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Technical Notes

A new definition of biological effective dose: The dose distribution effects

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ABSTRACT

A new biological effective dose (BED) is proposed in this note. This new BED definition takes into account the fact that dose distribution is non-uniform for tumors in patients' treatments. This new BED can be calculated from the dose distribution within a tumor, making it practical and useful for clinical applications.

Introduction

The encouraging clinical outcomes of stereotactic body radiation therapy (SBRT) have resulted in its practice at more and more clinical centers. Contrary to conventional radiation therapy in which a small amount dose (180 cGy) is delivered in many fractions (>35), SBRT delivers high doses in less than five fractions [1]. The image guidance technology [2,3] makes SBRT possible by reducing the margin between clinical target volume (CTV) and planning target volume (PTV) to several millimeter and increasing the treatment setup accuracy [4–9].

The high dose, similar to traditional stereotactic radiosurgery (SRS), requires a plan with a high degree of conformity to minimize damages to the issues that surround the target area. This can be achieved through the use of multiple co-planar beams, non-coplanar beams, dynamic arcs, or volumetric arc therapy techniques. The multileaf collimator (MLC) conform the beams to the PTV. Physicists are wondering if a new biology (namely an additional term in the survival curve, accounting for the vascular damage) needs to be invoked to explain the remarkable success of SBRT technology [10]. Whereas other researchers consider the linear-quadratic (LQ) model holding true also for SBRT [11].

In this latter work, the biological effective dose (BED) was calculated for both fractionated and hypofractionated treatments. The tumor control probability (TCP) as a function of BED was constructed, and the LQ model was used to fit the curve. The strong correlation obtained in these curves was considered to be proof the validity of the LQ model. Whatever the validity of this model, the BED was calculated assuming this model does not take into account the non-uniform dose distribution in the patient.

The LQ model was widely used in radiobiology and small animal studies [12–14] in which the tumor volumes are very small and the doses are assumed to be distributed uniformly within tumors. This assumption fails in patient treatments in which the tumor volume is large and the dose distribution is not uniform at all. For example, the maximum dose and minimum dose differences within a tumor are normally around 10% of the prescription dose [15,16]. This kind of non-uniform dose distribution should be included in the model.

In this note, a new BED is introduced that should be used in a patient study. By using this new BED, a patient specific BED can be calculated. Therefore, accurate data analysis can be done for patient studies.

Methods

In this section we will: (1) introduce a new definition of BED and (2) demonstrate that this new BED depends on the dose distribution.

The LQ model relates the expected survival fraction (SF) of clonogenic cells after a single delivered dose d in terms of the two tissue parameters α and β.

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

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For n-fraction treatments, we have the following survival fraction (by using Eq. (1) n times)

$$S = (SF)^n = \exp(-n\alpha d - n\beta d^2) \tag{2}$$

The BED is defined as

$$BED_S = (nd)\left[1 + \frac{d}{(\alpha/\beta)}\right] \tag{3}$$

Then Eq. (2) reads

$$S = \exp(-\alpha\, BED_S) \tag{4}$$

The advantage of using BED is that BED (Gy) represents the dose required for a given effect when delivered in small doses per fraction. To obtain the same effect with two fractioning schemes, with the total doses $D1$ and $D2$, the corresponding single dose fraction, d_1 and d_2, should satisfy the equation:

$$D1\left(1 + \frac{d_1}{\alpha/\beta}\right) = D2\left(1 + \frac{d_2}{\alpha/\beta}\right) \tag{5}$$

This BED can also be derived from the tumor control probability. For n-fraction of d Gy treatments, neglecting the tumor repopulation effect between the fractions [17]), the total probability is:

$$TCPN = \exp(-M\exp(-\alpha nd - \beta nd^2)) = \exp(-M\exp(-\alpha BED_S)) \tag{6}$$

Here M is the number of tumor cells.

For a patient with a tumor with volume $V_T(\mathrm{mm}^3)$, we divided it into N voxels (For lung, the typical size of voxel of CT image is $1\,\mathrm{mm}\times 1\,\mathrm{mm}\times 2.5\,\mathrm{mm}$; for brain, it is $1\,\mathrm{mm}\times 1\,\mathrm{mm}\times 1\,\mathrm{mm}$). We will assume that the dose within each voxel is uniform. Assuming that the tumor control probabilities of the different voxels are independent of each other, we have

$$TCP = \prod_{i=1}^{N} TCP_i \tag{7}$$

For voxel V_i, according to Eq. (6), the TCP_i reads

$$TCP_i = \exp(-\rho_i V_i \exp(-\alpha_i nd_i - \beta_i nd_i^2)) \tag{8}$$

Here α_i, β_i, d_i have the same meaning as in the Eq. (1) but for the voxel V_i. ρ_i and V_i are the cell density and volume for the voxel. $\rho_i V_i$ is the number of the tumor cells in the voxel V_i. For simplicity, we can assume that all $\alpha_i, \beta_i, \rho_i$ are the same and we denote them as α, β and ρ respectively.

For patient treatment, the dose distribution changes from patient to patient and is not uniformly distributed within a tumor. By considering this fact, Eq. (7) changes (with the help from Eq. (8)) to:

$$TCP = \prod_{i=1}^{N} TCP_i = \exp\left(-\rho \sum_{i=1}^{N} V_i \exp(-\alpha nd_i - \beta nd_i^2)\right) \tag{9}$$

We will define a new biological effective dose (BED_{TCP}) as:

$$\sum_{i=1}^{N} V_i \exp(-\alpha nd_i - \beta nd_i^2) = V\exp(-\alpha\, BED_{TCP}) \tag{10}$$

This new BED_{TCP} is defined as:

$$BED_{TCP} = -\frac{1}{\alpha}\ln\left[\sum_{i=1}^{N}\frac{V_i}{V}\exp(-\alpha nd_i - \beta nd_i^2)\right] \tag{11}$$

Considering that, $V_1 = \ldots = V_i = \ldots = V_N$ (the image voxel size), we have:

$$\frac{V_i}{V} = \frac{1}{N}$$

and Eq. (11) becomes:

$$BED_{TCP} = -\frac{1}{\alpha}\ln\left[\frac{1}{N}\sum_{i=1}^{N}\exp(-\alpha nd_i - \beta nd_i^2)\right]. \tag{11B}$$

One can use Eq. (11), or Eq. (11B), to calculate the BED_{TCP} by summing over the N voxels.

By re-arranging the dose values from the minimum to the maximum, Eq. (11) and Eq. (11B) can also be re-written as:

$$BED_{TCP} = -\frac{1}{\alpha}\ln\left[\sum_{d=d_{\min}}^{d_{\max}} f(d)\exp(-\alpha nd - \beta nd^2)\right]. \tag{12}$$

Here $f(d)$ is fraction of voxels receiving a specific dose d for a fraction treatment. This is the normalized differential dose-volume histogram (dDVH) for a fractionated treatment.

By noticing that the total dose for the that voxel V_i is going to be $D_i = nd_i$, Eq. (12) can be re-written as the

$$BED_{TCP} = -\frac{1}{\alpha}\ln\left[\sum_{D=D_{\min}}^{D_{\max}} g(D)\exp\left(-\alpha D - \frac{\beta D^2}{n}\right)\right] \tag{12B}$$

Here $D_{\min} = nd_{\min}$ and $D_{\max} = nd_{\max}$.In this, $g(D)$ is the normalized dDVH for the whole n fraction treatments. Here both $f(d)$ and $g(D)$ are normalized.

This is easily checked that when all voxels receiving the same dose (i.e., $d_1 = d_2 = \ldots = d_N$, $d_{\min} = d_{\max} = d$, $f(d) = 1$, $g(D) = 1$), Eq. (11), Eq. (11B), Eq. (12), Eq. (12B) change to

$$BED_{TCP} = BED_S. \tag{13}$$

One can also write Eq. (12) and Eq. (12B) in following formats for a continuous dose variable

$$BED_{TCP} = -\frac{1}{\alpha}\ln\left[\int_{d_{\min}}^{d_{\max}} f(x)\exp(-\alpha nx - \beta nx^2)dx\right] \tag{14}$$

and

$$BED_{TCP} = -\frac{1}{\alpha}\ln\left[\int_{D_{\min}}^{D_{\max}} g(y)\exp\left(-\alpha y - \frac{\beta y^2}{n}\right)dy\right] \tag{14B}$$

Here $g(y) = \frac{1}{n}f\left(\frac{y}{n}\right)$. The new concept of the biological effective dose is going to be the conventional BED (BED_S) when the dose distribution is uniform within the tumor. This condition does not exist for external beam patient treatments. This new BED (BED_{TCP}) depends on α and β. The conventional BED (BED_s) depends only on the ratio of α/β.

We approximate the differential DVH (dDVH) as a Gaussian function to demonstrate the difference between the BED_{TCP} and BED_s. The dDVH for a fractionated treatment is

$$f(d) = A\exp\left(-\frac{(d-d_0)^2}{2\sigma^2}\right) \tag{15}$$

Here, d_0 is the prescription dose for a fraction, σ is the standard deviation of the dDVH distribution for a fraction treatment and A is the normalization factor. We assume that the minimal dose is $d_0 - 2\sigma$ and the maximal dose is $d_0 + 2\sigma$. Then (we change the variable from d to x in Eq. (16))

$$\int_{d_0-2\sigma}^{d_0+2\sigma} A\exp\left(-\frac{(x-d_0)^2}{2\sigma^2}\right) = 1 \tag{16}$$