Original Article

Establishment of a New Three-Dimensional Dose Evaluation Method Considering Variable Relative Biological Effectiveness and Dose Fractionation in Proton Therapy Combined with High-Dose-Rate Brachytherapy

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Abstract

Purpose: The purpose of this study is to evaluate the influence of variable relative biological effectiveness (RBE) of proton beam and dose fractionation has on dose distribution and to establish a new three-dimensional dose evaluation method for proton therapy combined with high-dose-rate (HDR) brachytherapy. **Materials and Methods:** To evaluate the influence of variable RBE and dose fractionation on dose distribution in proton beam therapy, the depth-dose distribution of proton therapy was compared with clinical dose, RBE-weighted dose, and equivalent dose in 2 Gy fractions using a linear-quadratic-linear model ($EQD2_{LQL}$). The clinical dose was calculated by multiplying the physical dose by RBE of 1.1. The RBE-weighted dose is a biological dose that takes into account RBE variation calculated by microdosimetric kinetic model implemented in Monte Carlo code. The $EQD2_{LQL}$ is a biological dose that makes the RBE-weighted dose equivalent to 2 Gy using a linear-quadratic-linear (LQL) model. Finally, we evaluated the three-dimensional dose by taking into account RBE variation and LQL model for proton therapy combined with HDR brachytherapy. **Results:** The RBE-weighted dose increased at the distal of the spread-out Bragg peak (SOBP). With the difference in the dose fractionation taken into account, the $EQD2_{LQL}$ at the distal of the SOBP increased more than the RBE-weighted dose. In proton therapy combined with HDR brachytherapy, a divergence of 103% or more was observed between the conventional dose estimation method and the dose estimation method we propose. **Conclusions:** Our dose evaluation method can evaluate the $EQD2_{LQL}$ considering RBE changes in the dose distribution.

Keywords: Dose fractionation, high-dose-rate brachytherapy, linear-quadratic-linear model, proton therapy, relative biological effectiveness

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Introduction

Modern radiotherapy uses photon beams (X-rays and gamma rays) and particle beams (proton beams and carbon ion beams). In radiotherapy, combination of different kinds of radiation is often performed.[1-3] This is because a higher therapeutic effect can be obtained by taking advantage of the different characteristics of each radiation.[4] Combination that commingles these radiations has been implemented in recent years. There is proton therapy combined with high-dose-rate (HDR) brachytherapy, which uses proton beams and gamma rays.[5-7] To safely conduct such combination using different kinds of radiation, accurate dose evaluation is necessary. This is because the biological effects of each radiation are completely different, and radiation damage may occur. In combination of different types of radiation, the biological dose is commonly used for dose evaluation.

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The biological dose relies primarily on relative biological effectiveness (RBE) and dose fractionation.

There are two major problems with the conventional dose evaluation method for proton therapy combined with HDR brachytherapy. The first problem is RBE. At many facilities, RBE of 1.1 is widely used for the proton therapy.[8] However, recent studies reported that the RBE of proton therapy changes as they proceed deeper into the medium.[9,10] In the report of Takada *et al*.,[11] it was assumed that a difference in dose of 10% or more occurs between the dose calculated by the conventional method and the dose that takes into account RBE variation at the distal of the spread-out Bragg peak (SOBP) with 155 MeV proton beam. This is because the beam quality of the proton beam is different for each depth. However, conventional treatment planning systems (TPS) do not take into account the change in beam quality for each depth of proton beam, so dose evaluation taking into account RBE variation cannot be realized.

The second problem is dose fractionation. In general, the dose fractionation for proton beam therapy is 50–70 Gy/20–35 fractions,[12] and the dose fractionation for HDR brachytherapy is 28–30 Gy/4–6 fractions.[13,14] When considering biological effects, dose fractionation is as important as RBE. Dose fractionation depends on the total dose and the dose per fraction.[15] An equivalent dose in 2 Gy fractions (EQD2) is used for biological dose, taking into account dose fractionation. A linear-quadratic (LQ) model is generally used for the calculation of the EQD2.[16] However, the dose range in which the EQD2 can be accurately calculated using the LQ model is reported to be <3.25 Gy/fraction[17] or <2.57 Gy/fraction.[18] In the case of proton therapy combined with HDR brachytherapy, the dose administered ranges over a wide range, such as 2–7 Gy/fraction. Therefore, the EQD2 using a conventional LQ model is not suitable for dose evaluation in proton therapy combined with HDR brachytherapy.

To summarize the above, the conventional method uses a constant RBE or LQ model; therefore, accurate dose evaluation in proton therapy combined with HDR brachytherapy is not possible. We focused on the RBE variation in the depth direction and a dose evaluation using a linear-quadratic-linear (LQL) model in proton therapy combined with HDR brachytherapy, which has not been done in previous studies. There are some biophysical models that can compute the RBE variation in the depth direction in the medium: the local effect model (LEM)[19] and microdosimetric-kinetic-model (MKM).[20] Takada *et al*. used an MKM implemented in a Monte Carlo code and showed with a depth-dose distribution in proton beam that an RBE-weighted dose taking into account the RBE variation increases at the distal of the SOBP.[11] On the other hand, the LQL model is a computational model that takes into account cell repair.[21] It enables accurate evaluation up to the dose range used in HDR brachytherapy.[21] With this method, it is possible to accurately evaluate biological dose in proton therapy combined with HDR brachytherapy.

The purpose of this study is to evaluate the influence of variable RBE of proton beam and dose per fraction on dose distribution and to establish a new three-dimensional dose evaluation method for proton therapy combined with HDR brachytherapy.

Materials and Methods

The biological dose used in this study is clinical dose, RBE-weighted dose, and $EQD2_{LQL}$. The clinical dose was calculated by multiplying the physical dose by RBE of 1.1. The RBE-weighted dose was defined as the biological dose calculated by the microdosimetric function[22] of the Particle and Heavy-Ion Transport Code System (PHITS),[23] which is a Monte Carlo simulation code coupled with MKM. The RBE-weighted dose is a biological dose that takes into account RBE variation in the depth direction in the medium. The $EQD2_{LQL}$ was defined as a biological dose that makes the RBE-weighted dose equivalent to 2 Gy using an LQL model.

Influence of relative biological effectiveness and dose fractionation on dose distribution in proton beam

The calculation geometry of double-scattering system of the Proton Medical Research Center at the University of Tsukuba was reproduced by PHITS.[11] The RBE-weighted dose was calculated by PHITS coupled with MKM. The RBE-weighted dose was converted to the $EQD2_{LQL}$ using the LQL model. The survival fraction of the LQL model is expressed by equations (1) and (2).[21,24]

$$S_{LQL} = e^{(-\alpha D - \beta D^2 G(\lambda T + \delta D))} \quad (1)$$

$$G(x) = \frac{2}{x^2}\left(x - 1 + e^{-x}\right) \quad (2)$$

where, α and β characterize the intrinsic radiosensitivity of the cells, and D and d are the total and fractional dose, respectively. $G(x)$ is the reduction in survival owing to interaction between the lesions. δ is the additional LQL parameter. $\lambda = \ln 2/Tr$ is the repair rate. Tr and T are the repair half-time and the treatment delivery time, respectively. Here, the treatment delivery time is sufficiently shorter than the repair half-time, and $\lambda T \to 0$. Therefore, the time term can be ignored. The handling of treatment delivery time in this study is discussed in the discussion section. In this case, the $EQD2_{LQL}$ is represented by equation (3).

$$EQD2_{LQL} = D\frac{\left(\alpha/\beta\right) + dG(\delta d)}{\left(\alpha/\beta\right) + 2G(2\delta)} \quad (3)$$

The absolute dose in the depth direction for a proton beam at 2 Gy/fraction and 3 Gy/fraction was compared with the clinical dose, the RBE-weighted dose, and the $EQD2_{LQL}$. The proton beam energy was 155 MeV, and the width of SOBP was set as 30 mm. From the report of Guerrero *et al*.,[25] the target α/β ratio was set at 9.9, and target δ was set at 0.04.

Three-dimensional dose evaluation taking into account relative biological effectiveness and dose fractionation in proton therapy combined with high-dose-rate brachytherapy

For three-dimensional dose evaluation of proton therapy combined with ^{192}Ir HDR brachytherapy using cylinders, we used the PHITS coupled with MKM and the Tsukuba plan. The Tsukuba plan is a TPS developed by Kumada *et al*. that employs PHITS.[26] A plan simulating a gynecological disorder was prepared for a pelvic phantom (The Phantom Laboratory, USA), and the clinical dose and the RBE-weighted dose were calculated. Next, the RBE-weighted dose was converted to the $EQD2_{LQL}$ using equation (3), and the three-dimensional dose distributions of the clinical dose, the RBE-weighted dose, and the $EQD2_{LQL}$ were compared for the pelvic phantom in proton therapy combined with HDR brachytherapy. The dose fractionation for proton therapy was set at 69.0 Gy/23 fractions.[27] The dose fractionation of HDR brachytherapy was set at 28.0 Gy/4 fractions against a reference point (Point A).[13,14] Point A is the major critical point for the dose specification of HDR brachytherapy in the treatment of gynecological cancer. From the report of Guerrero *et al*.,[25] the target α/β ratio was 9.90, the target δ was 0.04, the normal organ α/β ratio was 3.25, and the normal organ δ was 0.09 for both proton therapy and HDR brachytherapy. Here, the RBE of ^{192}Ir used in HDR brachytherapy was set to 1.0.

Results

Influence of relative biological effectiveness and dose fractionation on dose distribution in proton beam

Figure 1 shows the clinical dose, the RBE-weighted dose, and the $EQD2_{LQL}$ in proton therapy. The units of the clinical dose and the RBE-weighted dose are GyRBE. The unit of the $EQD2_{LQL}$ is $GyEQD2_{LQL}$. As shown in Figure 1, the depth of the proximal, the center, and the distal of the SOBP are 95 mm, 110 mm, and 125 mm, respectively. In the SOBP, the clinical dose is almost flat. At the distal of the SOBP at 2 Gy/fraction, the RBE-weighted dose is 2.42 GyRBE, and the $EQD2_{LQL}$ is 2.52 $GyEQD2_{LQL}$ [Figure 1a]. At the distal of the SOBP at 3 Gy/fraction, the RBE-weighted dose is 3.63 GyRBE, and the $EQD2_{LQL}$ is 4.11 $GyEQD2_{LQL}$ [Figure 1b]. On the other hand, at the proximal of the SOBP at both 2 Gy/fraction and 3 Gy/fraction, the RBE-weighted dose was lower than the clinical dose.

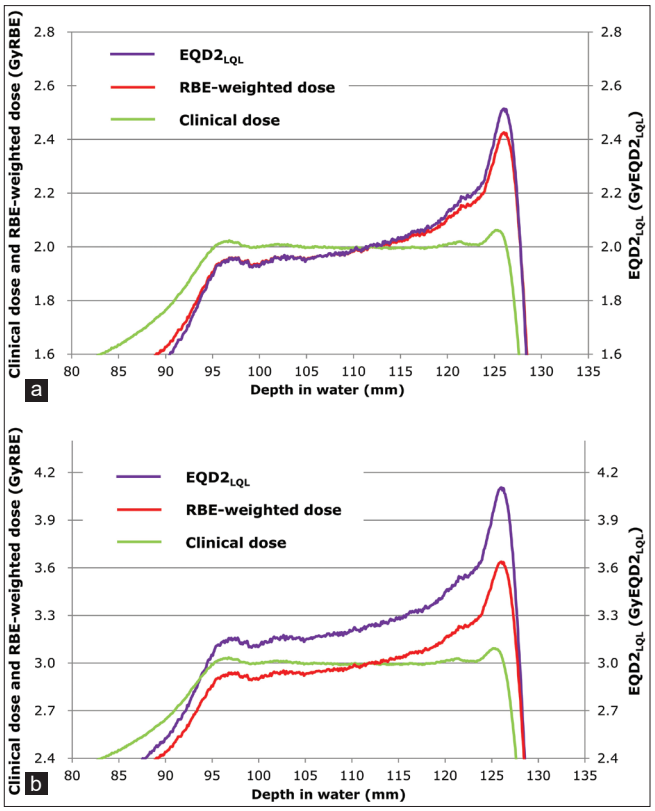

Figure 1: Comparison of the clinical dose, the relative biological effectiveness-weighted dose, and the equivalent dose in 2 Gy fractions using a linear-quadratic-linear model at the central axis in water phantom on irradiation by 155 MeV proton beam with 30 mm spread-out Bragg peak width: (a) 2 Gy/fraction and (b) 3 Gy/fraction. Linear-quadratic-linear model parameters of target α/β ratio and δ are 9.9 and 0.04, respectively

Three-dimensional dose evaluation taking into account relative biological effectiveness and dose fractionation in proton therapy combined with high-dose-rate brachytherapy

Figure 2 shows the three-dimensional dose distribution of proton therapy combined with HDR brachytherapy in the pelvic phantom. Target P is a primary lesion, and Target N is a lymph node lesion [Figure 2a]. Target N was irradiated by the proton beam from the dorsal direction. At the distal of the SOBP of the proton beam (ventral side of Target N), the clinical dose is 70–80 GyRBE [Figure 2b], the RBE-weighted dose is 90–100 GyRBE [Figure 2c], and the $EQD2_{LQL}$ is 100–110 $GyEQD2_{LQL}$ [Figure 2d]. HDR brachytherapy was performed on Target P. The clinical dose at the center of Target P is 100–110 GyRBE, and the dose decreases with distance from the center [Figure 2b]. The irradiation area of 100–110 $GyEQD2_{LQL}$ of the $EQD2_{LQL}$ is wider than that of the 100–110 GyRBE of the clinical dose [Figure 2d].

For a quantitative evaluation, Figure 3 shows the dose distribution of the cross-section in which the clinical dose, the RBE-weighted dose, and the $EQD2_{LQL}$ greatly changed at the distal of the SOBP of the proton beam and the irradiation range of HDR brachytherapy [red line in upper left of Figure 3]. Position 0 mm is the center of the pelvic phantom. Position 25–45 mm corresponds to the distal of the SOBP of the proton beam, and position-10 mm corresponds to the position irradiated with the same dose (28.0 Gy/4 fractions) as the reference point for HDR brachytherapy. The clinical dose, the RBE-weighted dose, and the $EQD2_{LQL}$ at position 40 mm are 77.3 GyRBE, 83.6 GyRBE, and 106.0 $GyEQD2_{LQL}$, respectively. The $EQD2_{LQL}$ at position-10 mm is 52.6 $GyEQD2_{LQL}$.

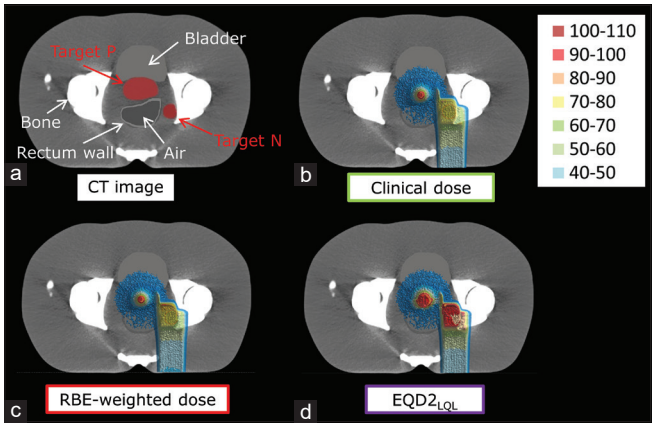

Figure 2: Comparison of the clinical dose, the relative biological effectiveness-weighted dose and the equivalent dose in 2 Gy fractions using a linear-quadratic-linear model for three-dimensional dose distributions in the pelvic phantom on irradiation proton therapy combined with high-dose-rate brachytherapy: (a) computed tomography image of the pelvic phantom, (b) clinical dose, (c) relative biological effectiveness-weighted dose, and (d) equivalent dose in 2 Gy fractions using a linear-quadratic-linear model. In three-dimensional dose distributions, the units of the clinical dose and the relative biological effectiveness-weighted dose are GyRBE, and the unit of the equivalent dose in 2 Gy fractions using a linear-quadratic-linear model is $GyEQD2_{LQL}$

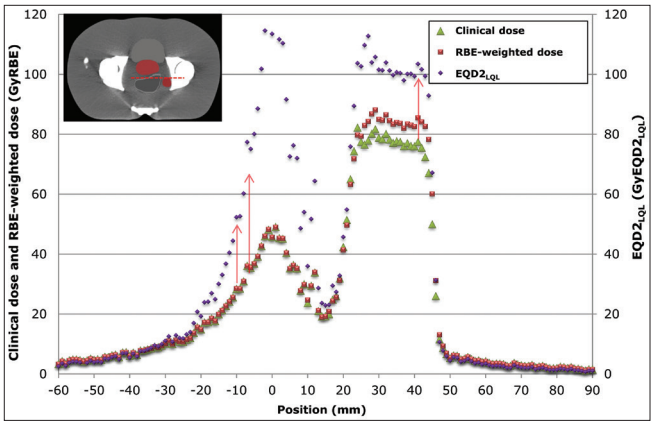

Figure 3: Comparison of the clinical dose, the relative biological effectiveness-weighted dose, and the equivalent dose in 2 Gy fractions using a linear-quadratic-linear model for dose profile in the pelvic phantom on irradiation proton therapy combined with high-dose-rate brachytherapy

Discussion

Validity of the results obtained in this study

From Figure 1, the RBE-weighted dose (2.42 GyRBE) at the distal of the SOBP (position 125 mm) was shown to increase by 21% compared to the clinical dose (2.0 GyRBE). In general, the lower the proton beam energy, the higher the beam quality.[9] Since the energy of the proton beam becomes lower as the depth increases,[8] the RBE-weighted dose of the distal of the SOBP becomes higher. On the other hand, the proton beam energy of the proximal of the SOBP (position 95 mm) is high. Therefore, RBE of the proximal of the SOBP is approximately 1.0. Since the clinical dose uses RBE of 1.1, the RBE-weighted dose is lower than the clinical dose at the proximal of the SOBP. The high reproducibility of the RBE-weighted dose calculated and experimental data in this system was reported.[11] The variable RBE of the proton beam in this study is considered reasonable and proper. On the other hand, we have to be careful about the potential differences between scanning and passively scattered beam, as noted by Paganetti[9] who refers to other papers.

The $EQD2_{LQL}$ (4.11 $GyEQD2_{LQL}$) at the distal of the SOBP (position 125 mm) increases the dose by 13% compared to the RBE-weighted dose (3.63 GyRBE). The report of Voyant *et al*.[28] shows by the point dose that the $EQD2_{LQL}$ increased by 16% compared to the clinical dose (4 Gy), which is the same as in our study.

From Figure 3, the difference between the clinical dose (77.3 GyRBE) and the $EQD2_{LQL}$ (106.0 $GyEQD2_{LQL}$) was 37% at the distal of the SOBP (position 40 mm). The difference between the clinical dose (28.0 GyRBE) and the $EQD2_{LQL}$ (52.6 $GyEQD2_{LQL}$) in HDR brachytherapy (position - 10 mm) was 88%. The clinical dose of ^{192}Ir used in the HDR brachytherapy sharply changes with the inverse square of the distance [Figure 2b]. That is, dose per fraction becomes higher than 7.0 Gy/fraction near the ^{192}Ir source. For example, at position - 5 mm in Figure 3, there is irradiation of 8.0 Gy/fraction (32.0 Gy/4 fractions) for HDR brachytherapy. The difference between the clinical dose (32.0 GyRBE) and the $EQD2_{LQL}$ (65.0 $GyEQD2_{LQL}$) in HDR brachytherapy (position - 5 mm) was 103%.

Voyant *et al*.[28] showed by the point dose that the difference between the clinical dose (8 Gy) and the $EQD2_{LQL}$ is 100%, in other words, more than twice, which is equivalent to our results. The more the dose per fraction exceeds 2 Gy/fraction, the greater the divergence between the clinical dose and the $EQD2_{LQL}$. Therefore, it is essential to take into account the RBE and dose fractionation since they have great impact on the $EQD2_{LQL}$.

Advantage of using the equivalent dose in 2 Gy fractions using a linear-quadratic-linear model

From Figure 1a, it was shown that the $EQD2_{LQL}$ (2.52 $GyEQD2_{LQL}$) at the distal of the SOBP (position 125 mm) at 2 Gy/fraction increases by 26% compared to the clinical dose (2.0 GyRBE). In the case of 2 Gy/fraction [Figure 1a], the clinical dose is almost uniformly irradiated with 2 GyRBE in the SOBP (position 95–125 mm). If $EQD2_{LQL}$ was calculated using the clinical dose, there is no difference between the clinical dose and $EQD2_{LQL}$ in the SOBP at 2 Gy/fraction. That is, when constant RBE of 1.1 is used, there is little necessity to evaluate by using $EQD2_{LQL}$. However, the RBE-weighted dose at the distal of the SOBP is >2 GyRBE. Therefore, even with 2 Gy/fraction, it is necessary to use the $EQD2_{LQL}$. Furthermore, the biological effects owing to the difference in dose fractionation increase with a higher dose per fraction, such as in HDR brachytherapy.

Therefore, in proton therapy combined with HDR brachytherapy, it is recommended to evaluate using the $EQD2_{LQL}$. Several reports concerning HDR brachytherapy combined with external beam therapy exist.[29,30] However, in most of these reports, evaluation is by the EQD2 using the LQ model, which is not suitable for dose evaluation in HDR brachytherapy combination. Jaikuna *et al*. reported that it is useful to use the LQL model for the dose evaluation of radiotherapy in which the dose per fraction is high, such as in HDR brachytherapy and stereotactic radiation therapy, that the LQ model cannot be used.[24] Their report supports the propriety of our dose evaluation method.

Advantage of a Monte Carlo simulation in high-dose-rate brachytherapy

Dose calculation for HDR brachytherapy treats the human body as homogeneous water and does not take into account heterogeneous medium such as bone and air.[31] A Monte Carlo simulation, which is the dose calculation algorithm used in this study, is capable of calculating heterogeneous medium accurately.[32,33] Therefore, even when air exists in the rectum [Figure 2a], the physical dose can be obtained with high accuracy. Our method uses PHITS coupled with MKM, which is a dose evaluation method that can obtain both a biological dose and a physical dose. We evaluated that the uncertainty of the dose calculation in brachytherapy was <2.3%. Moreover, Takada *et al*. evaluated that the uncertainty of dose calculation in proton therapy was <3.1%.[11] Therefore, the calculation accuracy is guaranteed for both HDR brachytherapy and proton therapy.

Limitations

Marshall *et al*. reported that the RBE of proton beam changes owing to differences in dose fractionation.[34] Marshall *et al*. defined an RBE that changes with dose fractionation as RBE_{frac}. RBE_{frac} is important when RBE varies greatly depending on the endpoint setting, as the shape of the cell survival curve varies greatly, such as with carbon-ion beam and photon beam.[35] RBE_{frac} is not taken into account in our proposed method. This is because RBE does not change significantly depending on where the endpoint is set because the shapes of the cell survival curves of proton beam and photon beam are similar. In fact, Marshall *et al*. showed that RBE_{frac} of the proton beam and photon beam is nearly constant above 2 Gy/fraction. Therefore, in the case where the dose is 2 Gy/fraction or higher, we consider that it is not necessary to use RBE_{frac} in proton therapy combined with HDR brachytherapy (photon beam). However, when considering carbon-ion beam and other forms of combination, which have significantly different shapes of photon beam and cell survival curves, it is essential to take into account RBE_{frac}.

In addition, we do not consider the time, such as treatment delivery time, but further improvement of biological dose calculation accuracy can be expected by using a model with improved MKM that takes into account time.[36]

Future prospects

There are many reports of proton therapy combined with HDR brachytherapy applied to gynecological disorders such as cervical cancer.[5-7] Proton beam is an excellent external irradiation method for gynecological disorders,[7,37] and the possibility of replacing the X-rays commonly used in HDR brachytherapy combination has been reported.[7] Therefore, it is essential to take into account the RBE and dose fractionation.

In addition, the MKM is a biophysical model used for various kinds of radiation including photon beams and particle beams.[11,38,39] The Tsukuba plan is a system that can calculate dose of various types of radiation, such as X-rays and neutron beams,[26] in addition to proton beams and gamma rays. That is, our three-dimensional dose evaluation using the Tsukuba plan and MKM can cope with new various combination therapies, which are highly versatile evaluation methods.

Conclusions

We evaluated the influence of RBE and dose fractionation for a proton therapy combined with HDR brachytherapy on dose distribution. Taking into account the RBE variation of the proton beam in the depth direction, it became clear that the RBE-weighted dose increases at the distal of the SOBP. Considering the difference in dose fractionation, it became clear that the $EQD2_{LQL}$ at the distal of the SOBP increases more than the RBE-weighted dose. In particular, the dose per fraction of proton therapy and HDR brachytherapy differ greatly. Since the conventional method uses a constant RBE or LQ model, it cannot accurately evaluate the dose of such a combination. Our dose evaluation method can evaluate the $EQD2_{LQL}$ considering RBE changes in the dose distribution.

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Conflicts of interest

There are no conflicts of interest.

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