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Clinical analysis of the approximate, 3-dimensional, biological effective dose equation in multiphase treatment plans

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ABSTRACT

A multiphase, approximate biological effective dose (BED_A) equation was introduced because most treatment planning systems (TPS) are incapable of calculating the true BED (BED_T). This work investigates the accuracy and precision of the multiphase BED_A relative to the BED_T in clinical cases. Ten patients with head and neck cancer and 10 patients with prostate cancer were studied using their treatment plans from Pinnacle^3 9.2 (Philips Medical, Fitchburg, WI). The organs at risk (OARs) that were studied are the normal brain, left and right optic nerves, optic chiasm, spinal cord, brainstem, bladder, and rectum. BED_A and BED_T distributions were calculated using MATLAB 2010b (MathWorks, Natick, MA) and analyzed on a voxel basis for percent error, percent error volume histograms (PEVHs), Pearson correlation coefficient, and Bland-Altman analysis. The maximum BED values that were calculated using the BED_A and BED_T methods were also analyzed. BED_A was found to always underestimate BED_T. The accuracy and precision of BED_A distributions varied between the organs: for optic chiasm and brainstem, 50% of the patients had an overall BED_A percent error of <1%; for left and right optic nerves, rectum, and bladder, 60% to 70% of the patients had an overall BED_A percent error of <1%; and for normal brain and spinal cord, 80% of the patients had an overall BED_A percent error of <1%. BED_A distributions had maximum errors ranging from 2% to 11%, with the 11% error occurring for bladder. BED_A produced much more accurate maximum BED values with adjacent organs such as normal brain, bladder, and rectum. This study has shown that BED_A can calculate BED distributions with acceptable accuracy under certain circumstances. However, its consistency and accuracy strongly depend on the dose distributions of the different treatment phases. One should be cautious when using BED_A.

Introduction

It has been more than 20 years since the introduction of the biological effective dose (BED).[1] Even though it has been proven to be a useful metric providing a closer relation to treatment outcome, it has not yet become a global standard because of its uncertainty.[2-7] The BED was extrapolated from the linear-quadratic (LQ) model, which was used to describe cellular survival curves acquired from *in vitro* assays.[8-11] The BED provides a relationship between different fractionation schemes that have the same clinical effect (*e.g.,* kills the same percentage of cells), and can be calculated for any

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treatment plan in radiotherapy. It has also been used to compare the relative effectiveness of different fractionation schemes.[12-14] Ideally, the BED allows one to determine the most optimal fractionation scheme and prescribed dose for a given clinical outcome. Until now, the BED has been mostly applied to single-phase treatment plans, where the same treatment configuration and prescribed dose per fraction (DPF) are applied for a number of fractions. However, it is very common for a treatment protocol to deliver additional sequential phases (*e.g.,* a boost phase), which are most likely prescribed with either a different DPF or a varying number of fractions than the primary phase.[15]

In the literature, there are a limited number of studies on the calculation of the BED when dealing with multiphase treatments (*e.g.,* patient treated with both primary and boost phases). Jones *et al.*[11] briefly mentioned the additive properties of the mathematical equation of the BED in multiphase circumstances but did not study its properties.[6] Mavroidis *et al.* studied 3 patients who received 2 phases (*e.g.,* primary and boost), and calculated the BED using 2 different equations, which were used to calculate the tumor control probability and the normal tissue complication probability.[15] They observed that the normal tissue complication probability and tumor control probability quantities differed largely when using an approximate formulation for BED (BED_A) instead of true BED (BED_T), concluding that dose homogeneity is an important factor in rendering BED_A accurate. However, usually, only the targets (*e.g.,* gross tumor volume [GTV], planning target volume) within both phases receive a homogeneous dose distribution, whereas organs at risk (OARs) typically receive heterogeneous dose distributions, by nature, within both phases. Mavroidis *et al.* used the BED_A equation because many current treatment planning systems (TPSs) do not calculate the BED for single- or multiphase treatment plans. Its purpose was to facilitate the BED calculation of multiphase treatments.

Kauweloa *et al.* analyzed the derivation of the BED_T, proving its additive property and also investigated the mathematical properties of the BED_A with respect to the BED_T.[16] This study examined the conditions in which BED_A would be equal to BED_T, and investigated the change in the percent error (P_{error}) of BED_A with respect to BED_T under many different hypothetical situations (*e.g.,* varying α-to-β ratios, number of fractions, and dose per fraction). Although Kauweloa *et al.* revealed the general mathematical properties of BED_A relative to BED_T, their results were not investigated in clinical treatment plans in a voxel-based, 3-dimensional (3D) manner. In clinical practice, the BED is primarily used as a metric for single-phase treatment plans, where the BED to different targets and OARs is used as a constraint associated to a certain clinical end point.

In cases involving treatments that are composed of multiple phases and serial OARs (*e.g.,* spinal cord), the maximum BED is used as a dose constraint. Usually, in such cases, the maximum physical doses within both the primary and the boost phases are found, converted to the corresponding BED values, and finally summed. As mentioned earlier, this is done because a voxel-based, 3D-BED calculation for multiphase treatments is not currently available. However, this approach excludes the spatial information and by definition will produce maximum BED values either equal to, or greater than, the actual maximum 3D-BED.

Another approach used to calculate the maximum BED is the summation of the physical doses within the different phases at the same location (voxel-wise) followed by the conversion of the maximum physical dose to the corresponding BED value (BED_A). In this case, the location is included because of the voxel-based calculation, but the additive property is excluded.

The present work focuses on 2 phase (primary and boost) applications, which are more common in clinical practice; however, the methodology could be performed for multiple phase treatments. The study focuses on the clinical precision and accuracy of BED_A with respect to BED_T, on a 3D basis, with the use of common treatment plan evaluation parameters. This study will help in obtaining a better insight of the strength of the BED_A calculation in multiphase treatments, and it will quantify the degree of over- or underestimation of the BEDs in clinical situations.

Materials and Methods

This study consisted of a total of 20 patients treated with 2 phases, involving a variety of number of fractions and prescription doses, see Tables 1 and 2. In this work, the first and second phases are termed as “primary” (pri) and “boost” (bst). An in-house software was developed using MATLAB 2010b (MathWorks, Natick, MA) to convert physical dose matrices to BED matrices. The patient treatment plans were created using Pinnacle^3 9.2 (Philips Medical, Fitchburg, WI). Ten of the patients were treated for prostate cancer and the remaining 10 patients were treated for brain cancer. The OARs that are studied in the prostate case are the bladder and rectum, whereas those for the brain are healthy brain (excluding tumor), brainstem, optic chiasm, spinal cord, right, and left optic nerves.

True and approximate BED formulas

The multiphase BED_T is calculated by converting the physical dose distributions (PD) of both the primary and the boost phases to BED distributions before summing them on a voxel basis (Appendix A). The term “true” BED refers to the mathematically correct way of deriving the multiphase BED based on the equations proposed by Fowler, rather than to the true biological response.[10] Other radiobiological factors such as