Radiobiological aspects of brachytherapy

Chapter 2

Brachytherapy Physics, AAPM Summer School, July 2005, Editors: B.R. Thomadsen, Mark Rivard, and Wayne Butler

Numerical results from: M Zaider and G N Minerbo, "Tumour control probability: a formulation applicable to any temporal protocol of dose delivery", Phys. Med. Biol. **45** (2000) 279–293

Outline

- Introduction
- Cell survival curves, dose-response curves, enhancement ratios
- Mechanisms of radiation action: Microdosimetry
- Applications: Equivalent treatments
- Summary

Introduction

- The present function of radiation biology in treatment planning is threefold:
  - (1) to provide information on biologically equivalent temporal patterns of dose delivery;
  - (2) to quantify the effect of radiation quality;
  - (3) to guide the implementation of biologically based optimization algorithms
- The first one is most often invoked in brachytherapy where LDR and HDR regimens are commonly employed

Quantitative radiobiology

- The final goal is to develop a quantitative model allowing
  - to calculate TCP – tumor control probability
  - with a given level of NTCP – normal tissue complication probability
- Start with an account of a stochastic effect of cell killing
- Increase in the radiation dose increases the probability of producing the effect (dose-response relationship)

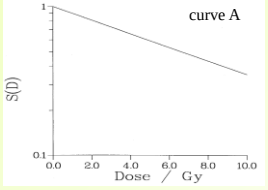
Quantitative radiobiology

- TCP – measures the likelihood that a particular treatment dose leaves all cancer cells sterilized (stochastic effect)
- NTCP – represents a deterministic effect:
  - the ability of that particular organ to function is progressively altered with increasing dose
  - a threshold is introduced that divides acceptable and unacceptable domains
- Probability of effect E(D); the absence of effect is the survival probability: S(D)=1-E(D)

Dose-response curves

- The dose-response relationship remains the principal tool for testing assumptions about the mechanisms responsible for radiation action
- Commonly asked questions:
  - (a) Is the effect a result of *single*-lesion action or a consequence of the accumulation of *multiple* sublesions?
  - (b) Does the temporal pattern of dose delivery matter?
  - (c) Does the response depend on the position of the cell in the cell cycle?
  - (d) Is radiation-induced damage repairable?

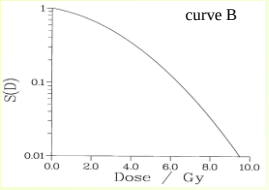
Dose-response curves



- Purely exponential function, exp(-αD)
- Equal increments in dose result in equal fractions of the exposed population acquiring the effect

- The interpretation is that surviving cells have *no memory* of previous exposure
- Single-hit mechanism: cell will either show the effect or remains unaffected

Dose-response curves



- Linear-quadratic model, $S(D)=\exp(-\alpha D-\beta D^2)$
- Sequential exposures to *equal* increments in dose result in an *increasing* fraction of affected cells

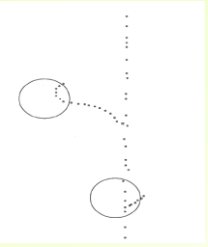
- Multi-hit mechanism: cells exposed to radiation carry and accumulate damage not sufficient to produce the effect on its own but enough to sensitize the cell to further exposure
- Discriminate between repairable *sub-lesion* and lethal *lesion*

Dose-response curves

- If cells become less radiosensitive with exposure to radiation, the curve may become concave upwards
- The function describing their behavior:

$$h(D)=-\frac{d\log(S)}{dD}=\begin{cases}\text{constant (curve A)}\\ \text{monotonically increasing (curve B)}\\ \text{monotonically decreasing}\end{cases}$$

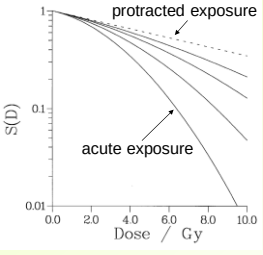
Hits



Two cells: one traversed by the main track and the other by a secondary electron (delta ray)

- The traversal of the radiation-sensitive region by an ionizing particle may result in a *hit* (or *event*) - the production of statistically correlated alterations in the sensitive site
- Alterations result from local energy deposition via ionizations or excitations along the same track
- Events are statistically independent

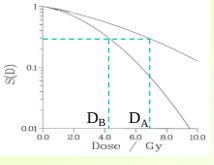
Temporal aspect



- In a single-hit mechanism temporal distribution of hits does not matter
- In multi-hit mode and in the presence of repair mechanisms sublesions may be eliminated *before* the next hit arrives - dose rate becomes relevant

- As the dose rate decreases the quadratic term (βD^2) becomes smaller
- At very low dose rates only the linear term, αD, remains

Enhancement ratios



- The shape of the dose-response curve depends on many factors (radiation quality, oxygen concentration, position in the cell cycle, etc.

- The ***enhancement ratio*** (***ER***) quantifies such differences. For isoeffective doses D_A and D_B corresponding to dose-response curves *A* and *B:*

$$ER=\frac{D_A}{D_B}$$

Enhancement ratios

- ***Relative biological effectiveness*** (***RBE***) is a quantity used to compare the biological effects of two different radiations. If *X* denotes the reference radiation, the RBE of *A* is given by

$$RBE = \frac{D_X}{D_A}$$

- Typically, high-energy electrons (or high-energy photons) are taken as reference radiation

Enhancement ratios

- Anoxic cells (poor in oxygen) are more resistant to radiation than aerobic (oxic) cells. To quantify the oxygen effect, one makes use of the ***oxygen enhancement ratio*** (***OER***) defined as:

$$OER = \frac{D_{anoxic}}{D_{oxic}}$$

- In general, the ER depends on the dose level (D_A)
- An agent for which the ER does not depend on dose is known as a ***dose-modifying factor*** (e.g., oxygen)

Cellular proliferation

- Cellular kinetics is affected by additional factors
- Stem cells (responsible for recovery of self-renewing tissues from radiation injury) and malignant cells (accounting for tumor growth) have the capability to proliferate
- Radiation response depends drastically on the cell position in the cell cycle:
  - cells are most radiosensitive in M phase and most radioresistant in the latter part of S;
  - exposure to radiation results in a lengthening of the G2 phase (this is known as the G2 block);
  - exposure to radiation decreases the division probability

Cell kinetics

- The kinetics of cell growth can be described in terms of three quantities:
  - (1) the average duration of the cell cycle, T_c;
  - (2) the ***growth fraction*** *GF* which is the fraction of cells actively proliferating;
  - (3) the ***cell loss factor*** φ which represents the rate of cell loss divided by the rate of cell production

Cell kinetics

- The ***cell number doubling time*** T_d is given by

$$T_d = T_c \frac{1}{1-\varphi} \frac{\ln 2}{\ln(1+GF)}$$

- If no cell loss occurs, potential doubling time

$$T_{pot} = T_c \frac{\ln 2}{\ln(1+GF)}$$

- Additional useful relationship $\varphi = 1 - \frac{T_{pot}}{T_d}$
- For a typical human tumor:
  Tc ~ 1-2 d, φ ~ 0.8-0.9, and GF ~ 0.4-0.5

Microdosimetry

- Generally the biological effects of radiation depend on the (highly non-uniform) macroscopic pattern of energy deposition
- The energy deposited by ionizing radiation in any given site is a stochastic quantity
- Absorbed dose is in fact only the average value of its distribution
- *Microdosimetry* is the systematic study and quantification of the spatial and temporal distribution of energy in irradiated matter

Specific energy

- If E is the energy imparted by ionizing radiation to matter of mass m, the ***specific energy*** z defined as

$$z = \frac{E}{m}$$

- The unit of z is the gray Gy =1 J/kg
- Specific energy z can be imparted to matter in single events or in multiple events; the respective distributions are labeled $f_1(z)$ and $f(z)$
- $f(z)dz$ - the probability that specific energy is in the interval dz about z - depends on the geometry and physical composition of the site where z is determined

Specific energy

- Absorbed dose D is defined at a point in matter

$$D = \lim_{\substack{m\to 0 \\ \rho=const}} \bar{z}$$

- Here $\bar{z}$ is the first moment of z. For sufficiently small site (~ micrometers) D = $\bar{z}$
- Two averages, frequency and dose, of the single-hit distribution can be defined:

$$z_F = \int_0^\infty z f_1 dz; \qquad z_D = \frac{1}{z_F}\int_0^\infty z^2 f_1 dz;$$

Specific energy distribution

- The average number of events for a given dose:

$$n = \frac{D}{z_F}$$

- If events are distributed with following the Poisson distribution

$$n = \sum_{k=0}^{\infty} kP(k,n)$$

- Here the probability of exactly k events

$$P(k,n) = e^{-n}\frac{n^k}{k!}$$

Specific energy distribution

- Specific energy z can be imparted to matter in single events or in multiple events with the respective distributions $f_1(z)$ and $f(z)$
- $f_k(z)$ is the distribution of z in exactly k events:

$$f_k(z) = \int_0^\infty f_1(z) f_{k-1}(z - z')dz'$$

- Given the single-event distribution $f_1(z)$, the distribution for any number of events n, or dose D:

$$f(z) = \sum_{k=0}^{\infty} P(k,n) f_k(z)$$

LQ model in microdosimetry

- Assume that the actual number of lesions ε (a stochastic quantity) is Poisson-distributed (works for low-LET radiation) with the probability:

$$P(\bar{\varepsilon},k) = e^{-\bar{\varepsilon}}\frac{\bar{\varepsilon}^k}{k!}$$

- Adopting the LQ model for the survival curve, the probability that following exposure to dose D, no lesions were produced in the organism is

$$P(\bar{\varepsilon},0) = e^{-\bar{\varepsilon}} = e^{-\alpha D-\beta D^2}$$

LQ model in microdosimetry

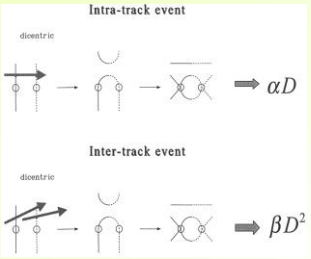
- The average number of lesions is

$$\overline{\varepsilon(D)} = \alpha D + \beta D^2$$

- It is compatible with an assumption that each lesion is the product of two sub-lesions
- Example: a dicentric aberration, responsible for preventing cell proliferation

LQ model in microdosimetry

dicentric chromosomal aberration



Two adjacent single-chromosome breaks (sublesions) rejoin to produce a chromosome with two centromeres (a lethal lesion)

- Each sublesion is the result of one particle (event, or hit) traversing a chromosome
- The pair of sublesions needed to produce a dicentric can be generated by:
  - (1) a single particle traversing both chromosomes, or
  - (2) two (independent) particles

LQ model in microdosimetry

- Microdosimetry offers a physical explanation of the constants α and β
- Assume that the yield of lesions (alterations responsible for the end point observed) depends quadratically on specific energy

$$\varepsilon(z) = \beta z^2$$

- On average

$$\overline{\varepsilon(D)} = \beta\,\overline{z^2} = \beta(z_D D + D^2)$$

LQ model in microdosimetry

- The dose averaged specific energy

$$z_D = \frac{\alpha}{\beta}$$

- The ratio α/β, a purely physical quantity depends on radiation quality *and* on the distribution of radiosensitive matter in the cell
- $\sqrt{\beta}$ is proportional to the yield of sublesions (e.g., single-chromosome breaks) per unit specific energy

Temporal aspect

- To account for sublesion repair need to add a factor affecting the quadratic term:

$$\overline{\varepsilon(D)} = \alpha D + q(t)\beta D^2$$

- The dose-rate function quantifying sublesion damage repair that occurs between events q(t):

$$q = \int_0^\infty \tau(t)h(t)dt$$

$$\tau(t) = \exp(-t/t_0)$$

$$h(t) = \frac{2}{D}\int_0^\infty I(s)h(s+t)ds$$

τ(t) - the rate of sublesion damage elimination;
t_0 - the sublethal repair time;
h(t)dt - the distribution of time intervals t between consecutive events

Temporal aspect

- For irradiation at a constant dose rate

$$q(t) = \frac{t_0}{t} - 2\left(\frac{t_0}{t}\right)^2\left(1 - e^{-t/t_0}\right)$$

- When $t >> t_0$:

$$q \cong \frac{2t_0}{t}$$

- For f well-separated fractions (complete sublesion repair between fractions:

$$q \cong \frac{1}{f}$$

Temporal aspect - LDR

- LDR treatments typically take several days (protracted exposure)
- Since t_0~1 hour for many cell lines, q-->0
- The probability of cell survival, $S(D)$, is quasi-exponential and the RBE is determined by the linear coefficient α, or in microdosimetric terms, by z_D

Temporal aspect - HDR

- HDR treatments are considered acute exposures, $t << t_0$

$$q(t) = \frac{t_0}{t} - 2\left(\frac{t_0}{t}\right)^2\left(1 - e^{-t/t_0}\right) \approx 1 - \frac{1}{3}\frac{t_0}{t}$$

- For the dose rate of the order of 1.5 Gy/min; prescription dose of 6 Gy and taking t_0 = 60 min (t_0/t=1/15) one obtains q = 0.978
- Thus both terms, linear (αD) and quadratic (βD^2), contribute significantly

Temporal aspect

- The terminology "low" or "high" dose rate must be understood in terms of the relative contribution of the quadratic term to the total yield of lesions
- If the dose rate is such that $\alpha D >> q\beta D^2$, one is in low dose rate regime.
- The lower the dose, the larger the range of dose rates that classify as "low"

Equivalent treatment

- Two treatments are different with respect to either one or any combination of the following: radiation quality, and type of tissue (α, β), dose rate, *Tpot*, sublesion repair constant (t_0)
- They can be made equivalent by changing the total dose, the dose rate, and/or the treatment time
- The temporal pattern of dose delivery is given by prescription
- Equivalency can be in terms of either equivalent TCP or equivalent NTCP

Equivalent treatment

- In a tumor containing n malignant cells treated uniformly to dose D, the average number of surviving cells is $nS(D)$
- If the number of surviving cells is Poisson-distributed (this is true only under certain conditions), the probability that no cell will survive the treatment is:

$$TCP = e^{-nS(D)}$$

- Iso-survival probability is equivalent to iso-TCP
- The simplest way to account for proliferation during time t is through a term $\exp(t/Tpot)$

Equivalent treatment

- Under these conditions to find biologically equivalent treatments, one would use the following expression:

$$\alpha D + \beta q D^2 - \frac{t}{T_{pot}} = \alpha_1 D_1 + \beta_1 q_1 D_1^{\,2} - \frac{t_1}{T_{pot,1}}$$

- This equation must be applied separately to early- (e.g., tumor) and late-responding tissues;
- If the dose is designed to match the effect on the tumor, one must evaluate if the effects on normal tissues (increase or decrease)

Equivalent treatment: Example

- A tissue is known to tolerate N = 30 daily fractions of 1.8 Gy each (total dose, D)
- Ignore cell proliferation
- Use α/β_{early} = 10 Gy, α/β_{late} = 3 Gy, T_{pot} = 2 d (early) or 60 d (late), b = 0.01 Gy^{-2}, t_0 = 1 h
- What is the equivalent total dose, D_1, required if the treatment is delivered in one single fraction over 7 days?

$$\alpha D + \beta q D^2 - \frac{t}{T_{pot}} = \alpha_1 D_1 + \beta_1 q_1 D_1^{\,2} - \frac{t_1}{T_{pot,1}}$$

Equivalent treatment: Example

- $q_1=1/N$, $q_2=2t_0/t$

$$\alpha D+\beta\left(\frac{1}{N}\right)D^2=\alpha D_1+\beta\left(\frac{2t_0}{t}\right)D_1^2$$

$$\left(\frac{2t_0}{t}\right)D_1^2+\frac{\alpha}{\beta}D_1-\left[\frac{\alpha}{\beta}D+\left(\frac{1}{N}\right)D^2\right]=0$$

$$D_1=\frac{-\frac{\alpha}{\beta}+\sqrt{\left(\frac{\alpha}{\beta}\right)^2+4\frac{2t_0}{t}\left[\frac{\alpha}{\beta}D+\left(\frac{1}{N}\right)D^2\right]}}{\left(\frac{4t_0}{t}\right)}$$

- For early responding tissues D_1 = 59.5 Gy
- For late-responding tissues D_1 = 68.0 Gy

Equivalent treatment: Example

- Including cell proliferation, assuming time between fractions Δt=1day

$$S(D)=e^{-\alpha D-\beta q D^2+r/T_{pot}}$$

$$\alpha D+\beta\left(\frac{1}{N}\right)D^2-\frac{\Delta t}{T}=\alpha D_1+\beta\left(\frac{2t_0}{t_1}\right)D_1^2-\frac{t_1}{T_1}$$

$$\left(\frac{2t_0}{t_1}\right)D_1^2+\frac{\alpha}{\beta}D_1-\left[\frac{\alpha}{\beta}D+\left(\frac{1}{N}\right)D^2-\frac{N\Delta t}{T\beta}+\frac{t_1}{T_1\beta}\right]=0$$

$$D_1=\frac{-\frac{\alpha}{\beta}+\sqrt{\left(\frac{\alpha}{\beta}\right)^2+4\frac{2t_0}{t_1}\left[\frac{\alpha}{\beta}D+\left(\frac{1}{N}\right)D^2-\frac{N\Delta t}{T\beta}+\frac{t_1}{T_1B}\right]}}{\left(\frac{4t_0}{t_1}\right)}$$

Equivalent treatment: General case

- A general formulation that describes the probability of tumor control, defined as the probability that at time *t* there are no clonogens alive, is

$$TCP(t|n,S)=\left[1-\frac{S(t)e^{(b-d)t}}{1+bS(t)e^{(b-d)t}\int_0^t\frac{dt'}{S(t')e^{(b-d)t'}}}\right]^n$$

- $S(t)$ is the survival probability at time t of the n clonogenic tumor cells present at the time treatment started (t = 0), and b and d are, respectively, the birth and (radiation-independent) death rates of these cells. Equivalently, b = 0.693/*Tpot* and d/b is the *cell loss factor* φ of the tumor

Radiation quality

- The photon or electron energies used in brachytherapy are generally low. At low doses or low *dose rates* the RBE of 100 keV photons relative to 1-MeV photons may exceed 2
- The RBE values of 1.2 to 2 for ^{125}I were found for the dose-rates of 0.03 to 9 Gy/h
- For ^{103}Pd a study performed at 0.07 to 0.8 Gy/h reported an RBE value of 1.9
- While considerably lower RBE values apply to the much higher doses or dose rates usually employed in external radiotherapy, differences in biological effectiveness of the order of 10% to 15% remain

Radiation quality

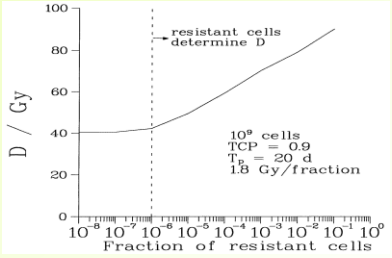
Radionuclide	$z_D/z_D(^{60}Co)$
^{103}Pd	2.3
^{125}I	2.1
^{241}Am	2.1
^{192}Ir	1.3
^{60}Co	1.0

- Numerical examples of ratios RBE = $z_D/z_D(^{60}Co)$ for radiations of interest in brachytherapy

Real world

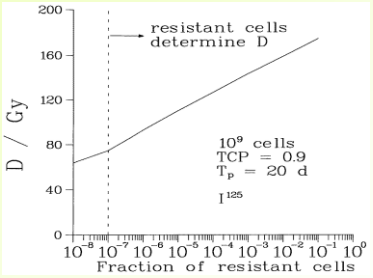
- In brachytherapy any given treatment area (tumor or healthy organ) is never uniformly exposed to the same dose. *Dose-volume histogram* (*DVH*) can be used
- Tissues (malignant or not) consist of cells that have a wide spectrum of α, β, T_{pot}, and φ values. Often one particular cell type dominates the response
- As actively proliferating cells progress through the mitotic cycle, they change radiosensitivity parameters by as many as one to two orders of magnitude
- Cells do not generally exist in isolation and their response to radiation may depend on many extracellular factors and fluctuating environments

Some numerical results



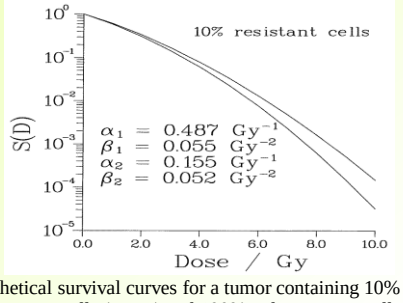
- The total dose, *D*, necessary to obtain TCP=0.9 in a tumor that contains a mixture of two cell lines (one resistant and the other sensitive) as a function of the fraction of radioresistant cells
- For any F> 10^{-6} (a total of 1000 resistant cells out of 10^9) the radioresistant cells determine D

Some numerical results



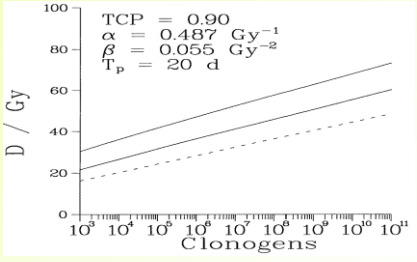
- For a permanent implant with ^{125}I seeds as few as 100 resistant cells (10^{-7} of 10^9) determine uniquely the TCP of the tumor (at the 90% level)

Some numerical results



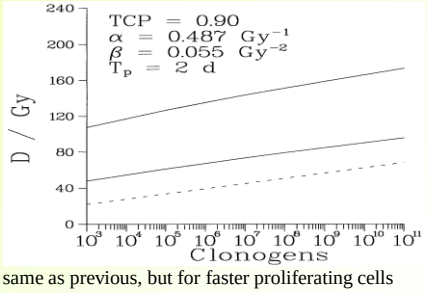
- Hypothetical survival curves for a tumor containing 10% radioresistant cells (upper) and 100% radiosensitive cells (bottom)
- Current techniques for measuring cell survival may be insensitive to the small difference between these two curves

Some numerical results



- Total dose needed to obtain TCP=0.9 as a function of the number of clonogens in the tumor
- Compare fractionated treatment (dashed) and permanent implant with ^{125}I seeds (upper solid) or ^{103}Pd seeds (lower solid curve)

Some numerical results



- The same as previous, but for faster proliferating cells
- The general result is that a better TCP is obtained whenever the dose rate is larger at the beginning of the treatment, as is the case here for the ^{103}Pd implant

Summary

- The analytical expression describing tumor control probability, defined as the probability that no clonogenic cells (i.e. capable of re-growing the tumor) will be left in the tumor at time *t* after the beginning of the treatment is available
- The application of this expression requires a model for the tumor-cell survival probability, S(D)
- May use more comprehensive version of LQ model, taking into account hypoxia and cell-cycle effect