BETWEEN FRACTIONS

Dose rate per pulse

Time

Creation of SLD

Repair of SLD

Δ no repair of SLD

Adapted from Fowler 1999
SUBLETHAL DAMAGE REPAIR: incomplete repair

Thames HD et al. Incomplete repair model for survival after fractionated and continuous irradiation. IJRO 1985; 47: 319

Dale RG et al. The application of the LQ formula dose-effect equation to fractionated and protracted radiotherapy. B J Radiol 1985; 58: 515

1. Conventional EBRT/HDR daily fractions (>24h) permit enough time between fractions for full repair to occur.

2. If interfraction time is reduced to less than approx 8h, repair between fraction may be incomplete and cell survival decreased.

3. A potential for therapeutic gain exists when the fractionation sensitivity \( \alpha/\beta \) for the host dose limiting late reacting normal tissues is greater than a tumor lying within such tissue.
BASIC MODEL FOR ISOEFFECT CALCULATION
PHYSICS CONTRIBUTION

A SIMPLE METHOD OF OBTAINING EQUIVALENT DOSES FOR USE IN HDR BRACHYTHERAPY

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\[
\text{BED} = nd \left[ 1 + \frac{d}{(\alpha/\beta)} \right] \tag{1}
\]

\[
D_{\text{Eq}} = \frac{\text{BED}}{\left(1 + \frac{d_{\text{REF}}}{(\alpha/\beta)}\right)} \tag{2}
\]
The Linear-Quadratic Model Is an Appropriate Methodology for Determining Isoeffective Doses at Large Doses Per Fraction

David J. Brenner, PhD, DSc

The tool most commonly used for quantitative predictions of dose/fractionation dependencies in radiotherapy is the mechanically based linear-quadratic (LQ) model. The LQ formalism is now almost universally used for calculating radiotherapeutic isoeffect doses for different fractionation/protraction schemes. In summary, the LQ model has the following useful properties for predicting isoeffect doses: (1) it is a mechanistic, biologically based model; (2) it has sufficiently few parameters to be practical; (3) most other mechanistic models of cell killing predict the same fractionation dependencies as does the LQ model; (4) it has well-documented predictive properties for fractionation/dose-rate effects in the laboratory; and (5) it is reasonably well validated, experimentally and theoretically, up to about 10 Gy/fraction and would be reasonable for use up to about 18 Gy per fraction. To date, there is no evidence of problems when the LQ model has been applied in the clinic.
The Use and QA of Biologically Related Models for Treatment Planning

Report of AAPM Task Group 166 of the Therapy Physics Committee
March 2012

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