

Analysis of Relative Biological Effectiveness of Proton Beams and Iso-effective Dose Profiles Using Geant4

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ABSTRACT

Background: The assessment of RBE quantity in the treatment of cancer tumors with proton beams in treatment planning systems (TPS) is of high significance. Given the significance of the issue and the studies conducted in the literature, this quantity is fixed and is taken as equal to 1.1.

Objective: The main objective of this study was to assess RBE quantity of proton beams and their variations in different depths of the tumor. This dependency makes RBE values used in TPS no longer be fixed as they depend on the depth of the tumor and therefore this dependency causes some changes in the physical dose profile.

Materials and Methods: The energy spectrum of protons was measured at various depths of the tumor using proton beam simulations and well as the complete simulation of a cell to a pair of DNA bases through Monte Carlo GEANT4. The resulting energy spectrum was used to estimate the number of double-strand breaks generated in cells. Finally, RBE values were calculated in terms of the penetration depth in the tumor.

Results and Conclusion: The simulation results show that the RBE value not fixed terms of the depth of the tumor and it differs from the clinical value of 1.1 at the end of the dose profile and this will lead to a non-uniform absorbed dose profile. Therefore, to create a uniform impact dose area, deep-finishing systems need to be designed by taking into account deep RBE values.

Keywords

Proton Therapy, Relative Biological Radiation Effectiveness, Geant4, Absorbed Dose, Iso-effective Dose, DSB

Introduction

Ionizing radiations, depending on their local energy loss rate per unit length, leave different biological effects even for a certain amount of absorbed dose in the substance. As an example, alpha particles lose their energy in the substance in a short distance, while gamma and beta rays and beta lose their energies at a relatively greater distance and thereby create less biological effects. The radiation biological effectiveness refers to the ratio of the absorbed doses of a reference to a given radiation with the same biological effect [1]. ⁶⁰Co gamma rays are usually selected as reference. RBE includes all biological processes up to the final step and is measured uniquely through biological experiments [1]. Usually, RBE is defined in a way that it reaches 10% survival level. However, it can clearly be defined for different biological consequences. Despite many studies which have been conducted on RBE, this concept

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is still a complex quantity. In general, RBE depends on the following factors:

- Dose
- The number of fractions
- Biological end point for the desired tissue
- Tissue type (different sensitivity levels of various tissues to radiation)
- Radiation quality

For therapeutic purposes, the common notions such as *Gray equivalent (GyE)*, *cobalt Gray equivalent (CGE)* or *D (RBE)*, and the dose based on relative biological effectiveness are not in line with the recommendations of the International System of Units (SI) [2]. In addition, the equivalent dose and the effective dose have specific definitions for protection against radiation at the low dose range, whose applications in radiation therapy raise a number of ambiguities. According to ICRU/IAEA, the absorbed dose as well as the iso-effective dose must be reported simultaneously at the same Gy unit for therapeutic purposes [1]. Besides, according to SI recommendations, in order to avoid confusion and possible consequences in patients, both quantities should be reported without any additional explanations concerning their units [2, 3] as both are expressed in Gy.

In proton therapy, the iso-effective dose weight factor (W_{IsoE}) refers to ratio of a given dose under reference conditions to a given dose under real therapeutic conditions with the same effects in a biological system. In a biological system, the relationship between the absorbed dose and radiobiological effect is not a unique relation as it depends on various factors such as dosing in each fraction, dose rate, number of fractions, radiation quality (type and energy of radiation) and exposure conditions (temperature or oxygen content). Thus, the weighting of the absorbed dose is essential when comparing or combining applied treatments under different technical conditions and weighting factors should be introduced. The iso-effective weight factor (W_{IsoE}) is an inclusive weight ratio that includes all factors

that possibly affect clinical outcomes. In other words, the iso-effective weight depends on the biological system, biological consequences and the absorbed dose at each time, the frequency and radiation quality, and that it only makes sense when all these factors are identified.

To determine the weighting factors and to calculate the iso-effective dose, the reference conditions must be clearly defined and presented. To conduct the treatment with conventional external beams, the reference conditions include 2Gy dose intervals at every time and 5 times a week and ^{60}Co photons. Therefore, it is obvious that when using the symbols D_{IsoE} and W_{IsoE} under any therapeutic circumstances, reference conditions must be specified. If the treatment is done in reference conditions, then the absorbed dose and iso-effective dose levels are equal suggesting that the iso-effective weighting coefficient is 1. In addition, if other radiation conditions of exposure (number of turns, the dose at a time, etc.) are assumed to be constant and the only difference is related to the quality of radiation, then $W_{\text{IsoE}} = W_{\text{RBE}}$.

In Monte Carlo calculations, after calculating the absorbed treatment dose in the target volume, other conditions are assumed to be the same as reference conditions. As such, Eq. (1) can be written as follows:

$$D_{\text{IsoE}} = W_{\text{RBE}} D_{\text{absorbed}} \quad (1)$$

Although the biological effect of radiation is not a fixed quantity and depends on many factors, the relevant values in clinical cases for proton and carbon are usually 1.1 and 3 [1]. This means that the absorbed 20 Gy dose creates a biological effective that is iso-effective with the absorbed 60 Gy dose under reference conditions at the same treatment. Being so, the therapeutic dose is reported in terms of the absorbed doses and the iso-effective dose in the target tissue. In addition, for secondary particles, the corresponding doses in other tissues and organs are measured using radiation weighting factors (W_{R}). Finally, the effective

doses in the whole body caused by secondary irradiations can be calculated using the tissue weighting factors.

Material and Methods

In this study, a smoothed depth dose profile for a proton therapy system based on passive dispersion was calculated in water phantom using Geant4 [4, 5]. Furthermore, the initial proton energy spectra at different depths were calculated for this adjusted profile. Based on these spectra, the relative biological effectiveness was measured as a function of depth. Using RBE values, the iso-effective dose profile was calculated and plotted. By applying these values, the in-depth dose-smoothing system was designed in a way that it results in a certain smoothed dose profile so the corresponding iso-effective does in the whole target volume remains uniform.

RBE Calculation

To calculate the relative biological effectiveness using the Geant4 toolkit base on Monte Carlo method, the number of lesions on DNA stranded must be determined. Besides, those damages caused on two opposite DNA strands with a distance of less than 10 base pair about 35 nm called double-strand breaks (DSBs) must be identified using the definitions outlined in biology. Since this requires the development of geometry with nanometer precision, and as the particles must be followed at very low energies with their range at this limit, the physical Geant4-DNA model was used [6, 7, 8].

This model simulates electromagnetic interactions, especially the ionization and excitation of charged particles up to an energy level of several electron volts.

DNA geometry was simulated using the model proposed by Bernal et al.[9]. However, to remove overlaps in this geometry, the model was rewritten and changes in some of its components. In addition, the sources of the initial particles used this simulation are the energy

spectra obtained from the previous section at different depths (to calculate the RBE at different depths).

After calculating and storing damages caused on DNA strands, an algorithm was designed to identify lesion types and its class was implemented.

The same procedure was repeated for gamma rays produced from cobalt-60, as a reference for calculating RBE. RBE values at different depths were calculated using the following equation:

$$RBE = \frac{DSB_{\text{proton}} (Gbp^{-1} Gy^{-1})}{DSB_{\gamma} (Gbp^{-1} Gy^{-1})} \quad (2)$$

Then, the resulting RBE values were used to calculate iso-effective depth dose profiles.

Results

Figure 1 shows a smoothed dose profile with the relevant linear energy transfer (LET) profile from a passive proton therapy system for the adjustment range of 16 mm and a practical range of 30 mm in terms of depth. The profile was plotted by taking RBE value fixed at all proton penetration depths. As it can be seen, unlike physical dose, the linear energy transfer is not constant at the target volume and increases with depth. Besides, this quantity increases at the end of spread-out Bragg peak (SOBP).

Accordingly, it is expected that the biological effect of radiation as a function of LET increases constantly across the dose profile. Based on the energy spectrum of protons corresponding to different depths in the water phantom that was calculated in separate implementations, RBE values for different depths of water phantom were calculated. These values vary in the range of 0.92 to 1.94 across water phantom, where the minimum value is achieved at the water phantom entrance while the maximum value is obtained at the end of the depth dose profile before protons are stopped. RBE values vary at the beginning and

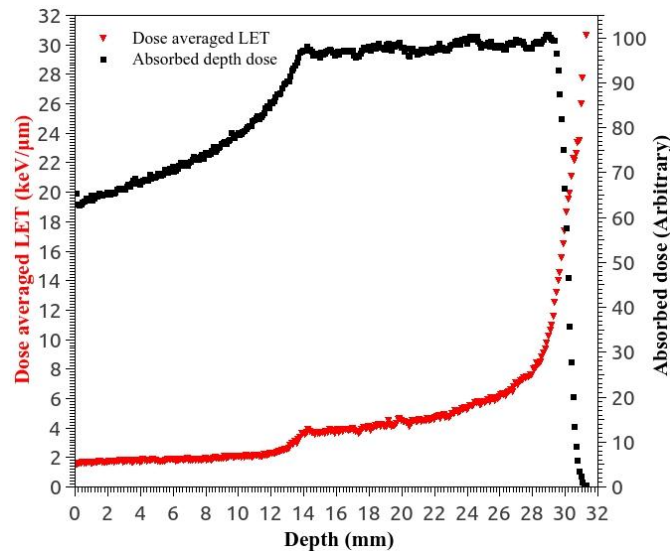


Figure 1: Absorbed dose profile and linear energy transfer for a typical adjusted beam profile

end of the smooth dose profile.

Figure 2 shows an iso-effective dose profile equivalent to the absorbed dose profile in Figure 1 that is obtained based on RBE values calculated in the simulations. As it can be seen, the uniform absorbed dose leads to a non-uniform iso-effective dose profile with a positive slope. So again, based on algorithms and methods developed by the authors in an earlier work [10], an appropriate absorbed

(physical) dose profile is designed that leads to a uniform iso-effective dose profile in the target volume. In other words, the weight of single energy peaks forming absorbed dose profiles, as shown in Figure 3, is calculated in a way that results in a non-smooth absorbed dose. It is worth noting that RBE values less than 1 RBE make iso-effective dose located at initial areas of the water phantom as before the target volume at a level lower than the ab-

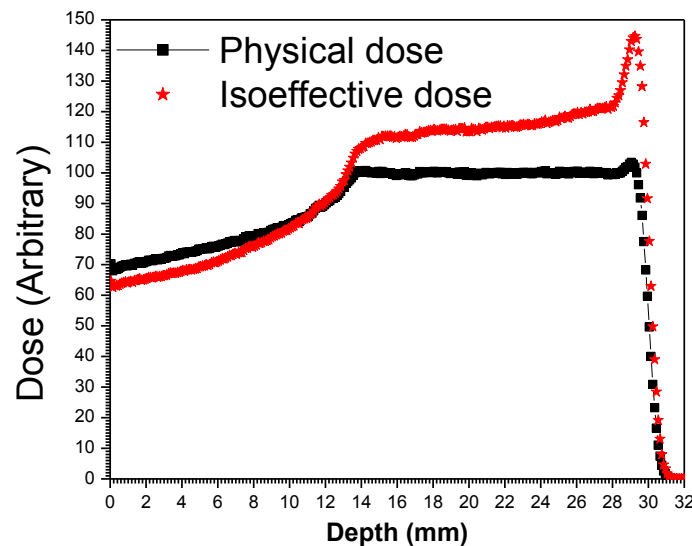


Figure 2: A uniform absorbed dose profile leading to a non-uniform iso-effective dose profile

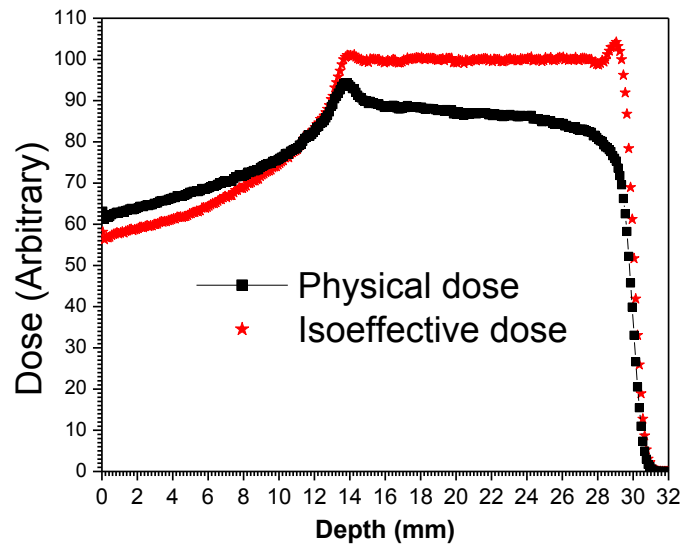


Figure 3: Depth absorbed dose profiles for cases in which the absorbed dose profile is designed in such a way that it leads to a uniform iso-effective dose profile in the target volume.

sorbed dose, which is considered a favorable outcome.

Discussion and Conclusion

Currently, RBE values are taken constant and equal to 1 in proton therapy centers, and beam transfer systems are designed in such a way that a uniform physical depth dose is produced in the target volume. In this study, RBE values were estimated for a passive dispersion system by using Geant4 and based on double-strand breaks (DSBs) in terms of depth. Calculations show that the biological effect of radiation increases from 0.92 at the beginning of the beam path up to almost 2 at the end of the beam path, resulting in a non-uniform dose profile with a roughness of about 40%. To avoid this, it is suggested that a beam transfer system is designed in such a way that instead of creating a uniform depth dose profile, leads to a suitable physical dose that forms a uniform iso-effective dose profile by applying biological effects of radiation. RBE values less than 1 before the smooth dose profile outside the target volume are an advantage, because as shown in Figures 2 and 3, it makes the iso-effective dose located before the target profile in

healthy tissues, lower than the absorbed dose used, which together with RBE values greater than 1 in the target profile makes the ratio of the iso-effective dose in the tumor to the healthy tissue become greater than the same ratio for the absorbed dose.

Conflict of Interest

None

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