Assessment of biological dosimetric margin for stereotactic body radiation therapy

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Abstract

Purpose: To develop a novel biological dosimetric margin (BDM) and to create a biological conversion factor (BCF) that compensates for the difference between physical dosimetric margin (PDM) and BDM, which provides a novel scheme of a direct estimation of the BDM from the physical dose (PD) distribution.

Methods: The offset to isocenter was applied in 1-mm steps along left-right (LR), anterior-posterior (AP), and cranio-caudal (CC) directions for 10 treatment plans of lung stereotactic body radiation therapy (SBRT) with a prescribed dose of 48 Gy. These plans were recalculated to biological equivalent dose (BED) by the linear-quadratic model for the dose per fraction (DPF) of $d = 3–20\text{ Gy/frac}$ and $\alpha/\beta = 3 – 10$. BDM and PDM were defined so that the region that satisfied that the dose covering 95% (or 98%) of the clinical target volume was greater than or equal to the 90% of the prescribed PD and BED, respectively. An empirical formula of the BCF was created as a function of the DPF.

Results: There was no significant difference between LR and AP directions for neither the PDM nor BDM. On the other hand, BDM and PDM in the CC direction were significantly larger than in the other directions. BCFs of $D_{95\%}$ and $D_{98\%}$ were derived for the transverse (LR and AP) and longitudinal (CC) directions.

Conclusions: A novel scheme to directly estimate the BDM using the BCF was developed. This technique is expected to enable the BED-based SBRT treatment planning using PD-based treatment planning systems.

KEY WORDS
biological equivalent dose, dosimetric margin, LQ model, SBRT

1 INTRODUCTION

In modern radiation therapy, dose-volume histogram (DVH) and isodose distribution are commonly used for treatment evaluation. Dose-volume constraints indicate organ volumes that should not receive doses exceeding certain limits 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.¹,² Fowler showed that the biological effective dose (BED) modeling is a valuable tool for understanding tumor and normal tissue response across different treatment modalities and fractionation schemes.³ Based on the idea of BED, it has been shown that the relative biological effectiveness depends on the dose per fraction (DPF) and the number of fractions.

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Particularly, stereotactic body radiation therapy (SBRT) requires the calculation of BED, as it uses hypo-fractions and results in the delivery of a high BED. In these studies, linear quadratic (LQ) model was used. The LQ model is the most commonly used tool to model the effect of fractionation in conventionally fractionated radiotherapy and to predict tumor response to altered fractionation regimens.

Technical advances in radiation therapy, including three-dimensional conformal radiotherapy (3D-CRT) and, more recently, intensity-modulated radiotherapy (IMRT) has simultaneously enabled dose escalation and enhanced normal tissue sparing. ICRU 50 and 62 Reports were widely used as an international reference for the prescribing, recording, and reporting of photon beam radiotherapy. However, the ICRU 83 Report was released in 2010 specifically addressing IMRT and introducing some different concepts and plan evaluation parameters such as volumetric planning target volume (PTV) prescribing. For SBRT, clinical trials RTOG 02367 and 08139 used the volume prescription method. The dose that covered 95% of the PTV (D95%) was conformal in the treatment plan using the van Herk formula.13 The ICRU 83 Report was released in 2010 specifically addressing IMRT and introducing some different concepts and plan evaluation parameters such as volumetric planning target volume (PTV) prescribing. 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### MATERIALS AND METHODS

Ten cases of patients with lung cancer, who underwent SBRT at (institution name), were analyzed. The characteristics of the patients and their tumors are presented in Table 1. The use of clinical materials in this study was approved by the Institutional Review Board of (institution name).

Figure 1 shows the process of the evaluating the BDM and PDM. The physical dose distribution was created in RayStation (RaySearch, Stockholm, Sweden). The physical dose distribution was converted to the BED distribution using the LQ model (Step 1). The dose distribution with the setup uncertainty was created using the van Herk formula, which is a margin achieved between the CTV and TV for a given isodose surface of interest (e.g., D95%). The α/β of the PTV includes the tumor was 3, 5, and 10 Gy, and that of the normal tissue was 3 Gy. To provide appropriate DM for each fractionation scheme in BED-based treatment planning, a biological conversion factor (BCF) between BDM and PDM was introduced by considering the DPF and α/β to create a simple model of the BDM.

#### TABLE 1 Patient characteristics.

| Age (years) | Median | 78 |
|-------------|--------|----|
| Range       |        | 58–90 |
| Gender      |        | Male (70%) |
|             | Female (30%) |
| Tumor location |     | Right lobe (60%) |
|             | Left lobe (40%) |
| Tumor diameter (mm) |     | 0–10 (30%) |
|             | 10–20 (40%) |
|             | 20–30 (30%) |
of the BDM, PDM, and BCF are given in Section 2.4. In addition, the dose gradient in the physical dose and BED was investigated in Section 2.5.

2.A | Treatment planning

All patients were immobilized using a Vac-Lok cushion (CIVCO, Kalona, IA, USA). Breath-holding was coordinated in the expiratory phase using Abches (APEX Medical, Tokyo, Japan) — a device that allowed patients to control their chest and abdominal respiratory motion.21 The tumor position reproducibility during several expiratory breath-hold intervals was verified to be within 5 mm using X-ray fluoroscopy. Computed tomography (CT) scans were performed during the expiratory breath-holding using a CT scanner (LightSpeed RT16, GE Healthcare, Little Chalfont, UK). Both the slice thickness and the slice interval were 1.25 mm. The diameter of the tumor was equal to or smaller than 3 cm in the clinical cases investigated in this study.

The CTV margin was 0 mm around the GTV. The reproducibility of the tumor position at respiratory breath-hold was suppressed within 5 mm using the breath-hold technique with Abches.22 Systematic error of the tumor position is corrected with the daily Cone-beam CT. A PTV margin of 5 mm in left-right (LR), anterior-posterior (AP), and cranio-caudal (CC) directions around the CTV including the respiratory motion reproducibility and the setup error was usually added. The isocenter (IC) was defined at the centroid of the GTV. Eight beams with coplanar and noncoplanar angles were used for every patient. If possible, the beam directions were set such that the beams did not cross the critical OARs, such as the contralateral lung and spinal cord. The dose constraint for normal lung was the combined percentage of lung volume receiving a dose of 20 Gy or higher (V_{20 Gy}) is below 20%. The dose constraint for the spinal cord was the maximum dose is below 25 Gy. A TrueBeam linear accelerator (Varian Medical Systems, Palo Alto, USA) was used for producing 6-MV flattening filter free beams. The treatment plans with a prescribed dose of 48 Gy for \(D_{95\%}\) of the PTV was created using the superposition/convolution algorithm on RayStation.

2.B | Biological equivalent dose

The BED was calculated using the LQ model as an example model to create the BED. The LQ model fits the cell-surviving fraction through a second-order polynomial on the DPF,

\[
\text{Cell survival fraction} = \exp\left(-\alpha d - \beta d^2\right),
\]

where \(d\) is the DPF. The BED is then defined by

\[
\text{BED} = nd\left(1 + \frac{d}{\alpha/\beta}\right),
\]

where \(n\) is the number of treatment fractions. The ratio \(\alpha/\beta\) describes the repair capacity of the cells, and thus the sensitivity to the fractionation. In the calculation of relative BED, DPF, and \(\alpha/\beta\) were mainly affected with a constant DPF. The BED distribution was calculated from the physical dose distribution using Eq. (2). In this study, \(\alpha/\beta\) was varied along 3, 5, and 10.23 The DPF was in the range 3–20 Gy, referring to the past clinical trials shown in Table 2.

2.C | Treated volume and dosimetric margin

Figure 2 shows illustrations of the TV and DM in this study in comparison with the ones by Gordon and Siebers.14 The TV by Gordon

| References | Total dose (Gy) | Daily dose (Gy) | Prescription |
|------------|----------------|----------------|--------------|
| Shien et al. | 33–50 | 3–5 | 50–60% margin |
| Onimaru et al. | 48–60 | 6–7.5 | Point dose |
| Uematsu et al. | 50–60 | 10 | 80% margin |
| Nagata et al. | 48 | 12 | Point dose |
| Taremi et al. | 48 | 12 | 80% margin |
| Wulf et al. | 45–56.2 | 15–15.4 | 80% margin |
| Olsen et al. | 50, 54 | 10, 18 | 80% margin |
| Timmerman et al. | 24–60 | 8–20 | 80% margin |
and Siebers [Fig. 2(a)] is defined by

$$TV^G = V_{PTV_{ROI}}$$ \quad (3)$$

where $D_{ROI}^X$ denotes the dose to the region of interest (ROI) and $X = \min, \max, 95\%$, etc. The DM by Gordon and Siebers$^{14}$ ($DM^G$) was then defined as a volume achieved between the CTV and TV. These definitions are given based on a treatment plan with no blurring of the isocenter.

In this study, the TV was defined so that the dose perturbation effects due to the setup error were taken into account [Fig. 2(b)]. The setup error was generated by shifting the isocenter (IC) along LR, AP, and CC directions from $-20$ to $+20$ mm with a 1-mm step ($\delta_L, \delta_R, \delta_A, \delta_P, \delta_Cr, \delta_Ca$, respectively). The dose distributions were calculated with the shifted isocenter. The TV is defined as a volume that satisfied

$$TV = V_{D_{ROI}^{CTV(95\% \text{ or } 98\%)}} \geq 0.9 \times D_{RX}$$ \quad (4)$$

where $D_{RX}$ denotes the prescribed dose. The $D_{ROI}^{X}$ denotes the dose to the region of interest (ROI) and $X = 95\%$, $98\%$ in the physical and biological dose distributions by shifting the isocenter. Next, the maximum shift toward the left, right, anterior, posterior, cranio, and caudal directions ($\Delta_L, \Delta_R, \Delta_A, \Delta_P, \Delta_Cr, \Delta_Ca$, respectively) that passed criteria of Eq. (5) were determined.

$$D_{CTV}^{95\% \text{ or } 98\%} \geq 0.9 \times D_{RX}$$ \quad (5)$$

Here, the scale of the DM in this study that is the distance and the $DM^G$ that is the volume are different. The DM along each direction was calculated by

$$DM_x = (\Delta_L + \Delta_R)/2, \quad (6)$$

$$DM_y = (\Delta_A + \Delta_P)/2, \quad (7)$$

$$DM_z = (\Delta_Cr + \Delta_Ca)/2.$$ \quad (8)$$

Thus, the DM in this study, ($DM_x, DM_y, DM_z$), is anisotropic which includes the dose perturbation effects induced by the isocenter shift. The DM was calculated for both the physical and biological dose distributions.

### 2.D Evaluations of BDM and PDM

The DM in physical dose distribution is defined as PDM and the DM in BED is defined as BDM. The physical dose distribution and BED are defined as the BDM and PDM. The mean value and standard error of the mean (SEM) of the BDM and PDM of the 10 cases were evaluated for DPF from 3 to 20 Gy/fr. The data were compared using Student’s t-test. The first test was performed to compare the BDM and PDM along the LR, AP, and CC directions. The LQ model was applied with $\alpha/\beta$ fixed to 10 Gy, as it is universally accepted for conventional fractionation.$^{32}$ The second test was performed to compare the BDM and PDM with $\alpha/\beta = 3, 5, \text{ and } 10 \text{ Gy.}$ All statistical analyses were performed using SPSS Statistics (IBM, Armonk, NY, USA). The statistical significance was defined for the $P < 0.05$. Also, the correlation factor ($r^2$) of the tumor volume and PDM or BDM is analyzed. Then, The BCF was defined as the ratio between the BDM and PDM:

$$BCF = \frac{BDM}{PDM} \quad (9)$$

The correlation of the BCF and $\alpha/\beta$ is evaluated. After confirming there is no significant difference for the BCF due to the $\alpha/\beta$, the BCF is fitted using the following function of $d/(\alpha/\beta)$.

$$BCF = A \exp \left[ - \left( \frac{d}{\alpha/\beta} \right)^\beta \right] + C, \quad (10)$$

where $A, B, \text{ and } C$ are the fitting parameters determined by a least squares method. These parameters were determined for the

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**Fig. 2.** Illustrations of the treated volume (TV) and dosimetric margin (DM) by (a) Gordon and Siebers$^{14}$ and (b) our study. See text for details.
measurement data of $D_{95\%}$ and $D_{98\%}$ in the LR, AP, and CC directions.

2.E | Evaluations of dose gradient in physical dose and BED

The dose gradient (DG) was calculated with dose profile in the physical dose and BED, as shown in Fig. 3. The dose distribution was normalized to the prescribed dose as 100%. The distance between the $d_h$ and $d_l$ that were the position at a certain relative dose of higher dose ($D_h$) (%) and lower dose ($D_l$) (%). The DG can be defined by

$$DG = \frac{|D_h - D_l|}{d_h - d_l}.$$  \hfill (11)

The average DG in the LR, AP, and CC directions were defined as $DG_{LR}$, $DG_{AP}$, and $DG_{CC}$, respectively.

$$DG_{LR} = (DG_R + DG_L)/2.$$  \hfill (12)

$$DG_{AP} = (DG_A + DG_P)/2,$$  \hfill (13)

$$DG_{CC} = (DG_C + DG_C)/2.$$  \hfill (14)

Then, the DG in physical dose distribution ($DG^{PD}$) and the DG in BED ($DG^{BED}$) were derived by

$$DG^{PD} = \frac{(DG^{PD}_{LR} + DG^{PD}_{AP} + DG^{PD}_{CC})}{3},$$  \hfill (15)

$$DG^{BED} = \frac{(DG^{BED}_{LR} + DG^{BED}_{AP} + DG^{BED}_{CC})}{3}. $$  \hfill (16)

3 | RESULTS

3.A | Dose gradient in physical dose and BED

Figure 4 shows the average $DG^{PD}$ and $DG^{BED}$ for the all directions in 10 patients. The average $DG^{PD}$ of 10 patients was 1.7%/mm and $DG^{BED}$ at the DPF of 3–20 Gy with $\alpha/\beta = 10$ Gy of 10 patients were 2.4%–2.9%/mm. The $DG^{PD}$ is significantly smaller than the $DG^{BED}$ at the DPF of 3–20 Gy with $\alpha/\beta = 10$ Gy.

3.B | Comparison of the physical and biological dosimetric margins

Figures 5 and 6 show the BDM and PDM ($\alpha/\beta = 10$ Gy) for the $DCTV_{95\%}$ and $DCTV_{98\%}$ of CTV in the LR, AP, and CC directions for all patients. The DPF ranged from 3 to 20 Gy. The difference between the BDM and PDM of $D_{95\%}$ was 0.5–1.3, 0.6–1.4, and 0.6–1.3 mm in the LR, AP, and CC directions, respectively (Fig. 5). The difference between the BDM and PDM of $D_{98\%}$ was 0.5–1.2, 0.6–1.3, and 0.5–
1.2 mm for the LR, AP, and CC directions, respectively (Fig. 6). The PDM was larger than the BDM, and the BDM was smaller for large DPF in all directions. There was no significant difference in LR and AP directions for neither the BDM nor PDM (P > 0.05). On the other hand, both the BDM and PDM in the CC direction were significantly larger than the ones in the other directions (P < 0.05) in both D95% and D98%.

### 3.C Correlation of the tumor volume and the DM

Figure 7 shows the correlation of the tumor volume and PDM for the DCTV95% of CTV in the LR, AP, and CC directions. The r² for the tumor volume and PDM in LR, AP, and CC directions were 0.18, 0.07, and 0.64, respectively. Figure 8 shows the correlation of the tumor volume and BDM (α/β = 10 Gy) for the DCTV95% of CTV with DPR = 3 and 20 Gy in the LR, AP, and CC directions. The r² for the tumor volume and BDM with DPR = 3 Gy in LR, AP, and CC directions were 0.18, 0.03, and 0.59, respectively. The r² for the tumor volume and BDM with DPR = 20 Gy in LR, AP, and CC directions were 0.20, 0.04, and 0.42, respectively.

### 3.D Biological conversion factor

Figures 9 and 10 show the BCF for the DCTV95% and DCTV98% of CTV with α/β = 3, 5, 10 Gy in the LR, AP, and CC directions. The BCF is smaller with higher DPF and lower α/β. Figures 11 and 12 show the BCF for the DCTV95% and DCTV98% of CTV with d/(α/β) in the LR, AP, and CC directions. The differences in the BCF due to α/β for the DCTV95% and DCTV98% of CTV were not significantly. The data of the transverse direction (LR and AP directions) were combined for the fitting since there was no significant difference between the LR and AP directions. The fitting results of the BCF are shown in Fig. 13. Figure 13(a) shows the measurement data and the fitted curve of D95% in the transverse and CC directions, respectively. Figure 13(b) show the measurement data and the fitted curve of D98% in the transverse and CC directions, respectively. The resulting parameters of the BCF are shown in Fig. 13.

### 4 DISCUSSION

In a past study, van Herk reported that the PTV should be a geometrical concept, and van Herk’s margin was defined to select the
appropriate beam sizes and arrangements, taking into consideration the net effect of all the possible geometrical variations and inaccuracies to obtain a clinically acceptable and specified probability that the prescribed dose is absorbed in the CTV.\textsuperscript{13} Gordon and Siebers reported the use of the DM, which extended the concept of the CTV-to-PTV margin.\textsuperscript{14} The DM by Gordon was defined as the

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**Fig. 6.** Measured biological dosimetric margin (BDM) and physical dosimetric margin (PDM) (the margin corresponding to the 90% coverage of the planned $D_{95\%}$ of clinical target volume [CTV] with biological equivalent dose [BED] and physical dose [PD] distribution) at the dose per fraction (DPF) of 3–20 Gy with $\alpha/\beta = 10$ Gy in (a) LR, (b) AP, and (c) CC directions. AP, anterior-posterior; CC, cranio-caudal; LR, left-right.

**Fig. 7.** The correlation of the tumor volume and the physical dosimetric margin (PDM) of the $D_{95\%}$ in (a) LR, (b) AP, (c) CC directions. AP, anterior-posterior; CC, cranio-caudal; LR, left-right.

**Fig. 8.** The correlation of the tumor volume and the biological dosimetric margin (BDM) of the $D_{95\%}$ with 10 Gy of $\alpha/\beta$ in (a) LR, (b) AP, (c) CC directions. AP, anterior-posterior; CC, cranio-caudal; LR, left-right.
distance between the CTV and the region of the minimum PTV
dose. These concepts were introduced as an isotropic margin from
the CTV. On the other hand, the DM along the LR, AP and CC direc-
tions were independently defined in this study. The DM in the CC
direction was found to be larger than the other directions. This
result is an indication that the anisotropic nature of the DM intro-
duced in this study would be useful to provide an appropriate 3D
margin. The importance of the anisotropic margin is supported by
the results in Caivano et al.33 They reported that the CT with a thin
slice thickness could be suggested for small targets, such as those
treatable with the stereotactic radiotherapy, to achieve a better
tumor definition and dose coverage. The resolution of the dose cov-
ervation of the target depends on the slice thickness in the CC direc-
tion. Thus, it would be beneficial to use the anisotropic DM to
create a reasonable 3D dose distribution with a minimum 3D margin.
Moreover, the correlation between the tumor volume and DM
(BDM and PDM) was evaluated. This correlation is weaker, which
indicates that the size of the target volume does not affect the
BDM and PDM in this study.

There are various patient positioning uncertainties such as respira-
tory motion, the breath-hold reproducibility, contouring, and resid-
ual set up errors for SBRT treatment.34,35 The manifestation of the
isocenter shift depends on the type of the immobilization, respira-
tory gating or breath-holding, and irradiation techniques. While the
dose perturbation due to the setup error was mimicked by systemat-
ically moving the isocenter along the LR, AP, and CC directions in
this study, the BCF can be adjusted to give a dedicated model for
specific technique by replacing the 3D isocenter shift by the actual
distribution of the setup error.

The essential outcome of this study is the novel scheme to
involve the biological effects into the DM. The BED suggested in
past studies3,24–31 has been an important subject to consider the
difference in the prescribed dose. Specifically, the SBRT is per-
formed with various fractionations and prescribed doses at differ-
ent institutions. The difference in the DPF affects the biological
damage. While the treatment plan review is usually performed on
the PD in the clinical practice, it is essential to consider the differ-
ence in the DPF. The BDM was smaller than PDM in all directions.
**Fig. 11.** The biological conversion factor (BCF) of $D_{98\%}$ with the $d/(\alpha/\beta)$ in the (a) LR, (b) AP, and (c) CC directions. Closed squares, closed triangles, and cross symbols show the BCFs for $\alpha/\beta = 3$, 5, 10 Gy, respectively. AP, anterior-posterior; CC, cranio-caudal; LR, left-right.

**Fig. 12.** The biological conversion factor (BCF) of $D_{98\%}$ with the $d/(\alpha/\beta)$ in the (a) LR, (b) AP, and (c) CC directions. Closed squares, closed triangles, and cross symbols show the BCFs for $\alpha/\beta = 3$, 5, 10 Gy, respectively. AP, anterior-posterior; CC, cranio-caudal; LR, left-right.

**Fig. 13.** The biological conversion factor (BCF) of the (a) $D_{95\%}$ and (b) $D_{98\%}$ with the $d/(\alpha/\beta)$. Closed red circles, plus symbols, and cross symbols are the data of the BCF along the LR, AP, and CC directions. Error bars represent the standard error of the mean. Solid black and green curves are the results of the fitting using Eq. (10) for the transverse (LR and AP) and longitudinal (CC) data. The $A_T$, $B_T$, and $C_T$ are fitting parameters for the transverse direction, and the $A_L$, $B_L$, and $C_L$ are fitting parameters for the longitudinal direction. AP, anterior-posterior; CC, cranio-caudal; LR, left-right.
for the DPFs examined through the comparison between the BDM and PDM in this study. The BDM is smaller with larger DPF and higher $\alpha/\beta$. It was affected by the dose gradient. The dose gradient in physical dose was significantly smaller than that in the BED at the $d/(\alpha/\beta)$ examined through the comparison. Also, the dose gradient in the BED is lager with higher $d/(\alpha/\beta)$. The plan in the BED with higher $d/(\alpha/\beta)$ is less forgiving of set-up inaccuracies owing to steep dose gradients. Therefore, in order to give the appropriate BDM in the BED-based treatment planning, the dependency of the BDM on the DPF and $\alpha/\beta$ should be taken into account.

This study introduced a new index, the BCF, to convert the PDM to BDM. Since the BDM and PDM in the CC direction were larger than the transverse direction, the BCF model was developed separately for the transverse and longitudinal directions. For the clinical introduction of the BCF, the flowchart is shown as Fig. 14. Using the BCF, a direct estimation of the BDM is possible without calculating the BED. Namely, the BCF provides the opportunities to give the biologically equivalent DM used in the current PD-based treatment planning in the SBRT clinical practice without built-in functions of the biological conversion of the dose distribution. In the clinical process, at first, the PDM is calculated obtained in commercially treatment planning. After that, the BDM can be obtained without built-in functions of the biological conversion of the dose distribution. Additionally, the optimal BDM for the BED when the dose per fraction is changed can also be derived.

The simple LQ model is not considered the proliferation and repair of tumors during the whole course of treatment. However, it should be noted that the concept of the BCF is not specific for the LQ model. There were several proposed models for SBRT therapeutic schemes except for LQ model, such as the Linear-Quadratic-Linear (LQL) model, the modified Linear-Quadratic (MQL) model, the generalized Linear-Quadratic (gLQ) model. The model of the BCF can be applied to these biological models and various tumor types through the procedure developed in this study.

The BCF developed in this study can be introduced in the SBRT clinical practice with the current PD-based treatment planning system with no built-in BED-related functions. In practice, the PDM is determined using the SBRT treatment plans for the commissioning. The BDM is then obtained using the BCF using Eqs. (9 and 10). This study analyzed 10 treatment plans and the BCF had variation. Further studies should be needed to reduce the variation. However, this study provides a new framework to give the BDM in the current PD-based treatment planning system. This novel scheme can be used as a substitute method of the BED-based treatment planning in the current PD-based treatment planning system.

The limitation of this study was that the BDM of only one combination of the treatment technique and the treatment site was evaluated with limited number of patients. The accuracy of the BDM for lung cancer and the other cancers will be evaluated in the further study.

5 | CONCLUSION

A novel scheme for the direct estimation of the BDM from the PD distribution was developed in this study. The setup error was taken into account for the DM used in this study. The effects of the DPF and $\alpha/\beta$ were involved into the BCF which provided the direct conversion from the PDF to BDM. This scheme is applicable for the various prescribed doses and fractionations. It is also possible to replace the BCF by replacing the LQ model by some other biological model. The BCF model is useful for evaluating the BED coverage to the target volume, which plays an equivalent role of the BED-based treatment planning of SBRT in the current PD-based treatment planning system.

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CONFLICT OF INTEREST
None.
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