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A graphical user interface (GUI) toolkit for the calculation of three-dimensional (3D) multi-phase biological effective dose (BED) distributions including statistical analyses

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ABSTRACT

A toolkit has been developed for calculating the 3-dimensional biological effective dose (BED) distributions in multi-phase, external beam radiotherapy treatments such as those applied in liver stereotactic body radiation therapy (SBRT) and in multi-prescription treatments. This toolkit also provides a wide range of statistical results related to dose and BED distributions. MATLAB 2010a, version 7.10 was used to create this GUI toolkit. The input data consist of the dose distribution matrices, organ contour coordinates, and treatment planning parameters from the treatment planning system (TPS). The toolkit has the capability of calculating the multi-phase BED distributions using different formulas (denoted as true and approximate). Following the calculations of the BED distributions, the dose and BED distributions can be viewed in different projections (e.g. coronal, sagittal and transverse). The different elements of this toolkit are presented and the important steps for the execution of its calculations are illustrated. The toolkit is applied on brain, head & neck and prostate cancer patients, who received primary and boost phases in order to demonstrate its capability in calculating BED distributions, as well as measuring the inaccuracy and imprecision of the approximate BED distributions. Finally, the clinical situations in which the use of the present toolkit would have a significant clinical impact are indicated.

1. Introduction

In modern radiation therapy, dosimetric quantities such as prescribed and tolerance doses, dose-volume histograms (DVH), and isodose distributions, are commonly used for treatment plan evaluations. Dose-volume constraints have been introduced for organs-at-risk (OAR) to prevent unwanted side effects [1–5]. The constraints indicate organ volumes that should not receive doses exceeding certain limits and they are normally

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derived from retrospective studies. Clinical and radiobiological studies have shown that two treatments delivering the same total dose through different fractionation schemes produce different biological results [6–11].

In external beam radiotherapy, the prescribed dose is commonly delivered through multiple fractions. For example, a dose of 60 Gy can be delivered in 30 fractions of 2 Gy. Barendsen showed how the biological effective dose (BED)—which was derived from the linear-quadratic (LQ) model—can quantitatively define the relative effectiveness (RE) of any fractionation scheme [6]. BED has shown that as the dose-per-fraction (DPF) increases, the RE of that fractionation scheme increases. That agrees with the clinical results seen in the infant days of radiotherapy, which led to more conservative fractionation schemes that deliver the total prescribed dose in more fractions with lower doses per fraction in order to prevent normal tissue complications.

During the last thirty years, research has confirmed the fact that different fractionation schemes leading to different BEDs produce different clinical results [7,8,12–15]. However, most of that research has involved single-phase treatments, which deliver a total dose using a certain number of fractions. For cases such as prostate cancer, certain treatment protocols include an additional treatment phase, typically called the boost phase, where the additional dose is delivered with a different beam configuration and fractionation scheme. For example, the first phase (primary phase) delivers a dose of 60 Gy in 30 fractions, and the additional phase (boost phase) delivers a dose of 12.6 Gy in 7 fractions. There has not been much research regarding the calculation of BED for patients who receive more than one phase (multi-phase treatments).

Another important factor for investigating the proper calculation of BED for multi-phase treatments is the common practice for approximately calculating the BED, possibly leading to errors in the estimation of the effectiveness of the treatments. Due to the lack of studies regarding three-dimensional (3D) multi-phase BED calculations, a toolkit was created in order to correctly calculate the total BED for fractionated treatment modalities such as intensity modulated radiation therapy (IMRT) and stereotactic body radiation therapy (SBRT). In addition to the calculation of the total BED for multi-phase treatments, the toolkit also provides statistical analysis algorithms, which are used to evaluate the accuracy of the approximate BED calculations. The toolkit uses the DICOM-RT communication protocol to access the data of a given treatment plan in order to calculate the 3D BED distributions, the DVHs, BED volume histograms (BEDVH) and the Bland–Altman analysis, which can subsequently be performed. This toolkit was built using MATLAB GUIs in order to provide a user-friendly interface.

When analyzing multi-phase treatment plans, the composite dose distribution is typically calculated, which is produced by summing up the dose distributions from the plans of all the phases [13]. In practice, it is common to use the composite dose distribution in the BED equation. By studying the mathematical formula of the LQ-model it can be realized that summing the dose distributions from the different phases prior to BED calculation contradicts the additive property of the LQ-model. That observation raises the question of how accurate is the common, but approximate, method of BED calculation against the conceptually correct method. Furthermore, under what circumstances does the approximate approach produce relatively accurate results with respect to the correct method? In a previous study, Kauweloa *et al.* derived the mathematical formulations of the approximate BED (BED_{App}), and the true BED (BED_{True}) and evaluated their deviation in different clinical settings [16].

2. Computation methods and theory

The graphical user interface (GUI) was created using the MATALB 2010a software (Mathworks, Natick, MA) and it was developed to calculate the BED distributions for single- and multi-phase treatments, as well as to calculate the corresponding inaccuracies when BED is applied on the composite physical dose distribution. The BED is the amount of total dose needed to reach a certain "effect" (clinical endpoint) when delivering the dose using infinitesimal doses-per-fraction. Barendsen derived the BED from the LQ-model using the following formula:

$$S = \left(e^{-\alpha d-\beta d^2}\right)^n, \tag{1}$$

where "n" is the number of fractions, α and β are the cell death due to single- and double-track ionizations [6]. The exponent of Eq. (1) has been defined as the "effect". BED is then derived as follows:

$$BED = \frac{ln\left(1/S\right)}{\alpha} = nd\left(1+\frac{d}{\alpha/\beta}\right). \tag{2}$$

The ratio α/β is typically assumed to be 3 Gy and 10 Gy for late- and early-responding tissues, and it is interpreted as the dose at which the amount of cell death due to single- and double-hits are equal. The value of α/β is typically derived from cellular survival curves where α and β correspond to the linear and quadratic components.

2.1. Multi-phase bed: true and approximate

2.1.1. True BED

When dealing with more than one treatment phase, Eq. (1) can be rewritten as follows:

$$S = \prod_{i=1}^{N}\left(e^{-\alpha d_i-\beta d_i^2}\right)^{n_i}, \tag{3}$$

where N is the total number of phases. Due to the fact that most protocols involve two phases, in the examples that will be demonstrated N will be 2. The survival function then becomes:

$$S = \left(e^{-\alpha d_1-\beta d_1^2}\right)^{n_1}\left(e^{-\alpha d_2-\beta d_2^2}\right)^{n_2}. \tag{4}$$

As mentioned earlier, the "effect" E is the whole exponent power, hence it is,