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Biologically Effective Dose (BED) or Radiation Biological Effect (RBEf)?

Terman Frometa-Castillo, Anil Pyakuryal, Amadeo Wals-Zurita and Asghar Mesbahi

Abstract

The current radiosensitive studies are described with linear-quadratic (LQ) cell survival (S) model for one fraction with a dose d . As result of assuming all sublethally damaged cells (SLDCs) are completely repaired during the interfractions, that is, no presence of SLDCs, the survived cells are calculated for a n -fractionated regimen with the LQ $S(n,D)$ model. A mathematically processed subpart of $LQS(n,D)$ is the biologically effective dose (BED) that is used for evaluating a so-called “biological dose.” The interactions of ionizing radiation with a living tissue can produce partial death or sublethal damage from healthy or sublethally damaged cells. The proportions of the killed and sub-lethally damaged cells define the radiation biological effects (RBEfs). Computational simulations using RBEfs for fractionated regimens let calculating tumor control probability. While the derivation of the LQ $S(n,D)$ considers a 100% cell repair, that is, 0% of sublethally damaged cells (SLDCs), the radiobiological simulators take into account the presence of SLDCs, as well as a cell repair $<100\%$ during the interfractions and interruption. Given “biological dose” does not exist, but RBEf, there was need for creating the BED. It is shown how some uses of BED, like the derivation of EQ2D expression, can be done directly with the LQ $S(n,D)$.

Keywords: BED, simulation, radiotherapy, brachytherapy, fractionation, linear-quadratic model, mathematical models, radiobiology

1. Introduction

In 1989, an article published in [1] introduced the term BED, biologically effective dose, as a linear-quadratic (LQ)-based formula. After 21 years, a new article was published in [2] for showing the wide use of BED in the radiation therapies. In this work, the BED was defined (of a given schedule) as: “the total dose required to give the same log cell kill as the schedule being studied, at an infinitely low dose-rate or with infinitely small fractions well-spaced out; now with an overall time factor for repopulation during continued irradiation.”

When ionizing radiation interacts with a determined volume of living tissue, this can or cannot interact with all cells, can or cannot produce effects as result of their interactions; and the first fraction of a fractionated treatment produces a partial number of killed and sublethally damaged cells (SLDCs) from the total initially

undamaged ones. During the second and successive fractions, the radiation can interact with these three kinds of cells, where the interactions can produce the same effects of the first fraction from the undamaged cells and SLDCs.

BED has direct relationship with the radiation biological effects (RBEfs), in particular the cell survival (S) in radiation treatments with n fractions, d dose per fractions delivered in tissues characterized with LQ parameters α and α/β . The BED expression was a result of a mathematical derivation of the exponential part of the LQ S model for treatments with n fractions and dose per fraction d, the LQ S(n,D) where $D = nd$; and this model was obtained assuming that all sublethally damaged cells are wholly repaired during the interfraction period.

“BED is a measure of the true biological dose delivered by a particular combination of dose per fraction and total dose to a particular tissue characterized by a specific α/β ratio” [3]. This expression is incoherent because only the physical dose is delivered, and produces biological effects. There is no “biological dose.”

The mathematical formulas have traditionally been used for calculating physical quantifications of deterministic and stochastic processes/effects (SP/Es). At this time there is high development in the computer science, where the computational simulators allow us determining probabilistic metrics some SP/Es, such as their means and probabilities, based on simulations of many possible cases.

The RBEfs should be estimated with computational radiobiological simulators or with the current LQ S(n,D) model.

2. The biologically effective dose (BED)

Nowadays, the radiosensitivity studies function of the absorbed dose (d) are described with the cell survival (S), which is complement of cell kill (K), and probabilistically $S = 1-K$. These studies are widely modeled with the LQ S(d) for one fraction as

$$LQS(d) = \exp(-\alpha d - \beta d^2) \quad (1)$$

where α and β are the LQ parameters.

d: dose of one fraction.

As result of assuming all sublethally damaged cells (SLDCs) are completely repaired during the interfractions, that is, no presence of SLDCs, the survived cells are calculated for a n-fractionated regimen as

$$LQS(n, D) = [LQ S(d)]^n = \exp(-\alpha D - \beta D^2/n) \quad (2)$$

where $D = n \cdot d$.

A mathematically processed subpart of LQ S(n,D) is the BED that is used for evaluating a called “biological dose,” and is written as

$$BED = D \left[1 + \frac{d}{\alpha/\beta} \right] \quad (3)$$

As an inherent part of the LQ S(n,D) model, the origin of BED is explained in [4] the following way.

1. The radiation cell kill (or effect, E) can be expressed as

$$\text{Cell kill} = E = n (\alpha d + \beta d^2) \quad (4)$$

2. Consider a progressive reduction in d such that it approaches a value of zero. Although the number of fractions n will then need to be increased to maintain the same effect, βd_2 will be very small in comparison with αd (since d will greatly exceed d_2 for very small values and α always exceeds β). Therefore, when d is very small, Eq. (4) is approximated as

$$E = n\alpha d = \alpha D \quad (5)$$

3. This demonstrates that the total dose (D) of radiotherapy given at a very low dose per fraction represents the highest total dose required to obtain a specific effect. The total dose required in these conditions constitutes the definition of BED in situations where cellular repopulation can be ignored, that is, in this limiting case:

$$BED = D = E/\alpha \quad (6)$$

The authors of [4] considered that: “BED represents the physical dose required for a given effect if the dose were to be delivered by infinitely small doses per fraction or, in the case of continuous radiation rates, at a very low dose rate.”

The procedure used in [4] is purely mathematical, since the cell kill (K) and its complement, the cell survival (S), are stochastic effects with a deterministic region for low values of d , where D does not produce any effect, that is, there will be 100% of S ; i.e. 0% of K .

To date, except the probabilistic treatments of the tumor control/normal tissue complication probability (TCP/NTCP), many stochastic processes/effects in areas of the ionizing radiations interacting with living tissues have not been probabilistically treated nor modeled, which has led deficiencies, like replacement in the evaluations of cell survival (S)—a probabilistic metric—by BED, a non-probabilistic, a mathematical derivation from the LQ $S(n,D)$ formalism.

2.1 The BED in radiotherapy

In [4], the authors have shown the use of BED in practical situations for normal tissues. For example, if a dose of 60 Gy in 30 fractions is received by a critical normal tissue, the associated BED may (for example) be expressed in terms of Gy_{1.5}, Gy₂, and Gy₃ (for α/β ratios of 1.5, 2, and 3 Gy). The initial BED value for a fractionation schedule of 60 Gy in 30 fractions ($BED = 140\text{Gy}_{1.5}$) is used to calculate the total dose and dose per fraction for the alternative schedule of 20 fractions. The result for alternative fractionation schedule is obtained from the solution of d in a rearrangement of following equation

$$20d \left(1 + \frac{d}{1.5} \right) = 140\text{Gy}_{1.5} \quad (7)$$

Really, we can use the Eq. (2) for determining the previous alternative fractionation schedule (n_2 fractions and d_2 dose per fractions) without need of creating the BED, based on the following procedure

$$LQS(n_1, D_1) = LQS(n_2, D_2) \quad (8)$$

where $D_1 = n_1 d_1$ and $D_2 = n_2 d_2$

$$\exp(-\alpha D_1 - \beta D_1^2/n_1) = \exp(-\alpha D_2 - \beta D_2^2/n_1) \quad (9)$$

$$-\alpha D_1 - \beta D_1^2/n_2 = -\alpha D_2 - \beta D_2^2/n_1 \quad (10)$$

On multiplication of Eq. (10) by $-1/\alpha$, then

$$n_1 d_1 + n_1 \frac{d_1^2}{\alpha/\beta} = n_2 d_2 + n_2 \frac{d_2^2}{\alpha/\beta} \quad (11)$$

Substituting $n_1 = 30$, $d_1 = 2$ Gy ($D_1 = n_1 d_1 = 60$ Gy), and $n_2 = 20$, we obtain the same Eq. (7) but without the dimension $Gy_{1.5}$

$$20d \left(1 + \frac{d}{1.5}\right) = 140 \quad (12)$$

From the Eq. (11) one can derive the current equivalent dose in 2-Gy fractions (EQD2) in Gy, that is, the Eq. (14), if one substitutes $n_1 = n_2$ and $d_2 = 2$ Gy transform the Eq. (11) as

$$D_1 + D_1 \frac{2Gy}{\alpha/\beta} = D_2 + D_2 \frac{d}{\alpha/\beta} \quad (13)$$

where $D_1 = EQD2$ and $D_2 = D = nd$, then

$$EQD2 = D(d + \alpha/\beta)/(2Gy + \alpha/\beta) \quad (14)$$

This derivation does not need creation of the BED.

With the introduction of BED in radiotherapy, the radiation biological effects of radiation treatments have been characterized with BED with generic values $\alpha/\beta = 10$ Gy for tumors and $\alpha/\beta = 3$ Gy for normal tissues.

While the BED expression, the Eq. (3), has only one parameter, α/β , the LQS(n,D) has two: α and β . Therefore, a tissue with $\alpha = 1$ Gy⁻¹ and $\alpha/\beta = 10$ Gy that receives 60 Gy in 30 fractions, that is, $d = 2$ Gy, will have a biological radiation effect of 9.1% of cell survival.

The cell repopulation (CR) has been introduced in Eq. (3) as

$$BED = D \left[1 + \frac{d}{\alpha/\beta}\right] - K(T - T_K) \quad (15)$$

where T is the overall treatment duration.

T_k is the time when the cell repopulation starts.

K is the factor in Gy/day. According to [4], it is the daily BED equivalent of repopulation.

The CR can be introduced in Eq. (2) as

$$LQS(n, D) = \exp(-\alpha D - \beta D^2/n) + KS(T - T_K) \quad (16)$$

where KS is the factor in 1/day that represents the rate of the CR per day.

The authors of [4] have highlighted that BEDs are additive. It means that if radiotherapy is given in multiple phases, then the BED for each phase can be summated to give the total BED.

Actually, the RBEfs are additive, that is, the biological damages increase when number of irradiation phases increase.

2.1.1 The BED in interrupted treatments

Many of the current works, such as [5–8] related with the interrupted treatment use directly the BED expression or with some modifications that involve elements, like the cell repopulation.

The BED is one of the most current important tools for compensating interrupted radiation treatments, where, as described in [5] three values of BED (original for the initial prescription, applied before the interruption and a new for compensating the interruption) are considered.

2.2 The BED in brachytherapy (BT)

The BT may be delivered at high, medium, or low dose rates, respectively HDR, MDR, or LDR.

The BED is also expressed as the product of the total physical dose (D) and a dimensionless factor RE as

$$BED = D * RE. \quad (17)$$

Within of the BED expression, they have tried of including other factors affecting the RBEfs, such as cell sublethal damage (SL), cell repair (Rt), and repopulation (Pt). These inclusions are notary in the BT as shown in [9].

The works of [9–11] are strongly based on the BED. Here the factors affecting RBEf are added in the BED expression or included in its dimensionless subpart, the RE. More than 16 equations modifying Eq. (17) have been developed in this work. The Pt effect is considered in the BED expression as:

$$BED = D * RE - RCF \quad (18)$$

$$RCF = K * (T - T_{delay}) \quad (19)$$

where T is the overall time, T_{delay} is the delay time after the beginning of treatment before the repopulation rate becomes significant, and K is a parameter of this model.

The Rt effect for a continuous low dose rate is considered into RE as a complex expression in [9]. In the same reference, for permanent implant, the decay of the radioactive sources is incorporated in the factor RE of Eq. (17) as

$$RE = 1 + \frac{R0}{(\mu + \lambda)(\alpha/\beta)} \quad (20)$$

where R0 is the initial dose rate, and λ is the radionuclide decay constant.

3. The radiation biological effect (RBEf)

After the first fraction of irradiation to a living tissue region with a dose d, a number of killed and sublethally damaged cells appear. The mean outcomes of the radiation interactions with the cells are probabilistically related as

$$K + SL + U = 1 \text{ (100\%)} \quad (21)$$

$$S = SL + U \quad (22)$$

$$K + S = 1 \text{ (100\%)} \quad (23)$$

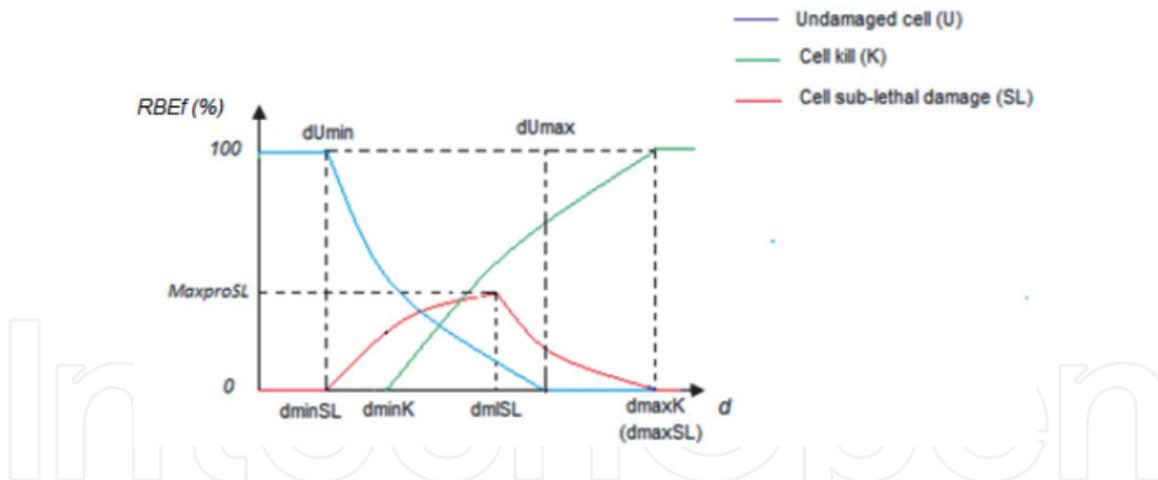


Figure 1. Representation of the radiation biological effects (RBEFs) defined by cell kill (K) and sublethally damaged cell (SL), and undamaged cell. Abbreviations: dU_{min} and dU_{max} : Respectively the lower and upper limit for stochastic region of U; dK_{min} and dK_{max} : Respectively the lower and upper limit for stochastic region of K; $dminSL$ and $dmaxSL$: Respectively the lower and upper limit for stochastic region of SL; $dmlSL$: Value of d with maximum of SL; $MaxproSL$: Maximum value of SL.

$$K = 1 - S \quad (24)$$

where K is the mean cell kill; SL is the mean cell sublethal damage; U is the mean undamaged cell; and S is the mean cell survival. **Figure 1** is a representation of RBEFs defined by the mean values of the cell kill, sublethally damaged cell, as well undamaged cell. These are the immediate results of first fraction of irradiation with a dose d in a living tissue.

4. The radiobiological computational simulators (RCSs)

The computational simulations have led to the development of three radiobiological simulators that determine TCP and mean RBEFs in normal tissue for regular/interrupted treatments, as well as one that obtains similar probabilistic distributions to binomial and Poisson ones. The first application is discussed in [12]. The MatLab applications of these simulators are publicly available in the repository of [13].

The TCP has been traditionally obtained from experimental/observational data, complex phenomenological/mechanistic models as shown in [14]. The TCP computational-calculation methodology simulates possible situations of an irradiated tumor, and is based on probabilistic analysis of three possible kinds of cells and their final results during the interactions for a tumor homogeneously irradiated in a fractionated regimen. The cell repair is taken into account as a temporal process during the interfractions.

Given there will be tumor control when tumor cells are all killed by radiation, it allows to determine TCP based on its probabilistic definition in the computational simulations.

In the region with the minimum dose per fraction of a tumor heterogeneously irradiated, there is the highest value of the cell survival shown by Eq. (1); that is, there is the lowest value of probability of cell kill. For this reason, the TCP should be calculated analyzing the results of interactions in this region, and it is not necessary to consider other tumor regions.

For simulating a fractionated/interrupted treatment, it is considered the following:

- The first fraction generates a mean nkc killed cells, $nslc$ sublethally damaged cells, and $nudc$ undamaged cells from the total cells NTC .
- For the second and successive fractions, the three kinds of cells are analyzed in their possible final outcomes in each fraction.
- The radiation can interact with a killed cell or a survived cell. If a random number $gnum$ is generated, and $gnum \leq nkc/NTC$, then the cell is killed, but is survived.
- For a killed cell, the simulator will analyze a new cell; but for a sublethally damaged cell, there are two possibilities: the cell is undamaged or sublethally damaged. This is defined with a new $gnum > nslc/(nslc + nudc)$ for a undamaged cell.
- For an undamaged cell, if a new $gnum <$ probability for cell kill (K), this cell will die, but if $gnum \leq (K + \text{probability for cell sublethal damage})$, this is become in a sublethally damaged.
- For a sublethally damaged cell (SLDC) there is a range of damage degree. Two new random numbers $gnum1$ and $gnum2$ are generated, and let us define $KSL = \max(gnum1; 1-gnum1)$. If $gnum2 \leq KSL$, the cell will die, but is kept as a SLDC. The previous condition is associated to a major probability of killing the SLDC.
- While the number of fractions increases, nkc increases, and $nudc$ decreases. The $nslc$ can increase or decrease after the second and successive fractions.
- The number of repaired cells is determined after each fraction or during an interruption.
- TCP is calculated as ratio of simulations with $nkc = NTC$ and total of them.
- The radiosensitivity for cell kill (K) is calculated from Eq. (1) as

$$K = 1 - LQS(d)$$
- Eq. (22) shows that survived cells involve sublethally damaged and undamaged cells. The current radiosensitivity studies only report mean values of probability for S that is the sum of probabilities for SL and U, so we have assumed the probability for SL as $SL \leq S$ in our radiobiological simulators.

Eq. (1) represents cell survival probability, that is, mean value of the ratio of the sublethally damaged cells and total of them, when a determined living tissue characterized with parameters α and α/β is homogeneously irradiated with one fraction of dose d . For this reason, this equation can be considered for whatever healthy cell of a determined tissue as probability of becoming in survived cell after irradiation. Given cell kill is a probabilistic complement of cell survival, then cell kill probability is equal to

$$K(q) = 1 - LQ S(d) \quad (25)$$

Our computational simulations have not been previously applied by the current Monte Carlo methods. In the radiobiological modeling and simulation field applied

to radiotherapy, this methodology will represent a big contribution due to one potential innovation being that rather than evaluating TCP by analytically calculating, the TCP is calculated based on its own probabilistic definition.

Contrary to TCP, the normal tissue complication probability (NTCP) calculation does not have easy way for being determined in the RCSs. Therefore, we have suggested assuming similar-Poisson distributions for the NTCPs, and evaluating safety in the radiation treatments with $NTCP_0$ (normal tissue non-complication probability).

4.1 The RCS in radiotherapy

In [15], authors recognize that BED formula does not take into account altered fractionation, like twice-daily fractionation. The radiobiological simulators do not have the quoted limitation of the BED. Using computational simulations one can simulate any schedule of fractionation.

Example 1. A normal tissue (NT) region that is characterized with $\alpha = 0.0683\text{Gy}^{-1}$ and $\alpha/\beta = 1.5\text{Gy}$; for $d = 0.1\text{Gy}$, its radiosensitivity for cell sublethal damage is equal to 1%. As result of simulating this NT region with cell repair equal to 40% and cell density 10^7cells/cm^3 , in 30 fractions, the mean cell kill is 30% and mean cell sublethal damage is 0.249%.

As external beam radiotherapy, BT is an activity that involves interactions of ionizing radiations with living tissues, which produce RBEfs into these tissues. The specific treatment duration will depend on many different factors, including the required rate of dose delivery and the type, size, and location of the cancer, and is still calculated from prescribed dose.

Although the authors have not developed radiobiological simulators for BT, the methodology of these tools can be extended to this radiation therapy.

4.1.1 The RCS in interrupted treatments

An interrupted treatment is a fractionated one, where there is a long-time period greater than the normal interfractions. During the interruption, the sublethally damaged cells have a major possibility of being repaired than during the interfractions of a regular treatment.

Nowadays, the interrupted treatment is evaluated with only a radiobiological tool, the BED. The implementation of the RCSs in the interrupted treatments will represent an extension of the new methodology already applied for the regular treatment.

Cell repopulation, like cell repair, is one of the temporal cellular processes, and is related with the tumor growth, so for an interrupted treatment should be compensating with an increase of the field of the radiation beam.

5. Conclusions

While the derivation of the LQ $S(n,D)$ model for fractionated regimen considers a 100% cell repair, that is, 0% of sublethally damaged cells (SLDCs), radiobiological simulator methodology takes into account the presence of SLDCs, as well as a cell repair $<100\%$ during the interfractions. This makes a better real simulation of the process of interaction of ionizing radiation with living tissues.

The BED is a virtual and redundant radiobiological concept because of this being just a processed subpart of the LQ $S(n,D)$ model by means of a mathematical derivation, and its expression does not model neither physical nor biological

quantity, is not associated to a real quantity. When you create models for establishing relationships among real quantities, you must not use them for creating new metrics, which happened with the LQ $S(n,D)$ formalism and the BED. Really there is not BED, but RBEf defined by cell kill and sublethal damage.

BED is commonly used for isoeffective dose calculations; but one can use Eq. (2), the LQ $S(n,D)$ for this purposes, that is, this usefulness has been possible without introducing the BED.

The radiobiological (RB) simulators show that radiation produces radiation biological effects (RBEfs) instead of BED, which is only a mathematical result of processing the exponential part of the linear-quadratic cell survival model for a fractionated treatment, the LQ $S(n,D)$. It will be a big incoherence if we continue using the BED that is not a real physical quantity. The killed and sublethally damaged cells define the RBEfs. The survived cells are complementing of the former, that is, $S = 1 - K$, where S: cell survival and K: cell kill.

BED is an unreal quantity, whose introduction in the radiation therapies has transformed the essential quantifications in the interactions of ionizing radiations with living tissues, where these should be quantified with ratios of cells affected by radiation and total of them in the irradiated tissues.

The parameters used in the RB simulators, such as killed, sublethally damaged, and undamaged cells are strongly associated to fractionated/interrupted treatments, but they have little familiarization compared with the widely used cell survival.

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