Use of radiation protraction to escalate biologically effective dose to the treatment target

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(Received 12 May 2011; revised 4 October 2011; accepted for publication 6 October 2011; published 21 November 2011)

Purpose: The aim of this study is to evaluate how *simultaneously* increasing fraction time and dose per fraction affect biologically effective dose for the target (BED_{tar}) while biologically effective dose for the normal tissue (BED_{nt}) is fixed.
Methods: In this investigation, BED_{tar} and BED_{nt} were studied by assuming mono-exponential repair of sublethal damage with tissue dependent repair half-time.
Results: Our results demonstrate that under certain conditions simultaneously increasing fraction time and dose per fraction result in increased BED_{tar} while BED_{nt} is fixed. The dependence of biologically effective dose on fraction time is influenced by the dose rate. In this investigation we analytically determined time-varying dose rate $\tilde{R}$ which minimizes *BED*. Changes in *BED* with fraction time were compared for constant dose rate and for $\tilde{R}$.
Conclusions: A number of recent experimental and theoretical studies have demonstrated that slow delivery of radiation (known as radiation protraction) leads to reduced therapeutic effect because of increased repair of sublethal damage. In contrast, our analysis shows that under certain conditions simultaneously increasing fraction time and dose per fraction are radiobiologically advantageous. [DOI: 10.1118/1.3656053]

Key words: biologically effective dose, radiation protraction, sublethal damage repair

I. INTRODUCTION

It is well known that prolonged delivery of radiation, referred to below as *radiation protraction*, reduces radiation-induced cell kill. The reduction in cell kill can be explained by the repair of sublethal damage which can be particularly important for low dose rate brachytherapy[1,2] or for external beam treatments with long fraction times.[3] The effect of radiation protraction is most commonly described with the help of the linear-quadratic (LQ) model in which the quadratic term is multiplied by the *protraction factor*.[1,4]

With the wide acceptance of stereotactic radiosurgery (SRS) and intensity modulated radiotherapy (IMRT) characterized by long treatment times, a potential reduction of therapeutic effect caused by the effect of radiation protraction has become a focus of recent investigations.[5–13] It should also be noted that long fraction times are frequently observed in stereotactic body radiation therapy (SBRT) primarily due to the use of noncoplanar radiation fields which necessitates repositioning the patient between the fields.

There exists a consensus in the literature that, in general, decreasing the effect of radiation protraction by shortening fraction time improves treatment outcome because long fraction times (e.g., greater than 10 min) result in reduced kill of malignant cells. In contrast, in this study we show that under certain conditions radiation protraction makes it possible to escalate biologically effective dose (*BED*) for the planning target volume (PTV) while maintaining fixed *BED* for the normal tissue. Alternatively, under the same conditions radiation protraction can be used to decrease *BED* for the normal tissue while maintaining fixed *BED* for the PTV. Second, we analytically derive an expression for the dose rate (referred to below as $\tilde{R}$) which minimizes the protraction factor if the dose per fraction is fixed. Third, the biological effect of radiation protraction is compared for two different cases: (a) constant dose rate R_0 and (b) $\tilde{R}$. It is demonstrated that the choice of $\tilde{R}$ can allow for further escalation of *BED* for the target or, alternatively, for further reduction in *BED* for the normal tissue.

This study is organized as follows: the analytical models and obtained results are considered in Secs. II and III, discussion and conclusions of the study are contained in Secs. IV and V.

II. METHODS

II.A. LQ model

The well known LQ model for cell kill forms the foundation of this study. In this model, the surviving fraction of irradiated cells is given by

$$S = \exp(-\alpha D - \beta G D d), \tag{1}$$

where d and D are the dose per fraction and cumulative dose, respectively; α and β are the radio-sensitivities; G is the so-called *protraction factor* which appears in the equation due to repair of sublethal damage (e.g., Refs. 1, 4, 14). Note that the expression for cell survival in Eq. (1) is valid only for fractionated treatments. In this study, we assume

that damage repair can be described as mono-exponential with a half-time $T_{1/2}$. Under the additional assumption that $T_{1/2}$ is much smaller than the interval between successive fractions so that sublethal damage is fully repaired between the fractions, the protraction factor G can be written as follows:

$$G = \frac{2}{d^2}\int_0^T R(t)dt \int_0^t R(t^{'}) \times \exp(-\mu(t-t^{'}))dt^{'}, \quad (2)$$

where T is the duration of one fraction; $R(t)$ is the dose rate; $\mu = \frac{\ln 2}{T_{1/2}}$. Note that the double integral in Eq. (2) can be calculated analytically in the case of constant dose rate R_0 (Ref. 15)

$$G(R_0) \equiv G_0 = \frac{2}{\mu T}\left[1 - \frac{1-\exp(-\mu T)}{\mu T}\right]. \quad (3)$$

In the derivation below, we will assume that normal and malignant tissue have different half-times $T_{1/2,nt}$ and $T_{1/2,\mathrm{tar}}$, respectively. The corresponding repair constants are $\mu_{nt} = \frac{\ln 2}{T_{1/2,nt}}$ and $\mu_{tar} = \frac{\ln 2}{T_{1/2,\mathrm{tar}}}$.

II.B. Dependence of biologically effective dose on fraction time

Our objective in this section is to analytically determine conditions under which increasing fraction time T can be used to increase cell kill in the target while cell kill in normal tissue is fixed. Let us first consider a case, referred to below as the *initial case*, when the target and the adjacent, sensitive normal organ are irradiated uniformly during N_f fractions and the fraction time is sufficiently small so that the effect of radiation protraction can be neglected. That is, $G_{\mathrm{tar}} = G_{nt} = 1$, where G_{tar} and G_{nt} are the target and normal tissue protraction factors, respectively. The target and normal tissue doses per fraction are $d_{\mathrm{tar},0}$ and $d_{nt,0}$, respectively.

In the considered case, the biologically effective dose for the target (BED_{tar}) and that for the normal tissue (BED_{nt}) are given by[16,17]

$$BED_{\mathrm{tar}} = N_f d_{\mathrm{tar},0}\left(1 + \frac{d_{\mathrm{tar},0}}{(\alpha/\beta)_{\mathrm{tar}}}\right) \quad \text{and}$$
$$BED_{nt} = N_f d_{nt,0}\left(1 + \frac{d_{nt,0}}{(\alpha/\beta)_{nt}}\right). \quad (4)$$

Since protraction factor decreases with increasing fraction time, BED_{nt} also decreases with increasing fraction time assuming fixed number of fractions and dose per fraction. Suppose now that fraction time is varied while BED_{nt} is fixed. One can maintain BED_{nt} by increasing the number of fractions and/or dose per fraction. Increasing number of fractions results in a longer treatment course which is generally undesirable. As a result, we will use the same number of fractions as in the initial case but increase dose per fraction to maintain BED_{nt}. Consequently, from Eq. (4), it follows that

$$d_{nt}\left(1 + \frac{G_{nt}d_{nt}}{(\alpha/\beta)_{nt}}\right) = d_{nt,0}\left(1 + \frac{d_{nt,0}}{(\alpha/\beta)_{nt}}\right). \quad (5)$$

Equation (5) has a unique, positive solution for the dose per fraction d_{nt}:

$$d_{nt} = -\frac{(\alpha/\beta)_{nt}}{2G_{nt}} + \sqrt{\frac{(\alpha/\beta)_{nt}^{\,2}}{4G_{nt}^2} + \frac{C}{G_{nt}}}, \quad (6)$$

where $C = d_{nt,0}((\alpha/\beta)_{nt} + d_{nt,0})$. After the increase in dose per fraction, the biologically effective dose to the target is given by

$$BED_{\mathrm{tar}} = N_f d_{\mathrm{tar}}\left(1 + \frac{G_{\mathrm{tar}}d_{\mathrm{tar}}}{(\alpha/\beta)_{\mathrm{tar}}}\right) = N_f \xi d_{\mathrm{tar},0}\left(1 + \frac{\xi G_{tar}d_{\mathrm{tar},0}}{(\alpha/\beta)_{\mathrm{tar}}}\right), \quad (7)$$

where ξ is the ratio of the initial and final dose per fraction; i.e., $\xi = \frac{d_{nt}}{d_{nt,0}} = \frac{d_{\mathrm{tar}}}{d_{\mathrm{tar},0}}$.

Note that in Eq. (7), the target protraction factor G_{tar} and parameter ξ depend on fraction time T. Consequently, BED_{tar} in Eq. (7) is a function of fraction time. Our aim here is to find conditions under which BED_{tar} increases with increasing T for fixed BED_{nt}. From Eq. (5) and condition $\xi = \frac{d_{nt}}{d_{nt,0}}$, it follows that in order to maintain fixed BED_{nt}, derivatives $\dot{\xi} \equiv \frac{d(\xi)}{dT}$ and $\dot{G}_{nt} \equiv \frac{d(G_{nt})}{dT}$ must satisfy the following equation:

$$\dot{\xi} = -\frac{\xi^2 d_{nt,0}\dot{G}_{nt}}{(\alpha/\beta)_{nt}\left(1 + \frac{2\xi d_{nt,0}G_{nt}}{(\alpha/\beta)_{nt}}\right)}. \quad (8)$$

By using Eq. (7), we obtain that derivative $\frac{dBED_{\mathrm{tar}}}{dt}$ is given by

$$\frac{dBED_{\mathrm{tar}}}{dT} = A\left[\dot{\xi}\left(1 + \frac{2G_{\mathrm{tar}}\xi d_{\mathrm{tar},0}}{(\alpha/\beta)_{\mathrm{tar}}}\right) + \frac{\dot{G}_{\mathrm{tar}}\xi^2 d_{\mathrm{tar},0}}{(\alpha/\beta)_{\mathrm{tar}}}\right], \quad (9)$$

where $A = N_f d_{\mathrm{tar},0}$ and $\dot{G}_{\mathrm{tar}} \equiv \frac{d(G_{\mathrm{tar}})}{dT}$. By substituting $\dot{\xi}$ from Eq. (8) into Eq. (9), we obtain

$$\frac{dBED_{\mathrm{tar}}}{dT} = A\xi^2\left[-\frac{d_{nt,0}\dot{G}_{nt}}{(\alpha/\beta)_{nt}\left(1 + \frac{2\xi d_{nt,0}G_{nt}}{(\alpha/\beta)_{nt}}\right)} \times \left(1 + \frac{2G_{\mathrm{tar}}\xi d_{\mathrm{tar},0}}{(\alpha/\beta)_{\mathrm{tar}}}\right) + \frac{\dot{G}_{\mathrm{tar}}d_{\mathrm{tar},0}}{(\alpha/\beta)_{\mathrm{tar}}}\right]. \quad (10)$$

Below, we will consider conditions under which $\frac{dBED_{\mathrm{tar}}}{dT} > 0$ which ensures that BED_{tar} increases with fraction time T.

Case 1: $G_{nt} = G_{\mathrm{tar}}$

In this case, one can obtain the following condition for $\frac{dBED_{\mathrm{tar}}}{dT} > 0$:

$$\frac{(\alpha/\beta)_{\mathrm{tar}}d_{nt,0}}{(\alpha/\beta)_{nt}d_{\mathrm{tar},0}} > 1. \quad (11)$$

Case 2: short fraction time

To elucidate the role of different repair constants for the target and normal tissue, we consider the case of short fraction time for which the following approximations can be used:

$$G_{nt} = 1 - a\mu_{nt}T \quad \text{and} \quad G_{\mathrm{tar}} = 1 - a\mu_{\mathrm{tar}}T, \quad (12)$$

where a = constant, $a\mu_{nt}T \ll 1$, and $a\mu_{\mathrm{tar}}T \ll 1$. It is easy to show that $a = 1/3$ in the case of constant dose rate described by Eq. (3). For another analytical solution used in this study, $a = 1/2$ [see Eq. (22) below].

From Eq. (10), it follows that in the considered case the condition for $\frac{dBED_{\text{tar}}}{dT} > 0$ is given by

$$\frac{(\alpha/\beta)_{\text{tar}} d_{nt,0}\left(1+\frac{2d_{\text{tar},0}}{(\alpha/\beta)_{\text{tar}}}\right)}{(\alpha/\beta)_{nt} d_{\text{tar},0}\left(1+\frac{2d_{nt,0}}{(\alpha/\beta)_{nt}}\right)} > \frac{\mu_{\text{tar}}}{\mu_{nt}}. \tag{13}$$

Note that in the case $\mu_{\text{tar}} = \mu_{nt}$, the above condition is reduced to Eq. (11).

So far, we have shown that there exist conditions under which BED_{tar} can be increased by simultaneously increasing fraction time and dose per fraction while maintaining fixed BED_{nt} for the normal tissue. Alternatively, BED_{tar} can be fixed instead. In the latter case, under the conditions (11) or (13), BED_{nt} decreases with increasing fraction time. This can be shown as follows: assuming that conditions in Eq. (11) or (13) are satisfied, we can increase BED_{tar} first while maintaining fixed BED_{nt} as shown previously. Second, we can lower the dose per fraction to decrease BED_{tar} to the level achieved when the fraction time is short enough so that the effect of radiation protraction is negligibly small. It is apparent, that the decrease in dose per fraction will produce a corresponding decrease in BED_{nt} which will bring it below the level achieved when the fraction time is short. We shall confirm these conclusions in Sec. III by considering several examples with typical values of alpha/beta ratios for late responding normal tissues and tumors.

In the considered model, biologically effective dose depends on the protraction factor G which, in turn, depends on fraction time T, dose rate and repair half-time. It should be realized that G approaches unity in the case when delivery time is short enough so that sublethal damage repair is negligible; i.e., the upper bound for G is unity (see proof in Appendix A). For the purpose of our discussion it is important to determine the lower bound for the protraction factor G which is not a trivial task. In Sec. II C, we consider the following problem: find dose rate which minimizes G in Eq. (2) for given fraction time T and dose per fraction $d = \int_0^T R(t)dt$. Below we shall also show the following: (a) the minimum G (denoted by $G_{\min}$) depends on the maximum dose rate $R_{\max}$ and (b) the smallest achievable $G_{\min}$ is obtained when $R_{\max} \to \infty$.

II.C. Dose rate which minimizes protraction factor under the condition of fixed dose per fraction

Theorem 1. Let $T, \mu, d, R_{\max} > 0$ with $TR_{\max} \geq d = \int_0^T R(t)dt$ and $0 \leq R(t) \leq R_{\max}$ for all $t \in [0,T]$. Then, the protraction factor in Eq. (2) has its minimum value when the dose rate (denoted by $\tilde{R}$) is given by

$$\tilde{R} = \begin{cases} R_{\max}; 0 \leq t < \hat{T}; \\ k; \hat{T} \leq t \leq T - \hat{T}; \\ R_{\max}; T - \hat{T} < t \leq T, \end{cases} \tag{14}$$

where k and $\hat{T}$ satisfy

$$(R_{\max} - k)\exp(\mu\hat{T}) - R_{\max} = 0, \tag{15}$$

$$2\hat{T}R_{\max} + (T - 2\hat{T})k = d, \tag{16}$$

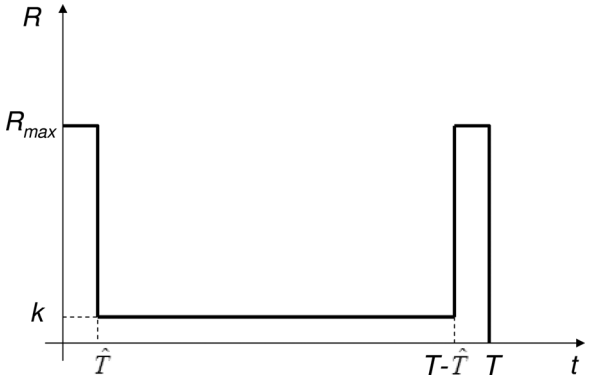

FIG. 1. $\tilde{R}$ as a function of time.

with $0 < k < R_{\max}$ and $0 < \hat{T} < d/(2R_{\max}) < T/2$ (see Fig. 1). The proof of this theorem is given in Appendix B.

If we now consider the minimum of protraction factor $G_{\min}$ as a function of $R_{\max}$, then the following theorem is valid.

Theorem 2. Let $G_{\min}(R_1)$ and $G_{\min}(R_2)$ be the minimum values of the protraction factor when $R_{\max} = R_1 > 0$ and $R_{\max} = R_2 > 0$, respectively. If $R_1 < R_2$, then $G_{\min}(R_2) < G_{\min}(R_1)$.

Proof. Let $G_{\min}(R_1)$ and $G_{\min}(R_2)$ be achieved when $R = \tilde{R}(R_1) \leq R_1$ and $R = \tilde{R}(R_2) \leq R_2$, respectively. Let us first assume that $G_{\min}(R_2) \geq G_{\min}(R_1)$. Since $G(\tilde{R}(R_1)) = G_{\min}(R_1)$, then, as a result of our assumption, $G(\tilde{R}(R_1)) \leq G_{\min}(R_2)$. Because $\tilde{R}(R_1) < R_2$, the latter condition can be realized only if $\tilde{R}(R_1) = \tilde{R}(R_2)$ which is impossible since $\tilde{R}(R_1) \leq R_1 < R_2$. The obtained contradiction completes the proof.

An important conclusion from the latter theorem can be summarized as follows: the global minimum of protraction factor $G_{\min}$ with an additional condition $d = \text{constant} = \int_0^T R(t)dt$ can be obtained by considering the limit $R_{\max} \to \infty$. Analytical dependence of $G_{\min}$ on μ and T in the case of large $R_{\max}$ is considered in Sec. II D.

II.D. $G_{\min}$ in the case of large $R_{\max}$

In this section, we consider the case of large enough $R_{\max}$ such that $\max(d/(TR_{\max}), \mu d/R_{\max}) \ll 1$. Since $\hat{T} < d/(2R_{\max})$, we also have $\mu\hat{T} \ll 1$. By using expansion $\exp(\mu\hat{T}) = 1 + \mu\hat{T}$, we obtain from Eq. (15)

$$k = \mu\hat{T}R_{\max}. \tag{17}$$

By substituting Eq. (17) into Eq. (16), we obtain

$$2\hat{T}R_{\max} + (T - 2\hat{T})\mu\hat{T}R_{\max} = d. \tag{18}$$

Since in the considered case $\hat{T} < d/(2R_{\max}) \ll T/2$, we have

$$\hat{T} = \frac{d}{R_{\max}(2 + \mu T)} \tag{19}$$

and

$$k = \frac{\mu d}{(2 + \mu T)}. \tag{20}$$

We can now calculate doses d_1 and d_3 delivered with the two narrow pulses on the edges of the interval [0, T] and the dose d_2 delivered with constant dose rate k:

$$d_1 = d_3 = R_{\max}\hat{T} = \frac{d}{(2+\mu T)}$$
$$d_2 = kT = \frac{\mu T d}{(2+\mu T)}. \quad (21)$$

As shown in Appendix C, in the considered case the protraction factor is

$$G_{\min} = \frac{2}{2+\mu T}. \quad (22)$$

The comparison between G_0 from Eq. (3) and $G_{\min}$ is shown in Fig. 2. Note that Eq. (22) is used to obtain the results shown in Figs. 5 and 6 in Sec. III.

II.E. Protraction factor in the case of discrete radiation beams

In the discussion above, protraction factor was determined by considering dose rates [see Eq. (3) and Eq. (14)] which are not typically used in clinical practice. The commonly used treatment approach employs a number of x-ray beams incident on the patient at different angles. Schematic diagrams of equidistant, equally weighted and nonequally weighted beams are shown in Fig. 3. Protraction factor in the case of discrete, equally spaced radiation beams with duration much shorten than μ^{-1} is given by

$$G = \frac{2}{d^2}\left(\sum_{i=1}^{N}\frac{d_i^2}{2} + \sum_{i=1}^{N-1}\sum_{j=i+1}^{N} d_i d_j \exp(-\mu(j-i)\Delta)\right) \quad (23)$$

where d_i is the dose per fraction generated by the ith beam, d is the total dose per fraction given by the sum $d = \sum_{i=1}^{N} d_i$, and Δ is the interval between successive beams. Calculated protraction factors for 2, 3, and 10 equally weighted beams are displayed in Fig. 4. It is easy to see that for $\mu T \leq 10$ the difference between protraction factors given by Eqs. (3) and (23) becomes small when the number of beams is large (i.e., $\geq$10).

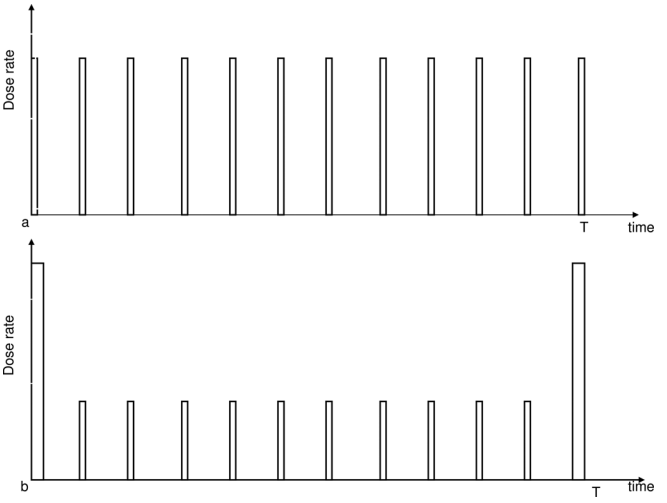

FIG. 3. (a) Equally weighted, equidistant beams approximate the effect of constant dose rate [see Eq. (3)]. (b) A train of nonequally weighted beams which minimize protraction factor. Note that the first and last beams in (b) deliver dose $d_1 = d/(2+\mu T)$. These beams are separated by N equally weighted beams each delivering dose $d_{2,N} = \mu T d N^{-1}/(2+\mu T)$.

III. RESULTS

To demonstrate the effect of increased fraction time, we consider two different cases: (a) fixed BED_{nt} and (b) fixed BED_{tar}. In our calculations we use $\alpha_{nt} = \alpha_{\text{tar}} = 0.15\ \text{Gy}^{-1}$, $(\alpha/\beta)_{\text{tar}} = 10$ Gy and $(\alpha/\beta)_{nt} = 3$ Gy, and equal half-times $T_{1/2,nt} = T_{1/2,\text{tar}} = 0.5$ h, where $T_{1/2,nt}$ and $T_{1/2,\text{tar}}$ are the half-times for normal tissue and target, respectively. In the utilized fractionation protocol, the normal tissue and target

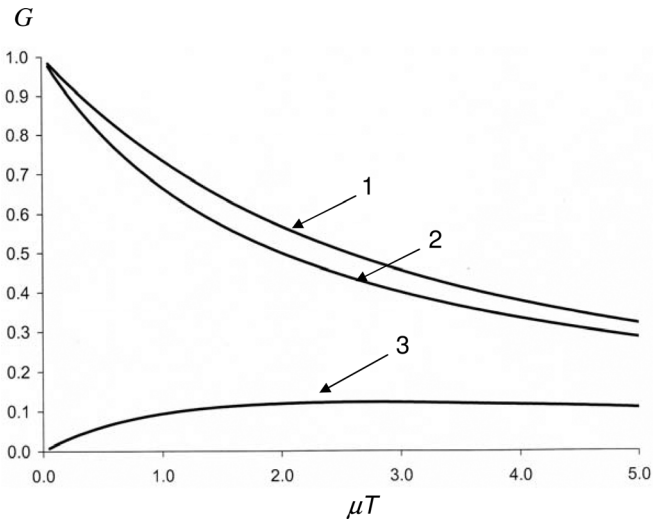

FIG. 2. Comparison between G_0 from Eq. (3) and $G_{\min}$ from Eq. (22): (1) G_0, (2) $G_{\min}$ and (3) $(1 - G_{\min}/G_0)$.

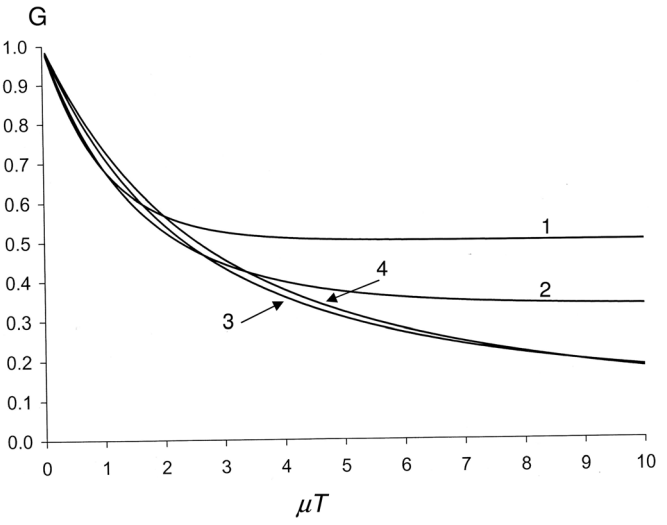

FIG. 4. Protraction factor G in the case of equally weighted, equidistant beams: (1) two beams; (2) three beams; (3) ten beams; and (4) G_0 described by Eq. (3)

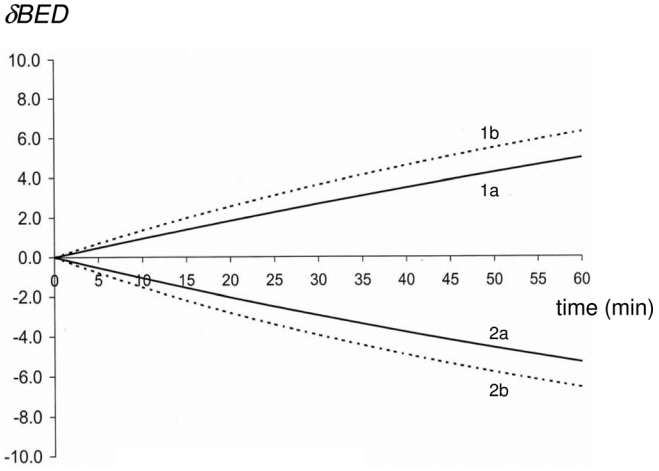

FIG. 5. Percent change in biologically effective dose (δBED) as a function of fraction time: 1(a) and 1(b) depict δBED_{tar} while BED_{nt} is fixed; 2(a) and 2(b) show δBED_{nt} while BED_{tar} is fixed. Solid curves represent the effect of constant dose rate; dashed curves correspond to variable dose rate $\tilde{R}$. Other parameters: $d_{\text{tar},0} = 2$ Gy; $d_{nt,0} = 1.5$ Gy; $T_{1/2,\text{tar}} = T_{1/2,nt} = 30$ min.

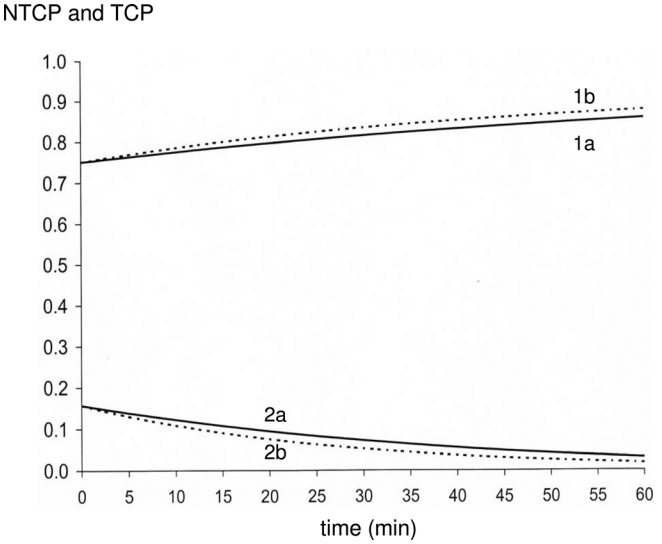

FIG. 6. TCP and NTCP versus fraction time: 1(a) and 1(b)—TCP for fixed BED_{nt}; 2(a) and 2(b)—NTCP for fixed BED_{tar}. Solid curves and dashed curves correspond to constant dose rate and variable dose rate $\tilde{R}$, respectively. The radiobiological parameters are the same as in Fig. 5.

are irradiated in 35 fractions to the total doses of 52.5 and 70 Gy, respectively.

For illustrative purposes, we consider normal tissue complication probability given by

$$\text{NTCP} = \exp(-K_{nt}S_{nt}), \tag{24}$$

where K_{nt} and S_{nt} are the number of colony forming units and survival probability for normal cells, respectively (e.g., Ref. 2). In the calculations, we use $K_{nt} = 2.5 \times 10^5$ which results in NTCP of 0.16 for the considered fractionation when protraction is negligible. Conversely, tumor control probability is given by

$$\text{TCP} = \exp(-K_{\text{tar}}S_{\text{tar}}), \tag{25}$$

where K_{tar} and S_{tar} are the number of malignant cells and their survival probability, respectively. In our calculations we use $K_{\text{tar}} = 8.5 \times 10^4$ which results in TCP of 0.75 for the above described fractionation and when the effect of radiation protraction is negligible.

The dependences of BED_{tar} and BED_{nt} on fraction time for the considered two cases are displayed in Fig. 5. The corresponding plots of TCP and NTCP are shown in Fig. 6. In the case of fixed BED_{nt}, expanding fraction time to 1 h increases TCP from 0.75 to 0.86 for constant dose rate and to 0.88 for variable dose rate $\tilde{R}$ described in Eq. (14). Conversely, in the case of fixed BED_{tar} and, therefore, fixed TCP of 0.75, increasing treatment time to 1 h reduces NTCP from 0.16 to 0.03 for constant dose rate and from 0.16 to 0.02 for the dose rate $\tilde{R}$.

IV. DISCUSSION

A number of investigations have demonstrated that prolonged radiation delivery is undesirable because of the associated decrease in tumor cell kill. As a result, shortening fraction time is considered beneficial for treatment outcome. However, our analysis demonstrates that under certain conditions increasing fraction time and *simultaneously* increasing dose per fraction can lead to increased BED_{tar} while BED_{nt} is fixed. Alternatively, if BED_{tar} is fixed, then under the same conditions increasing fraction time and dose per fraction leads to decreased BED_{nt}. It should be noted that the utilized methodology and obtained results are potentially applicable to different treatment techniques associated with long fraction times (e.g., IMRT, SRS and SBRT).

The obtained conclusions can be elucidated by considering a case when tumor and normal tissues have the same repair times. Increasing fraction time results in the decrease of both BED_{tar} and BED_{nt}. Suppose that tumor and normal tissue are irradiated with the same dose per fraction. Then, relative changes in BED_{tar} and BED_{nt} are dependent on the ratios $\alpha_{\text{tar}}/\beta_{\text{tar}}$ and α_{nt}/β_{nt}. Since $\alpha_{\text{tar}}/\beta_{\text{tar}}$ of 10 Gy is normally assumed for tumors while lower ratio α_{nt}/β_{nt} of 3 Gy is typically used for normal tissue, the decrease in BED_{nt} will be greater than the corresponding decrease in BED_{tar}. As a result, if dose per fraction are increased to maintain fixed BED_{nt}, the biologically effective dose for the target will increase above its value achieved in the case when radiation protraction is negligibly small. Alternatively, if the increase in dose per fraction is such that BED_{tar} is unchanged, then BED_{nt} will remain below its level obtained with short fraction time. The suggested explanation is in agreement with the results shown in Fig. 5.

It seems that increases in BED_{tar} with fraction time should be more significant for large dose per fraction if BED_{nt} is fixed; however, this conclusion is not correct. For example, consider the case when both target and normal tissue experience doses per fraction large enough so that the effect of the linear term in the LQ model can be neglected. Then, assuming fixed BED_{nt}, we obtain from Eq. (6): $d_{nt} = \frac{d_{nt,0}}{\sqrt{G_{nt}}}$. The new dose per fraction to the target is proportional to the ratio $\frac{d_{nt}}{d_{nt,0}}$ and is given by $d_{\text{tar}} = \frac{d_{\text{tar},0}}{\sqrt{G_{nt}}}$. Consequently, BED_{tar} is

proportional to $G_{\text{tar}}d_{\text{tar}}^2 = \frac{G_{\text{tar}}d_{\text{tar},0}^2}{G_{nt}}$. In the case, when target and normal tissue have equal repair times, we have $G_{\text{tar}}d_{\text{tar}}^2 = d_{\text{tar},0}^2$. The latter equality indicates that BED_{tar} remains unchanged.

Note that variations in *BED* due to varying fraction time are influenced by the time dependence of protraction factor G. The latter dependence, in turn, is defined by dose rate and repair half-time. To study the effect of fraction time on *BED*, we have considered two different dose rates: (a) constant dose rate and (b) dose rate $\tilde{R}$ described in Eq. (14). It is shown that $\tilde{R}$ minimizes protraction factor under the condition of fixed dose per fraction. It should be mentioned that, in a previous study by Brenner *et al.*,[2] it was also found that the dose rate shown in Fig. 1 minimized protraction factor. The analysis by Brenner *et al.* is valid in the case of infinitely large $R_{\max}$; i.e., when the two peaks at the beginning and at the end of the interval $[0,T]$ in Fig. 1 are both delta functions. In contrast, in our study we solved the general case with a bounded dose rate $0 \le R \le R_{\max}$. The obtained results indicate that $\tilde{R}$ depends on four parameters: repair half-time, fraction time, dose per fraction and maximum dose rate. We have shown that the global minimum of G is obtained when $R_{\max}$ approaches infinity which is the case considered previously by Brenner *et al.*[2]

The performed calculations indicate that under the condition of fixed BED_{nt}, the increase in BED_{tar} is greater for $\tilde{R}$ than that achieved for constant dose rate R_0. The obtained results can be explained as follows: for a given fraction time and dose per fraction the use of variable dose rate, $\tilde{R}$ leads to a greater repair of sublethal damage in the normal tissue as compared to that in the presence of R_0. Consequently, the use of $\tilde{R}$ also leads to a greater decrease in BED_{nt} compared to that achieved with R_0. As a result, when dose per fraction is increased to maintain BED_{nt}, biologically effective dose for the target increases more in the case of $\tilde{R}$.

Although the focus of our study is on the dependences of biologically effective doses to normal tissue and target on fraction time, the related variations in TCP and/or NTCP are generally more important clinically. If we further assume that both TCP and NTCP monotonically increase with increasing *BED*, then the main conclusion of our study can be restated as follows: under certain conditions increasing fraction time results in increased TCP if NTCP is fixed. Alternatively, under the same conditions increasing fraction time leads to decreased NTCP if TCP is fixed. These conclusions are in agreement with the results of performed TCP and NTCP calculations (see Fig. 6). The calculations also confirm that the use of variable dose rate $\tilde{R}$ can lead to greater changes in TCP or NTCP than those achieved with constant dose rate. More importantly, the obtained results indicate that significantly increased TCP or significantly reduced NTCP can be achieved in certain cases by increasing fraction time from several minutes to 1 h with a simultaneous increase in dose per fraction.

Finally, the obtained results rely on the applicability of the LQ model for cell kill. Several recent studies found that the LQ model is inappropriate for small and large doses per fraction.[18–20] It is interesting that these conclusions, in turn, were put in doubt.[21,22] As a result, it appears that caution should be exercised while considering the effect of long fraction times in radiotherapy with dose per fraction significantly different from the standard fraction size of 2 Gy.

V. CONCLUSIONS

Increasing fraction time and simultaneously increasing dose per fraction can lead to increased BED_{tar} while BED_{nt} is fixed if conditions (11) or (13) are satisfied. Alternatively, under the same conditions, simultaneously increasing fraction time and dose per fraction lead to decreased BED_{nt} in the case when BED_{tar} is fixed. The changes in both tumor and normal tissue biologically effective doses are defined by the dependences of the corresponding protraction factors on fraction time. It is shown that variable dose rate $\tilde{R}$ described in Eq. (14) minimizes protraction factor for given dose per fraction and fraction time. Compared to constant dose rate the use of $\tilde{R}$ can result in greater increase in BED_{tar} when BED_{nt} is fixed.

APPENDIX A: PROOF THAT $G \le 1$

Using the formula

$$\int_0^T f(t)\int_0^t g(t')dt'dt = \int_0^T g(t)\int_t^T f(t')dt'dt, \tag{A1}$$

we have

$$\begin{aligned} G &= \frac{2}{d^2}\int_0^T R(t)\exp(-\mu(t))\int_0^t R(t')\exp(\mu t')dt'dt \\ &= \frac{1}{d^2}\int_0^T R(t)\exp(-\mu(t))\int_0^t R(t')\exp(\mu t')dt'dt \\ &\quad + \frac{1}{d^2}\int_0^T R(t)\exp(\mu(t))\int_t^T R(t')\exp(-\mu t')dt'dt \\ &= \frac{1}{d^2}\int_0^T R(t)\int_0^T R(t')\exp(-\mu|t-t'|)dt'dt \\ &\le \frac{1}{d^2}\int_0^T R(t)\int_0^T R(t')dt'dt = \frac{1}{d^2}\left(\int_0^T R(t)dt\right)^2 = 1. \end{aligned}$$

APPENDIX B: PROOF OF THEOREM 1 IN SEC. 2.3

Define $f(x) = \frac{TR_{\max}-d}{T-2x}\exp(\mu x) - R_{\max}$. We have $f(0) = -\frac{d}{T} < 0$ and $f(d/(2R_{\max})) = R_{\max}(\exp(\mu d/(2R_{\max})) - 1) > 0$. From the intermediate value theorem, it follows that there exists $\hat{T} \in (0, d/(2R_{\max}))$ with $f(\hat{T}) = 0$. Note that in the interval $(0, d/(2R_{\max}))$, the derivative $df(x)/dx$ is positive. Consequently, $df(x)/dx$ monotonically increases as a function of x and, as a result, the solution for $f(\hat{T}) = 0$ is unique. Then, from Eq. (17) it follows that

$$0 < k = \frac{d - 2\hat{T}R_{\max}}{T - 2\hat{T}} < R_{\max}. \tag{B1}$$

Note that $\tilde{R}$ in Eq. (14) satisfies the constraint $\int_0^T \tilde{R}dt = d$ because of Eq. (16). Let $R_1(t)$ be an arbitrary dose rate in the interval $(0,T)$ which satisfies the following conditions:

$\int_0^T R_1 dt = d$ and $0 \le \min(R_1(t)) \le \max(R_1(t)) \le R_{\max}$. Below, we will show that $G(R_1) > G(\tilde{R})$.

In order to simplify our derivations we will use $I(R_1) = d^2 G(R_1)/2$, where the dose per fraction d is fixed. Let $w = R_1 - \tilde{R}$. Then

$$I(R_1) = I(\tilde{R} + w) = I(\tilde{R}) + \int_0^T w(t) \int_0^t \tilde{R}(t') \times \exp(-\mu(t-t'))dt'dt + \int_0^T \tilde{R}(t) \int_0^t w(t') \times \exp(-\mu(t-t'))dt'dt + I(w). \quad \text{(B2)}$$

By using the equality

$$\int_0^T \tilde{R}(t) \int_0^t w(t') \exp(-\mu(t-t')dtdt' = \int_0^T w(t) \int_t^T \tilde{R}(t') \exp(\mu(t-t'))dt'dt. \quad \text{(B3)}$$

we can write (B2) as follows:

$$I(R_1) = I(\tilde{R}) + \int_0^T w(t) \int_0^T \tilde{R}(t') \exp(-\mu|t-t'|)dtdt' + I(w). \quad \text{(B4)}$$

Lemma. For an arbitrary, real function w which does not vanish almost everywhere and which is defined on the interval $[0, T]$, the following condition is satisfied:

$$I(w) \ge \mu \exp(-2\mu T) \int_0^T \left(\int_0^t w(t') \exp(\mu s) ds \right) dt > 0. \quad \text{(B5)}$$

Proof of lemma. Let us define $g(t) = \int_0^t w(s) \exp(\mu s) ds$. We have $g(0) = 0$ and $g'(t) = w(t) \exp(\mu t)$. Using integration by parts we obtain:

$$\begin{aligned} &\int_0^T w(t) \int_0^t w(t') \exp(-\mu(t-t'))dt'dt \\ &= \int_0^T w(t) \exp(-\mu t) \int_0^t w(t') \exp(\mu t')dt'dt \\ &= \int_0^T g'(t) \exp(-2\mu t) g(t) dt \\ &= \frac{1}{2} g^2(t) \exp(-2\mu t)|_{t=0}^{t=T} + \mu \int_0^T g^2(t) \exp(-2\mu t) dt \\ &\ge \mu \exp(-2\mu T) \int_0^T g^2(t) dt > 0. \end{aligned} \quad \text{(B6)}$$

Now we need to show that the second term on the right side of (B4) is non-negative. Define

$$v(t) = \int_0^T \tilde{R}(t') \exp(-\mu|t-t'|)dt'. \quad \text{(B7)}$$

An elementary but tedious integration yields:

$$v(t) = \begin{cases} \frac{2R_{\max}}{\mu} - \frac{R_{\max}}{\mu}[\exp(-\mu t) + \exp(\mu t - 2\mu\hat{T})], & 0 \le t < \hat{T} \\ \frac{2k}{\mu}, & \hat{T} \le t \le T - \hat{T} \\ \frac{2R_{\max}}{\mu} - \frac{R_{\max}}{\mu}[\exp(-\mu(T-t)) + \exp(\mu(T-t-2\hat{T}))], & T - \hat{T} < t \le T \end{cases} \quad \text{(B8)}$$

From Eq. (B8), it follows that $v(t) < 2k/\mu$ for $0 \le t < \hat{T} \cup T - \hat{T} < t \le T$. Note that since $\tilde{R}(t) = R_{\max}$ for $0 \le t < \hat{T} \cup T - \hat{T} < t \le T$ and $w = R_1 - \tilde{R}$, $w \le 0$ for $0 \le t < \hat{T} \cup T - \hat{T} < t \le T$. Also, since $\int_0^T R_1(t)dt = \int_0^T \tilde{R}(t)dt = d$, then $\int_0^T w(t)dt = 0$. Now we can estimate the double integral on the right side of (B4) as follows:

$$\begin{aligned} \int_0^T w(t)v(t)dt &= \int_0^{\hat{T}} w(t)v(t)dt + \int_{\hat{T}}^{T-\hat{T}} w(t)v(t)dt \\ &+ \int_{T-\hat{T}}^T w(t)v(t)dt \ge \int_0^{\hat{T}} w(t)\frac{2k}{\mu}dt \\ &+ \int_{\hat{T}}^{T-\hat{T}} w(t)\frac{2k}{\mu}dt + \int_{T-\hat{T}}^T w(t)\frac{2k}{\mu}dt \\ &= \frac{2k}{\mu}\int_0^T w(t)dt = 0. \end{aligned} \quad \text{(B9)}$$

This completes the proof that for any arbitrary R_1, we have $I(R_1) > I(\tilde{R})$. Consequently, for a given $R_{\max}$, the function $\tilde{R}$ in Eq. (14) provides the minimal value of the protraction factor $G = \frac{2}{d^2} I$.

APPENDIX C: PROOF OF EQ (22)

Using Eq. (A1), we can write

$$G = \frac{1}{d^2} \int_0^T \tilde{R}(t) \left[\int_0^T \tilde{R}(t') \times \exp(-\mu|t-t'|)dt' \right] dt. \quad \text{(C1)}$$

In the considered case $\mu\hat{T} << 1$, from Eqs. (B7) and (B8), it follows that the inner integral in Eq. (C1) equals $2k/\mu$. Because of the condition $\int_0^T \tilde{R}(t)dt = d$, we have

$$G = \frac{2k}{\mu d}. \quad \text{(C2)}$$

By substituting expression for k from Eq. (20) into Eq. (C2), one can easily show that the global minimum of protraction factor is given in Eq. (22).

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