Dose fractionation in radiotherapy and the linear-quadratic model

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Abstract: In this TFG we review the Linear-Quadratic (LQ) model of cell survival to ionizing radiation and the concept of biological effective dose (BED). We will explain the effect of dose protraction and incomplete damage repair, cell repopulation, the kind of radiation and oxygenation, and how to introduce them into the LQ model and the BED.

I. INTRODUCTION

The aim of radiotherapy, like chemotherapy or surgery, is to eradicate all the malignant (cancer) cells that form a tumour while keeping as low as possible the damage to the healthy tissues. There are many variables that can be taken into account to make radiotherapy more precise and to predict better the outcome of the treatment. The most important ones are the effect of incomplete repair of radiation damage when the delivery of absorbed dose is protracted (i.e. extended in time), cell repopulation, the relative biological effectiveness and the presence of oxygen.

II. GENERAL CONCEPTS

A. Lethal and sublethal damages

Ionizing radiations may produce substantial damage to the irradiated cells. The damages that relate better to cell killing are the ones inflicted to the DNA, although not all lesions produce the death of the cell. Some can be repaired and the cells may continue their cycle even with mutations. We will define two kinds of lethal damages:

- Type A: the lethal damage is inflicted when a single ionizing event produces a double strand break in the DNA. The amount of damage (yield) is proportional to absorbed dose, $y_{\mathrm{A}} \propto D$, but independent of absorbed dose rate and exposure time [1–5] (Fig. 1a).

- Type B: the lethal damage is the result of independent sub-lethal damages induced by *separate* ionizing events. The yield is proportional to absorbed dose square, $y_{\mathrm{B}} \propto D^2$, and in this case it also depends on the dose rate and the exposure time. If the absorbed dose rate is low enough and the time between events increases, the first sub-lethal damage can be repaired before the second one is inflicted and, therefore, they cannot interact to produce a lethal lesion [1–5] (Fig. 1b).

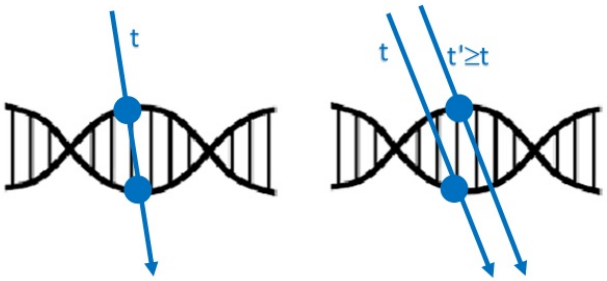

FIG. 1: (a) Type A: $y_{\mathrm{A}} = \alpha D$. (b) Type B: $y_{\mathrm{B}} = \beta G D^2$.

B. Linear-Quadratic model

The Linear-Quadratic (LQ) model is nowadays widely used to design radiotherapy schedules as it provides an explanation to the fact that tumours and healthy tissues react differently to irradiation and that different schedules may result in a sparing effect for the healthy tissues while still controlling the tumour [3]. Also, its predictive properties are well documented and there is no evidence of it leading to significant overdosing or underdosing [6].

The equation that predicts the survival probability of a cell after being irradiated with a total absorbed dose D is

$$s(D) = \mathrm{e}^{-(y_{\mathrm{A}}+y_{\mathrm{B}})} = \mathrm{e}^{-\alpha D-\beta G D^2}, \qquad (1)$$

where the yields of lethal damages of types A and B are αD and $\beta G D^2$, respectively. The constants α and β are specific to the cell line and ionizing radiation. The *Lea–Catcheside* (LC) factor G modifies the βD^2 term, being $G = 1$ for a single acute irradiation and $0 < G < 1$ for protracted radiotherapy, and it depends on the damage repair rate μ [7]; the LC factor will be addressed in more depth in section III.

C. Biological Effective Dose

The biological effective dose (BED) is defined as the theoretical total absorbed dose required to produce a certain effect using an infinite number of infinitesimally

small absorbed dose fractions or with an infinitesimal absorbed dose rate [8]. It is a useful concept to assess the biological effect of an irradiation and to compare two different schedules of radiotherapy. The BED is

$$\text{BED} = D \times \text{RE}, \qquad \text{RE} = 1 + \frac{\text{type A damage}}{\text{type B damage}}, \quad (2)$$

where D is the total absorbed dose and RE (relative efficiency) is a factor that considers the biological parameters and how the irradiation is delivered [1, 2]. Using the LQ model the expression of the BED becomes [2, 7]

$$\text{BED} = -\frac{\ln s(D)}{\alpha} = D\left(1 + \frac{GD}{\alpha/\beta}\right). \quad (3)$$

This definition shows that we only need to know two parameters, namely the α/β ratio and the LC factor, to be able to predict the effect of a certain irradiation strategy. As will be explained below, α/β may have significant differences between tumour and normal tissues, and G is related to incomplete damage repair.

D. The α/β ratio

This ratio quantifies the relation between intrinsic radiosensitivity (α) and the potential sparing effect (β) [2] (Fig. 2). Hence, it is an indicator of the sensitivity to changes in fractionation or absorbed dose rate of each tissue or tumour. α/β can be determined by plotting, for a given effect $E = -\ln s(D)$, the reciprocal of the number of fractions ($1/n$) against the absorbed dose per fraction ($d = D/n$) and fitting a parabola $1/n = (\alpha/E)d + (\beta/E)d^2$ [8].

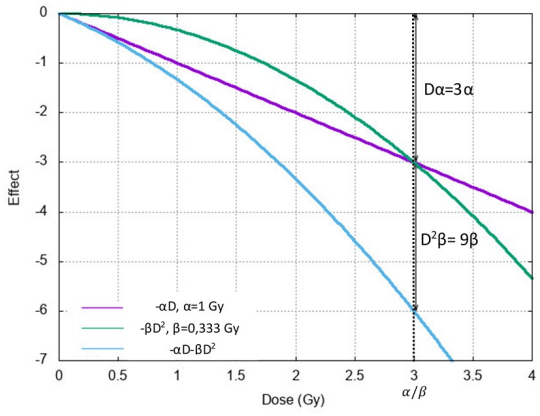

FIG. 2: Effect of an irradiation according to the LQ model (taking $G = 1$). At $D = \alpha/\beta$ the contributions of both types of damages are equal.

Considering this ratio we can distinguish two groups:

- High α/β ratio (7–20 Gy), typical of early-responding tissues and most tumours [8]. Tissues with a high α/β ratio are fast proliferating [7]. The surviving fraction of these tissues after irradiation is not influenced by changes in the schedule provided that the overall time remains the same [9].
- Low α/β ratio (0.5–6 Gy) is common in late-responding tissues and some tumours such as melanomas, sarcomas and early-stage prostate cancer [8]. The surviving fraction of these tissues is influenced by changes in fractionation, and they can be spared if D is delivered in small absorbed dose per fraction [9, 10].

III. DOSE PROTRACTION

Cells can repair the sub-lethal damage caused by irradiation if given enough time (between 6 hours and 1 day [8]), and therefore the amount of lesions decreases. This damage repair can be modelled as an exponential [5, 7],

$$R(t) = R_0\, \mathrm{e}^{-\mu t}, \quad (4)$$

where $R(t)$ is the amount of damage at time t and μ is the damage recovery constant; typical repair half times span from 0.5 h to 3 h, hence $\mu \sim 1\ \text{h}^{-1}$ [3]. Considering the repair as an exponential process is an oversimplification and probably it is better described as a combination of exponentials, but we will use the former as a first approximation. If the repair of the sub-lethal damages is successful before another irradiation produces more sub-lethal lesions (Fig. 3), the cell survives. This recovery can happen between radiotherapy sessions or during the irradiation if the absorbed dose rate is low enough. To introduce the possibility of incomplete repair into the LQ model we add the LC factor G that modifies the βD^2 component. Its general expression is

$$G = \frac{2}{D^2}\int_0^T \dot{D}(t)\,\mathrm{d}t \int_0^t \mathrm{e}^{-\mu(t-t')}\,\dot{D}(t')\,\mathrm{d}t', \quad (5)$$

where $\dot{D}(t)$ is the dose rate, D the total absorbed dose and T is the overall treatment time. This factor takes values $0 \le G \le 1$, being $G = 1$ for a single acute dose [7]. In the following subsections we will give the expressions for a few common radiotherapy modalities that we have derived from the general definition.

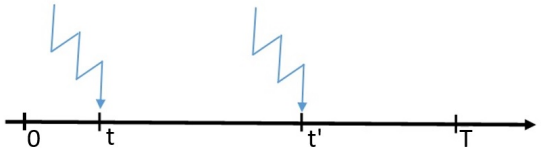

FIG. 3: Time line: the first sub-lethal lesion is produced at t and the second one at $t' > t$. There is a time interval $t' - t$ during which the cell may repair the first lesion before it can interact with the second one.

A. High-dose-rate fractions

D is split into n fractions of absorbed doses $d = D/n$, each delivered in a few minutes (high dose-rate) by an external photon or electron beam generated by a linac. The conventional schedule is to deliver fractions of about 2 Gy, 5 times per week for about 6 weeks [10] (the total absorbed dose and therefore the overall time depends on the tumour that has to be controlled). Now the LC factor takes the form [6, 10]

$$G = \frac{1}{n}\left[1 + \frac{2}{n}\,\frac{\theta}{1-\theta}\left(n - \frac{1-\theta^n}{1-\theta}\right)\right]; \qquad \theta = \mathrm{e}^{-\mu\,\Delta T}. \tag{6}$$

When the time between fractions ΔT is large enough $\theta \to 0$ so that [6]

$$G = \frac{1}{n} \qquad \text{and} \qquad \mathrm{BED} = D\left(1 + \frac{d}{\alpha/\beta}\right). \tag{7}$$

B. Continuous low dose rate

The absorbed dose is delivered continuously, during hours or days, either with an external radiation beam (teletherapy) or with an encapsulated radioactive source (brachytherapy) (e.g. using temporary implants such as ^{192}Ir [23] seeds in the form of ribbons or strands to treat breast and head & neck tumours [11]). An absorbed dose rate ~ 0.05 Gy/h (equivalent to fractions of 2 Gy) allows repair to take place during irradiation [7, 8]. Considering that the decay half life of the radionuclide is much greater than the overall time T, the absorbed dose rate is simply $\dot{D}(t) = D/T$ and the LC factor becomes [7]

$$G = \frac{2}{\mu T}\left(1 - \frac{1-\mathrm{e}^{-\mu T}}{\mu T}\right). \tag{8}$$

When T is long [2, 4]

$$G = \frac{2}{\mu T} \qquad \text{and} \qquad \mathrm{BED} = D\left(1 + \frac{2D}{\mu T(\alpha/\beta)}\right). \tag{9}$$

C. Exponentially decaying dose rate

When a radioactive source is implanted in the body for a long enough time, comparable or greater than the half life of the radionuclide, the absorbed dose rate cannot be considered constant. These sources can be either encapsulated, like in permanent brachytherapy implants (e.g. ^{125}I [24] seeds to treat prostate and brain tumours [12]), or unencapsulated. The latter are used in targeted radiotherapy, also called molecular radiotherapy, in which a radionuclide is attached to a biomolecule that selectively delivers it to the tumour (e.g. ^{131}I-mIBG [25] to treat pheocromacytomas or neuroblastomas [13]). A particular case of targeted radiotherapy is radio-immunotherapy, in which the molecular vehicle is an antibody [14] (e.g. ^{90}Y-ibritumomab tiuxetan [26] to treat non-Hodgkin lymphoma [14]).

In these modalities $\dot{D}(t)$ decreases exponentially with decay constant λ from an initial absorbed dose rate $\dot{D}(0)$ to a smaller value (or 0, if left a long enough time) [2]. Given that its time evolution is given by $\dot{D}(t) = \dot{D}(0)\,\mathrm{e}^{-\lambda t}$ we have

$$D = \frac{\dot{D}(0)}{\lambda}\left(1 - \mathrm{e}^{-\lambda T}\right) \tag{10}$$

and the LC factor takes the form

$$G = \frac{2\lambda^2}{\mu - \lambda}\,\frac{A - B}{C^2} \tag{11}$$

with [2]

$$A = \frac{1-\mathrm{e}^{-2\lambda T}}{2\lambda}, B = \frac{1-\mathrm{e}^{-(\mu+\lambda)T}}{\mu+\lambda}, C = 1-\mathrm{e}^{-\lambda T}. \tag{12}$$

When the radioactive source is allowed to decay completely ($T \to \infty$) we have $D = \dot{D}(0)/\lambda$ and then [3, 4]

$$G = \frac{\lambda}{\mu+\lambda}, \qquad \mathrm{BED} = \frac{\dot{D}(0)}{\lambda}\left(1 + \frac{\dot{D}(0)}{(\mu+\lambda)\,(\alpha/\beta)}\right). \tag{13}$$

IV. REPOPULATION

The tumours' response to irradiation is to grow (which they do in a disorganized manner, forming different nodules [10]). This growth has been modelled in many ways, being the simplest one to consider the increase in number of cells as an exponential

$$V(t) = V_0\,\mathrm{e}^{\gamma T}, \tag{14}$$

where $\gamma = \ln 2/T_\mathrm{D}$ and T_D is the duplication time [7, 10] (Fig. 4a). However, tumours slow down their growth rate as they get bigger because the distribution of nutrients within the tumour changes and produces hypoxic zones and necrotic zones in the center (Fig. 4b). As a consequence, Eq. (14) does not fit the experimental data when the tumours get big. The reduction in the growth rate can be described by the Gompertz model

$$V(t) = V_0\,\mathrm{e}^{A(1-\mathrm{e}^{-at})}, \tag{15}$$

where A and a are adjustable parameters (Fig. 4a). This model fits better the data than the exponential, but it predicts a maximum volume which contradicts the evidence [7, 8].

To a first approximation, to account for repopulation in the BED, we will use the exponential model, although as already mentioned it does not always fit the data and, therefore, it will be an oversimplification.

Notice that for late responding tissues, which are slowly proliferating, no factor to describe repopulation needs to be added [8, 15]. Repopulation will be included in the BED (for fast proliferating tissues or tumours) by adding a term that decreases the effectiveness, as it counteracts the cell killing [2, 15]

$$\mathrm{BED} = D \times \mathrm{RE} - \mathrm{RF}, \qquad \mathrm{RF} = \frac{\gamma}{\alpha} T. \tag{16}$$

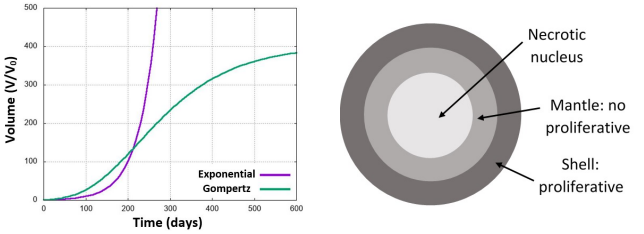

FIG. 4: (a) Models of tumour proliferation (b) tumour structure (taken from [7]).

V. RELATIVE BIOLOGICAL EFFECTIVENESS

The linear energy transfer (LET) is the energy transfered per unit length by the ionizing radiation. In the case of charged particles it can also be defined as the restricted linear electronic stopping power, as it is the electronic stopping power ($S = -\mathrm{d}E/\mathrm{d}x$) minus the mean sum of the kinetic energies of secondary electrons greater than a preselected value, usually 100 eV [16].

Conventional radiotherapeutic treatments use radiations with low LET such as photons or electrons. Low LET radiations produce ionizations (and therefore damage) far apart form each other [8, 17], hence it is likely that they generate more single strand breaks (repairable) than double strand breaks (prone to result in lethal damage) (Fig. 5a). On the other hand, high LET radiations (e.g. α particles, neutrons) produce ionizations closer together and, as the damages are nearer from each other, it is more probable that they cause double strand breaks in the DNA and, as a consequence, more lethal damages [3, 4, 17] (Fig. 5a).

The Relative Biological Effectiveness (RBE) is introduced to take into account the different LETs. The RBE is defined as the experimentally determined ratio of absorbed doses required to produce a given degree of cell kill ($\mathrm{RBE}_{\mathrm{x-rays}} = 1$ by convention) [3, 4]. The RBE maximizes when using low absorbed dose rates and, therefore, to incorporate it into the BED we merely have to replace the 1 in Eq. (3) (and Eqs. deduced from it) with this factor [3, 4]. For instance, Eq. (13) is now written as

$$\mathrm{BED} = \frac{\dot{D}(0)}{\lambda}\left(\mathrm{RBE}_{\max} + \frac{\dot{D}(0)}{(\mu+\lambda)\,(\alpha/\beta)}\right). \tag{17}$$

This equation with $\mathrm{RBE}_{\max} = 5$ is adopted when ^{223}Ra [27] is used to treat bone metastases [18].

VI. OXYGEN

Oxygen is a radiosensitizer, which means that well-oxigenated (oxic) cells are more sensitive to radiation than hypoxic cells. This is because the presence of oxygen reacts with $\mathrm{H}^\bullet$ free radicals

$$\mathrm{H}^\bullet + O_2 \to \mathrm{HO}_2^\bullet; \quad \begin{cases} \mathrm{HO}_2^\bullet + \mathrm{HO}_2^\bullet \to \mathrm{H_2O_2} + \mathrm{O_2} \\ \mathrm{HO}_2^\bullet + \mathrm{H}^\bullet \to \mathrm{H_2O_2} \end{cases}$$

causing a decrease of $\mathrm{H}^\bullet$ free radicals , which prevents the recombination of radicals $\mathrm{OH}^\bullet$ allowing them to interact with the DNA inducing damages. It may also capture electrons preventing from recombining with ions or even forming new radicals

$$\mathrm{e}_{ac}^- + O_2 \to \mathrm{O}_2^-; \quad \mathrm{O}_2^- + \mathrm{H_2O} \to \mathrm{H_2O}^\bullet + \mathrm{HO}^-.$$

Or it can interact with organic radicals producing toxic substances [7, 10]

$$\mathrm{R}^\bullet + O_2 \to \mathrm{ROO}^\bullet; \quad \begin{cases} \mathrm{ROO}^\bullet + \mathrm{R'H} \to \mathrm{ROOH} + \mathrm{R'}^\bullet \\ \mathrm{ROO}^\bullet + \mathrm{R'} \to \mathrm{ROOR'}. \end{cases}$$

The effect of ionizing radiation on oxic and hypoxic cells is quantified by the oxygen enhancement ratio (OER), which is the ratio of the absorbed doses required in hypoxic to oxic conditions to achieve the same biological effect (a specified survival fraction s_0, e.g. 10^{-2}) [19, 20] (Fig. 5b) [8]

$$\mathrm{OER} = \frac{D(s_0, \mathrm{hypoxic})}{D(s_0, \mathrm{oxic})}. \tag{18}$$

Owing to their rapid growth, tumours typically contain both oxic and hypoxic cells, the surviving fractions of each type being different. Using the LQ model, oxic cells will follow Eq. (1) [20, 21] whereas for hypoxic cells [20]

$$s(D) = \exp\left(-\frac{\alpha}{\mathrm{OER}}\,D - \frac{\beta}{\mathrm{OER}}\,GD^2\right). \tag{19}$$

Because of this effect, the fractionation of the treatment has another advantage: between fractions the hypoxic cells may be re-oxygenated, making them more sensitive to radiation and therefore more likely to be killed in the next fraction [17, 20].

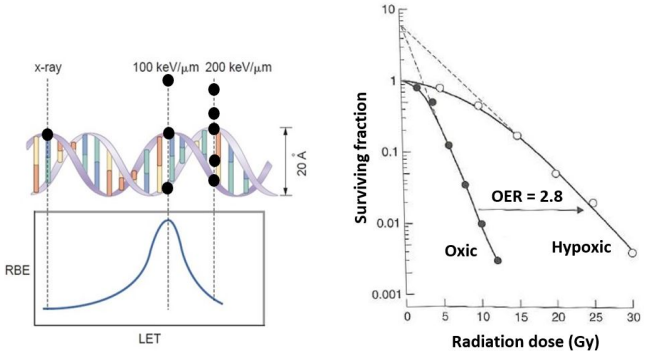

FIG. 5: Effects of (a) LET and (b) oxygen.

VII. CONCLUSIONS

The LQ model and the BED concept admit, at first, very simple expressions that only depend on the α/β ratio. Nevertheless, they adapt rather well to the experimental data and allow us to compare radiotherapy treatments. As we contemplate more aspects that may influence the outcome of the treatment (such as the effect of time in the cells, i.e. that they may repair sublethal damage and/or reproduce, the kind of radiation used or the presence of oxygen) the expressions become more complicated because new parameters (μ, γ, RBE and OER, respectively) are introduced which can be difficult to know in a precise way.

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[22] URL `www.nucleide.org`
[23] ^{192}Ir decays to an excited level of ^{192}Pt mainly by via β^- and then to the ground level emitting γ radiation; $\lambda = 0.0094$ days^{-1} [22].
[24] ^{125}I decays to an excited level of ^{125}Te via electron capture and then to the ground state emitting γ radiation; $\lambda = 0.012$ days^{-1} [22].
[25] ^{131}I decays to an excited level of ^{131}Xe via β^- and then to the ground level emitting γ radiation; $\lambda = 0.086$ days^{-1} [22].
[26] ^{90}Y decays to the ground state of ^{90}Zr via β^-; $\lambda = 0.011$ h^{-1} [22].
[27] ^{223}Ra decays to various excited levels of ^{219}Rn via α emission and then to the ground level emitting γ radiation; $\lambda = 0.06$ days^{-1} [22]