Received: 14 June 2021 | Revised: 3 September 2021 | Accepted: 24 September 2021

DOI: 10.1002/mp.15267

TECHNICAL NOTE

MEDICAL PHYSICS

Technical Note: Break-even dose level for hypofractionated treatment schedules

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Funding information
ISREC Foundation, thanks to Biltema donation,; Fondation pour le soutien de la recherche et du développement de l'oncologie (FSRDO)

Abstract

Purpose: To derive the isodose line R relative to the prescription dose below which irradiated normal tissue (NT) regions benefit from a hypofractionated schedule with an isoeffective dose to the tumor. To apply the formalism to clinical case examples.

Methods: From the standard biologically effective dose (BED) equation based on the linear-quadratic (LQ) model, the BED of an NT that receives a relative proportion r of the prescribed dose per fraction for a given α/β-ratio of the tumor, $(\alpha/\beta)_T$, and NT, $(\alpha/\beta)_{NT}$, is derived for different treatment schedules while keeping the BED to the tumor constant. Based on this, the "break-even" isodose line R is then derived. The BED of NT regions that receive doses below R decreases for more hypofractionated treatment schedules, and hence a lower risk for NT injury is predicted in these regions. To assess the impact of a linear behavior of BED for high doses per fraction (>6 Gy), we evaluated BED also using the LQ-linear (LQ-L) model.

Results: The formalism provides the equations to derive the BED of an NT as function of dose per fraction for an isoeffective dose to the tumor and the corresponding break-even isodose line R. For generic α/β-ratios of $(\alpha/\beta)_T = 10$ Gy and $(\alpha/\beta)_{NT} = 3$ Gy and homogeneous dose in the target, R is 30%. R is doubling for stereotactic treatments for which tumor control correlates with the maximum dose of 100% instead of the encompassing isodose line of 50%. When using the LQ-L model, the notion of a break-even dose level R remains valid up to about 20 Gy per fraction for generic α/β-ratios and $D_T = 2(\alpha/\beta)$.

Conclusions: The formalism may be used to estimate below which relative isodose line R there will be a differential sparing of NT when increasing hypofractionation. More generally, it allows to assess changes of the therapeutic index for sets of isoeffective treatment schedules at different relative dose levels compared to a reference schedule in a compact manner.

KEYWORDS
BED, hypofractionation, isoeffect, LQ model, LQ-L model

1 | INTRODUCTION

Biologically effective dose (BED) and the related equivalent total dose in 2-Gy-fractions (EQD_2) are a well-established formalism with a widespread day-to-day clinical use for comparing different fractionation schemes in terms of their tumor control probability and expected normal tissue (NT) toxicities.[1–3]

Other prior studies have developed formalisms using BED that quantify the differential effect of NT at different relative dose levels r of the prescribed dose for matched isoeffective treatment schedules for the tumor.[4–9] The objective of this work is to give additional information about the effect of hypofractionation on NT using a compact mathematical formalism and graphical representation. It explores and illustrates the differential

effects of hypofractionated treatment schemes for tumors compared to NT at different relative dose levels r using clinical examples. Based on the BED formalism for the linear-quadratic (LQ) model, it derives for given α/β-ratios of tumor and NT, the relative isodose line r below which irradiated NT regions benefit from a hypofractionated schedule with an isoeffective dose to the tumor using the same relative dose distribution as the original treatment schedule. This relative dose level is referred to in the following as break-even dose level R. Furthermore, BED based on the LQ-linear (LQ-L) model[10] is evaluated using the same scheme to examine differences with respect to the BED formalism based on the LQ model for the high dose region ($\gtrsim$ 6 Gy per fraction), where the applicability of the LQ model is debated.[3, 10–15]

2 | MATERIALS AND METHODS

2.1 | Formalism

Using the LQ model, the BED of a given treatment schedule of n fractions with d dose per fraction is given by

$$\mathrm{BED}\ (n, d, \alpha/\beta) = n \cdot d \left(1 + \frac{d}{\alpha/\beta}\right), \qquad (1)$$

where α/β may be the α/β-ratio of the respective tumor ($(\alpha/\beta)_\mathrm{T}$) or NT ($(\alpha/\beta)_\mathrm{NT}$).[1,4–6,8]

For a given fractionated treatment planning schedule (n, d), the BED for an NT region (e.g., a voxel) with $(\alpha/\beta)_\mathrm{NT}$ that receives a dose per fraction $d_\mathrm{NT} = r \cdot d$ of the (prescribed) dose per fraction d is then given by:

$$\mathrm{BED}\left(n, d, r, \left(\frac{\alpha}{\beta}\right)_\mathrm{NT}\right) = n \cdot r \cdot d \left(1 + \frac{r \cdot d}{\left(\frac{\alpha}{\beta}\right)_\mathrm{NT}}\right), \qquad (2)$$

using the NT sparing factor r. For a given normofractionated treatment schedule with 2-Gy-fractions, one can derive a set S of hypofractionated treatment schedules with pairs of (n, d) with an isoeffect to the tumor (IET) of $(\alpha/\beta)_\mathrm{T}$, that is, a constant $\mathrm{BED}_{(\alpha/\beta)_\mathrm{T}}$, by inverting Equation 1. In the following, such a set is denoted as $S_{\mathrm{BED}_{(\alpha/\beta)_\mathrm{T}}} := \{(n_1,\ d_1), (n_2,\ d_2),\ \ldots\}$.

Clinical dose distributions are generally not homogeneous in the target. Consequently, IET may correlate better with a relative dose t that is different to the prescribed dose per fraction d, that is, IET may correlate with a dose $t \cdot d$ (with $t \neq 100\%$). This is specifically the case for stereotactic treatments. For instance, it was reported for stereotactic body radiotherapy (SBRT) of early stage non-small cell lung cancer (NSCLC) that using BED of isocentric maximum doses results in better local tumor control dose-response relationships than using the BED of the planning target volume (PTV) encompassing doses.[16] For such situations, sets of treatment schedules $S_{\mathrm{BED}_{(\alpha/\beta)_\mathrm{T}}}$ with a constant $\mathrm{BED}_{(\alpha/\beta)_\mathrm{T}}$ at relative dose level t can be obtained by evaluating:

$$\mathrm{BED}\left(n, d, t, \left(\frac{\alpha}{\beta}\right)_\mathrm{T}\right) = n \cdot t \cdot d \left(1 + \frac{t \cdot d}{(\alpha/\beta)_\mathrm{T}}\right). \qquad (3)$$

By solving Equation 3 for n and substituting it in Equation 2, one obtains

$$\mathrm{BED}^{\mathrm{IET}}_{(\alpha/\beta)_\mathrm{NT}} \equiv \mathrm{BED}\left(d, t, r, \mathrm{BED}_{(\alpha/\beta)_\mathrm{T}}, \left(\frac{\alpha}{\beta}\right)_\mathrm{NT}, \left(\frac{\alpha}{\beta}\right)_\mathrm{T}\right) = \mathrm{BED}_{(\alpha/\beta)_\mathrm{T}} \cdot \frac{r}{t} \cdot \frac{1 + \frac{r \cdot d}{(\alpha/\beta)_\mathrm{NT}}}{1 + \frac{t \cdot d}{(\alpha/\beta)_\mathrm{T}}}. \qquad (4)$$

$\mathrm{BED}^{\mathrm{IET}}_{(\alpha/\beta)_\mathrm{NT}}$ can be divided by the $\mathrm{BED}^{\mathrm{IET}}_{(\alpha/\beta)_\mathrm{NT}}$ of a respective reference treatment schedule with the same $\mathrm{BED}_{(\alpha/\beta)_\mathrm{T}}$ (i.e., usually a normofractionated treatment schedule using the same parameters, except that d = 2 Gy) to be independent of the prescribed $\mathrm{BED}_{(\alpha/\beta)_\mathrm{T}}$. This is referred to in the following as the "normalized $\mathrm{BED}^{\mathrm{IET}}_{(\alpha/\beta)_\mathrm{NT}}$" and represents the therapeutic gain (<1) or loss (>1) factor compared to a reference treatment[17] for the NT region receiving a relative dose r.

From differentiation of Equation 4, it follows that one can derive the relative dose level R (i.e., a relative isodose line) below which NT benefit from a more hypofractionated schedule to be[4–6,8]

$$R \equiv R\left(\left(\frac{\alpha}{\beta}\right)_\mathrm{T}, \left(\frac{\alpha}{\beta}\right)_\mathrm{NT}, t\right) = t \frac{\left(\frac{\alpha}{\beta}\right)_\mathrm{NT}}{\left(\frac{\alpha}{\beta}\right)_\mathrm{T}}. \qquad (5)$$

The derivative of Equation 4 with respect to d is monotonically increasing for $r > R$ and is monotonically decreasing for $r < R$. Note that R, is independent of both $\mathrm{BED}_{(\alpha/\beta)_\mathrm{T}}$ and d and that normalized $\mathrm{BED}^{\mathrm{IET}}_{(\alpha/\beta)_\mathrm{NT}}$ is equal to one for R.

2.2 | Example applications

Example 1: Late-reacting NTs are commonly approximated by $(\alpha/\beta)_\mathrm{NT}$ = 3 Gy, and tumors are typically approximated by $(\alpha/\beta)_\mathrm{T}$ = 10 Gy.[1,3,17] This is referred to in the following as "generic α/β-values." For a homogenous dose distribution in the target, IET can be assumed to correlate with prescribed dose per fraction d, that is, t = 100%.

Example 2: Henderson et al.[18] use α/β-values of 2.45 Gy for chordoma and 2.2 Gy for surrounding central nervous system (CNS) and peripheral nerve tissues for CyberKnife treatments of 5×8 Gy and compare them to normofractionated treatments. We evaluated and visualized $\text{BED}^{\text{IET}}_{(\alpha/\beta)_{\text{NT}}}$ and normalized $\text{BED}^{\text{IET}}_{(\alpha/\beta)_{\text{NT}}}$ for the LQ using the generic α/β-values and the α/β-values from the clinical example from Henderson et al. IET is assumed to correlate with prescribed dose per fraction d, that is, $t = 100\%$.

Example 3: For heterogeneous dose distributions of stereotactic treatments, often the encompassing prescription isodose line is used to determine isoeffective treatment schedules with the BED formalism.[18] Instead, as already mentioned, it was found for instance for stage I NSCLC treated with SBRT that dose-response and local control correlates better with the maximum dose $d_{\max}$ than with the PTV encompassing isodose when comparing different treatment schedules using BED.[16] Assuming a relative dose distribution with a target encompassing isodose line of 50% and a maximum dose of 100%, to illustrate a rather large dosimetric heterogeneity in the target of a factor of two, two sets of isoeffective treatment schedules for the tumor can be constructed assuming that IET correlates either with the target encompassing 50% isodose line ($t = 50\%$) or the maximum dose of 100% ($t = 100\%$). Using $(\alpha/\beta)_{\text{T}} = 10$ Gy and the same normofractionated treatment schedule as reference, for which 2 Gy corresponds to the 50% encompassing isodose line for both sets, it follows that two sets of isoeffective treatment schedules for the tumor can be constructed using Equation 4 with $t = 50\%$ and $t = 100\%$ respectively, that is: $S^{50\%}$ and $S^{100\%}$.

2.3 | Comparison with LQ-L model for high doses

The LQ model was shown to have shortcomings in predicting responses for large doses per fraction ($\gtrsim$ 6 Gy).[3,10,12,19] Some experimental data suggest a transition from a quadratic to a linear behavior at such high doses, and several models introducing this behavior have been proposed to describe high dose data more accurately.[10,19,20] The LQ-L model is one of these models that has the advantage of maintaining a relatively simple functional form.[10] For the LQ-L model, BED is given by[10]

$$\text{BED}\ (n, d, \alpha/\beta,\ D_{\text{T}},\ \gamma/\alpha) = \begin{cases} n \cdot d\ \left(1 + \frac{d}{\alpha/\beta}\right) & \text{for } d \le D_{\text{T}} \\ n\left[D_{\text{T}}\ \left(1 + \frac{D_{\text{T}}}{\alpha/\beta}\right) + \frac{\gamma}{\alpha}(d - D_{\text{T}})\right] & \text{for } d > D_{\text{T}} \end{cases} \quad (6)$$

where D_{T} is the threshold parameter for the onset of the linear behavior at high doses, and γ determines the slope in this region ($\log_e$ cell kill per Gy). To evaluate the effect of a transition to a linear behavior, we use this formula to compute $\text{BED}^{\text{IET}}_{(\alpha/\beta)_{\text{NT}}}$ analogous to Equation 4. For this purpose, we required a continuous derivative at D_{T}, implying that $\gamma/\alpha = 1 + (2D_{\text{T}}/(\alpha/\beta))$, and approximated D_{T} by $2(\alpha/\beta)$, as suggested by Astrahan,[10] thereby reducing the number of tissue-dependent parameters in Equation 6 from three to one, that is, α/β.

We evaluated differences between LQ and LQ-L model predictions of normalized $\text{BED}^{\text{IET}}_3$ for generic α/β-values.

3 | RESULTS

3.1 | Example applications

Example 1: Two sets of treatment schedules $S_{72\ \text{Gy}_{10}}$ and $S_{93.6\ \text{Gy}_{10}}$ (both $t = 100\%$) with iso-BED to the tumor with $(\alpha/\beta)_{\text{T}} = 10$ Gy of 72 Gy_{10} (30×2 Gy) and 93.6 Gy_{10} (39×2 Gy), respectively, are shown in Figure 1 (left) as dose per fraction d versus number of fractions n. Values of $\text{BED}^{\text{IET}}_3$ using the LQ model (Equation 4) are shown in Figure 1 (right) for the same treatment schedules as a function of d for different r with $(\alpha/\beta)_{\text{T}} = 10$ Gy and $(\alpha/\beta)_{\text{NT}} = 3$ Gy. Corresponding example BED calculations for a normofractionated reference treatment schedule and a hypofractionated treatment schedule are provided in the supplementary material file. As expected, $\text{BED}^{\text{IET}}_3$ is constant for $r = R = 30\%$ (Equation 5). For $r > R$, $\text{BED}^{\text{IET}}_{(\alpha/\beta)_{\text{NT}}}$ is monotonically increasing when shifting to hypofractionated schedules with larger d and lower n. Instead, for $r < R$, $\text{BED}^{\text{IET}}_3$ is monotonically decreasing. Hence, when shifting to a hypofractionated schedule, there is a lower risk for NT injury in NT regions below the 30% isodose line, while there is a higher risk for NT injury for NT regions above this isodose line. Normalized $\text{BED}^{\text{IET}}_3$ that quantifies changes in the therapeutic index relative to a normofractionated treatment is shown for the same generic α/β-values in Figure 2 (left) as a function of dose per fraction for the two different prescribed $\text{BED}_{(\alpha/\beta)_{\text{T}}}$. Integer fraction numbers n for the two prescribed $\text{BED}_{(\alpha/\beta)_{\text{T}}}$ are indicated by markers. Figure 2 (left) illustrates that for normalized $\text{BED}^{\text{IET}}_{(\alpha/\beta)_{\text{NT}}}$, there is no dependence on the chosen $\text{BED}_{(\alpha/\beta)_{\text{T}}}$ and number of fractions, and that dose per fraction d is the only remaining parameter defining the treatment schedule.

Example 2: Using α/β-values from Henderson et al.[18] ($(\alpha/\beta)_{\text{T}} = 2.45$ Gy, $(\alpha/\beta)_{\text{NT}} = 2.2$ Gy) with the LQ model and $t = 100\%$, results in a break-even isodose R of 90%, implying that all NT regions with $(\alpha/\beta)_{\text{NT}} \ge 2.2$ Gy that receive a total dose below 36 Gy are additionally spared

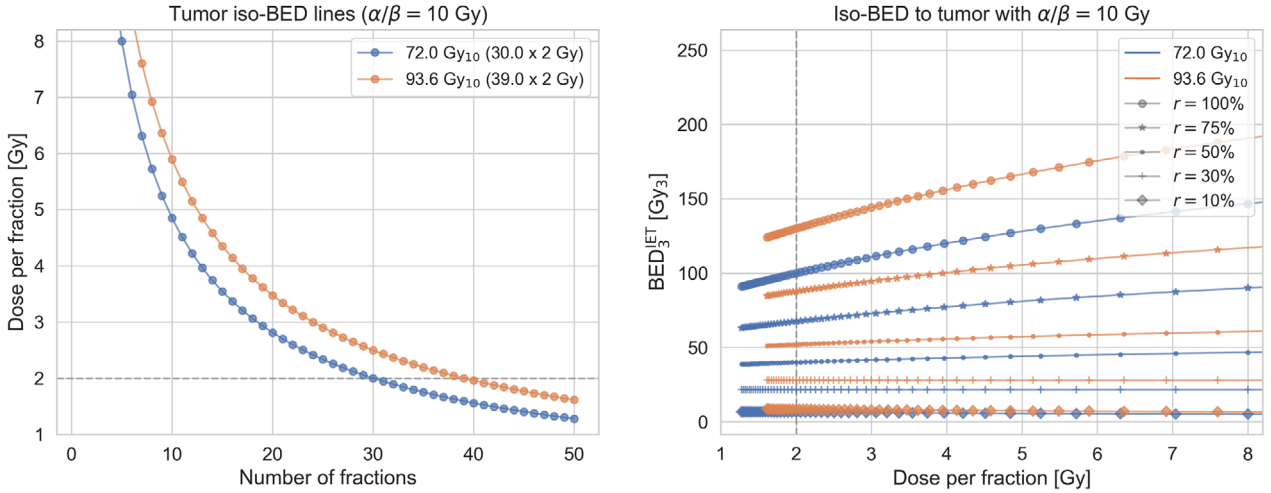

FIGURE 1 Left: Dose per fraction d versus number of fractions n for two sets of treatment schedules (n, d) with iso-BED to tumor: $S_{72\ Gy_{10}}$ and $S_{93.6\ Gy_{10}}$. Right: BED_3^{IET} for $S_{72Gy_{10}}$ and $S_{93.6\ Gy_{10}}$ as a function of d for five normal tissue (NT) sparing factors r. In this example, BED_3^{IET} decreases as dose per fraction increases for NT regions where $r < (\alpha/\beta)_{NT}/(\alpha/\beta)_T = 30\%$ (see text for more details). Markers indicate integer fraction numbers. Normofractionated treatments with $d = 2$ Gy are indicated by a grey dashed line here and in the following figures.

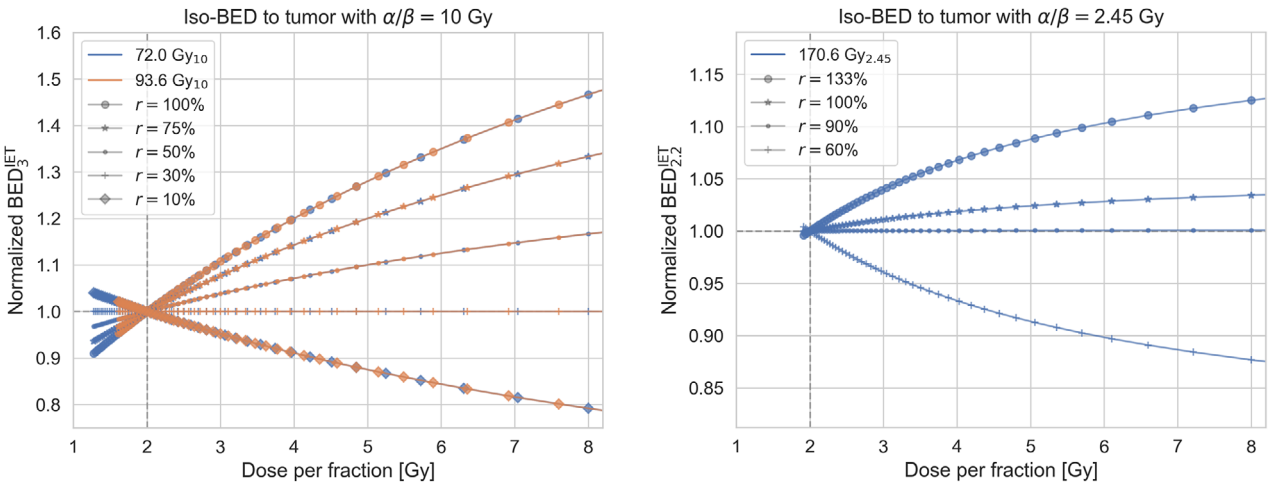

FIGURE 2 Left: Normalized BED_3^{IET} for two sets of treatment schedules: $S_{72Gy_{10}}$ and $S_{93.6Gy_{10}}$ as a function of dose per fraction d for five NT sparing factors r and generic α/β-values. Markers indicate integer fraction numbers. Right: Same as in the left panel, but illustrating the clinical case from Henderson et al.[18] with $S_{170.6\ Gy_{2.45}}$ (5×8 Gy) and α/β-values of 2.45 Gy (chordoma) and 2.2 Gy (CNS and nerves). In these examples, normalized BED_3^{IET} and normalized $BED_{2.2}^{IET}$ decrease as dose per fraction increases for NT regions where $r < (\alpha/\beta)_{NT}/(\alpha/\beta)_T$ (see text for more details).

by hypofractionation when administering 5×8 Gy. On the other side, it implies that NT regions receiving higher doses are less spared compared to a normofractionated treatment. Henderson et al. estimate for their treatment plans that $r = 60\%$ for the spinal cord at most. Using Equation 4, this results in a normalized $BED_{2.2}^{IET}$ of 0.88. Since the normalized $BED_{2.2}^{IET}$ is below one, this indicates a decreased risk for spinal cord injury and hence an improved therapeutic index compared to a normofractionated treatment. Using α/β-values of 2.45 Gy and 2.2 Gy, Figure 2 (right) visualizes normalized $BED_{2.2}^{IET}$ as a function of d for different r of interest.

Example 3: Normalized BED_3^{IET} for generic α/β-values is displayed in Figure 3 (left) as a function of dose per fraction at the encompassing isodose line of 50% for both $S^{50\%}$ ($t = 50\%$) and $S^{100\%}$ ($t = 100\%$). Note that 100% represents the maximum dose per fraction d_{max}, that r and t are specified relative to d_{max} for both sets of treatment schedules, and that NT receive usually doses of $r < 50\%$, as they are mostly located outside the target encompassing isodose line of 50% of d_{max}. Figure 3 (left) illustrates that when IET correlates with the maximum dose d_{max} ($t = 100\%$), the normalized BED_3^{IET} for a given r decreases substantially for hypofractionated

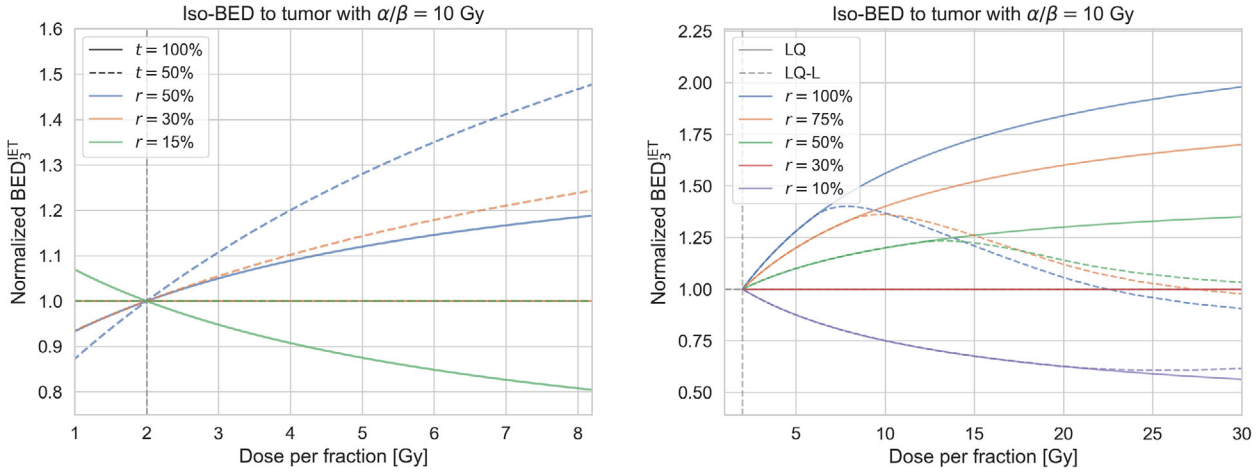

FIGURE 3 Left: Normalized BED_3^{IET} for two sets of treatment schedules: $S^{50\%}(t = 50\%)$ and $S^{100\%}$ $(t = 100\%)$ as a function of dose per fraction at the encompassing isodose line of 50% for three normal tissue (NT) sparing factors r and generic α/β-values. Note that r and t are specified relative to the maximum dose per fraction d_{max}. Right: Normalized BED_3^{IET} as a function of dose per fraction for doses up to 30 Gy as predicted by the linear-quadratic (LQ) and the LQ-linear (LQ-L) model for five NT sparing factors r and generic α/β-values.

treatments compared to a scenario where the IET correlates with the encompassing isodose line ($t = 50\%$). As a consequence, also the break-even dose R (Equation 5) increases from 15% to 30%. Corresponding example BED calculations for a normofractionated reference treatment schedule and a hypofractionated treatment schedule are provided in the supplementary material file.

3.2 | Comparison with LQ-L model for high doses

A comparison of normalized BED_3^{IET} $(t = 100\%)$ as predicted by the LQ and the LQ-L model for generic α/β-values is shown in Figure 3 (right) for five NT sparing factors and for doses per fraction up to 30 Gy.

4 | DISCUSSION AND CONCLUSIONS

Steep dose gradients achieved by modern intensity modulated and stereotactic radiation therapy facilitate conformal treatments that, by sparing NT in the vicinity of the target effectively, allow delivering hypofractionated treatment schedules. From the perspective of the presented formalism, such steep dose gradients help to minimize NT volumes that are irradiated with doses larger than R, thereby minimizing NT volumes near the tumor that are "punished" by a hypofractionated treatment. An additional sparing of all NT regions receiving doses smaller than R may then be an incentive to shift toward a more hypofractionated treatment schedule. It can be understood as the inverse of the effect present for hot spots in hypofractionated treatments that was termed "treble trouble" effect.[21]

For the generic α/β-values and a homogeneous dose in target (Example 1, $t = 100\%$), R is 30% and therefore clinically mostly of little relevance, as dose limiting toxicities are usually encountered in higher dose regions. However, for cases where $(\alpha/\beta)_T$ and $(\alpha/\beta)_{NT}$ of critical NT endpoints are more similar, such as the case from Henderson et al.[18] (Example 2), and for cases where local control correlates with a higher isodose line of a non-homogenous dose in the target, such as d_{max} (e.g., Example 3, Figure 3 [left] with $t = 100\%$), additional NT protection for isodose levels below R may be a quantified incentive to shift to a more hypofractionated treatment schedule. Furthermore, the normalized $BED_{(\alpha/\beta)_{NT}}^{IET}$ factor provides a metric of the relative change of the therapeutic index of hypofractionated schedules, compared to a normofractionated treatment. By using an r value of 100% and larger, it provides also information about the magnitude of the "treble trouble" effect.

Different authors have used prior to this approaches similar or equivalent to the one presented here to derive a break-even dose level R. In the context of high dose rate (HDR) and low dose rate (LDR) brachytherapy regimens of the cervix, Brenner and Hall[8] obtained an equivalent relation for R for different HDR and LDR treatments regimens. A similar methodology for HDR and LDR brachytherapy was also followed by Dale.[22] Furthermore, several authors have derived similar or equivalent relations for R to optimize fractionation schemes of external beam radiotherapy.[4–9] Compared to these studies, this work proposes with normalized $BED_{(\alpha/\beta)_{NT}}^{IET}$ a quantification of the therapeutic gain with respect to a normofractionated treatment using a relatively compact formula and graphical representation that depend only on dose per fraction d, but have no further dependencies on other parameters of the prescribed treatment

schedule (number of fractions, total dose, tumor BED). This may be useful for theoretically evaluating different treatment options or even different planning strategies for a given patient.

Results presented in this work are valid within the range of applicability of the BED formalism using the LQ and the LQ-L model.[1,3,10,17] Repopulation effects have been ignored. However, if tumor repopulation effects need to be accounted for in a given clinical scenario, this would result in an additional incentive to shift to a hypofractionated treatment scheme[23–26] and would not counteract the rationale presented here. Some have argued that the LQ model is experimentally and theoretically reasonably well validated up to about 10 Gy/fraction and is reasonable to use up to about 18 Gy/fraction,[11,13,16] while others disagree with that view.[10,12] In the comparison between LQ and LQ-L model shown in Figure 3 (left), one can observe, as expected, differences in model predictions due to a linear behavior for doses to the NT that are higher than the threshold D_T used for NT, that is, where $r \cdot d > 2 \cdot 3$ Gy. Instead, the onset of a linear response behavior for the tumor at high doses is less relevant for the shown dose range, as it occurs only for dose per fractions above $2 \cdot 10$ Gy. For high doses per fraction and relative dose levels $r > R$, the LQ-L model predicts a decrease of the normalized BED_3^{IET} (i.e., an improvement of the therapeutic index), contrary to the LQ model. For doses per fraction above 20 Gy, the LQ-L model predicts that the normalized BED_3^{IET} for $r = 100\%$ drops even below one, indicating an improved therapeutic index for strongly hypofractionated treatments compared to a normofractionated treatment. This is caused by the much earlier onset of the linear behavior at high doses for NT compared to the tumor, as assumed in this example, and represents an incentive for strong hypofractionation if these conditions apply. This behavior has been previously observed by Astrahan and is discussed in more detail elsewhere.[10] Figure 3 (right) also indicates that for this case and r up to 100%, the concept of a break-even dose level R remains valid up to doses of about 20 Gy, even when assuming a linear behavior at high doses. However, not only quantitative predictions of the LQ model but also those of the LQ-L model should be interpreted with caution at high doses, and adequate high dose model parameters (D_T and γ/α) are not well established and validated for clinical cases.[10] More generally, isoeffect curves for large fraction doses (>10 Gy) and underlying mechanisms are not yet well modelled.[12] Tumor reoxygenation and heterogeneous radiosensitivities are other potentially influential effects that need dedicated consideration.[26–29]

Another limitation of the presented calculations is that dose distributions encountered in the clinics are heterogeneous, and that no volume effects were considered. Equation 4 allows the computation for cases where isoeffect curves for the tumor can be associated with a certain relative isodose line t, which is not equal to the prescription dose. Using a single dose point for the computation of BED in an organ-at-risk (OAR), as in Equation 4, to assess NT complication probabilities is in principle only valid for serial organs that are only sensitive to the maximum dose to the OAR. More considerate approaches[4–7,30–32] can be used to construct sets of isoeffective treatment schedules and to model tissue responses more accurately, but augment the complexity of the necessary formalism and do not change the principal behaviors discussed here. In that respect, it should also be underlined that BED isoeffect curves using the LQ model with single dose levels, including all its shortcomings, remain the standard method of choice used in clinics to compare different fraction schedules and lead to clinically acceptable results.[1,3,15,17]

In summary, for a given dose distribution and doses where the LQ model applies, NT regions below the relative isodose line $R = (\alpha/\beta)_{NT}/(\alpha/\beta)_T$ (Equation 5, assuming $t = 100\%$) are additionally spared when shifting toward a more hypofractionated treatment schedule. This may serve as a corollary to the BED formalism. More generally, for two treatment schedules that are isoeffective to the tumor, differences in BED doses for NT at a given relative dose level r can be obtained from Equation 4.

ACKOWLEDGMENTS

This research has been partially funded by ISREC Foundation, thanks to Biltema donation, and by Fondation pour le soutien de la recherche et du développement de l'oncologie (FSRDO).

FUNDING INFORMATION

ISREC Foundation; Fondation pour le soutien de la recherche et du développement de l'oncologie (FSRDO)

CONFLICT OF INTEREST

The authors have no conflicts to disclose.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

REFERENCES

1. Fowler JF. 21 years of biologically effective dose. *Br J Radiol*. 2010;83(991):554-568.
2. Jones B, Dale RG, Deehan C, Hopkins KI, Morgan DAL. The role of biologically effective dose (BED) in clinical oncology. *Clin Oncol*. 2001;13(2):71-81.
3. Hall EJ, Giaccia AJ. *Radiobiology for the Radiologist*. 8th ed. Wolters Kluwer; 2019.
4. Mizuta M, Takao S, Date H, et al. A mathematical study to select fractionation regimen based on physical dose distribution

and the linear–quadratic model. *Int J Radiat Oncol*. 2012;84(3): 829-833.
5. Keller H, Hope A, Meier G, Davison M. A novel dose-volume metric for optimizing therapeutic ratio through fractionation: retrospective analysis of lung cancer treatments: optimal dose fractionation. *Med Phys*. 2013;40(8):084101.
6. Unkelbach J, Craft D, Salari E, Ramakrishnan J, Bortfeld T. The dependence of optimal fractionation schemes on the spatial dose distribution. *Phys Med Biol*. 2013;58(1):159-167.
7. Vogelius IS, Westerly DC, Cannon GM, Bentzen SM. Hypofractionation does not increase radiation pneumonitis risk with modern conformal radiation delivery techniques. *Acta Oncol*. 2010;49(7):1052-1057.
8. Brenner DJ, Hall EJ. Fractionated high dose rate *versus* low dose rate regimens for intracavitary brachytherapy of the cervix. I. General considerations based on radiobiology. *Br J Radiol*. 1991;64(758):133-141.
9. Gay HA, Jin J-Y, Chang AJ, Ten Haken RK. Utility of normal tissue-to-tumor α/β ratio when evaluating isodoses of isoeffective radiation therapy treatment plans. *Int J Radiat Oncol Biol Phys*. 2013;85:(1):e81–e87.
10. Astrahan M. Some implications of linear-quadratic-linear radiation dose-response with regard to hypofractionation. *Med Phys*. 2008;35(9):4161-4172.
11. Brenner DJ. The linear-quadratic model is an appropriate methodology for determining isoeffective doses at large doses per fraction. *Semin Radiat Oncol*. 2008;18(4):234-239.
12. Song CW, Glatstein E, Marks LB, et al. Biological principles of stereotactic body radiation therapy (SBRT) and stereotactic radiation surgery (SRS): indirect cell death. *Int J Radiat Oncol Biol Phys*. 2019;110(1):21-34.
13. Brown JM, Brenner DJ, Carlson DJ. Dose escalation, not "new biology," can account for the efficacy of stereotactic body radiation therapy with non-small cell lung cancer. *Int J Radiat Oncol Biol Phys*. 2013;85(5):1159-1160.
14. Song CW, Terezakis S, Emami B, et al. Indirect cell death and the LQ model in SBRT and SRS. *J Radiosurgery SBRT*. 2020;7(1): 1-4.
15. Grimm J, Mahadevan A, Brown JM, et al. In reply to Song et al, and in reply to Brown and Carlson. *Int J Radiat Oncol Biol Phys*. 2021;110(1):253-254.
16. Guckenberger M, Klement RJ, Allgäuer M, et al. Applicability of the linear-quadratic formalism for modeling local tumor control probability in high dose per fraction stereotactic body radiotherapy for early stage non-small cell lung cancer. *Radiother Oncol*. 2013;109(1):13-20.
17. Joiner M, van der Kogel A. *Basic Clinical Radiobiology*. 4th ed. Hodder Arnold; 2009.
18. Henderson FC, McCool K, Seigle J, Jean W, Harter W, Gagnon GJ. Treatment of chordomas with cyberknife. *Neurosurg*. 2009;64(suppl_2):A44-A53.
19. Andisheh B, Edgren M, Belkić D, Mavroidis P, Brahme A, Lind BK. A comparative analysis of radiobiological models for cell surviving fractions at high doses. *Technol Cancer Res Treat*. 2013;12(2):183-192.
20. McKenna FW, Ahmad S. Fitting techniques of cell survival curves in high-dose region for use in stereotactic body radiation therapy. *Phys Med Biol*. 2009;54(6):1593-1608.
21. Jones B, Dale RG, Finst P, Khaksar SJ. Biological equivalent dose assessment of the consequences of hypofractionated radiotherapy. *Int J Radiat Oncol Biol Phys*. 2000;47(5):1379-1384.
22. Dale RG. The use of small fraction numbers in high dose-rate gynaecological afterloading: some radiobiological considerations. *Br J Radiol*. 1990;63(748):290-294.
23. Saberian F, Ghate A, Kim M. Optimal fractionation in radiotherapy with multiple normal tissues. *Math Med Biol*. 2016;33(2):211-252.
24. Bortfeld T, Ramakrishnan J, Tsitsiklis JN, Unkelbach J. Optimization of radiation therapy fractionation schedules in the presence of tumor repopulation. *Inf J Comput*. 2015;27(4):788-803.
25. Sugano Y, Mizuta M, Takao S, Shirato H, Sutherland KL, Date H. Optimization of the fractionated irradiation scheme considering physical doses to tumor and organ at risk based on dose–volume histograms. *Med Phys*. 2015;42(11):6203-6210.
26. Yang Y, Xing L. Optimization of radiotherapy dose-time fractionation with consideration of tumor specific biology. *Med Phys*. 2005;32(12):3666-3677.
27. Kuperman VY, Lubich LM. Effect of reoxygenation on hypofractionated radiotherapy of prostate cancer. *Med Phys*. 2020; 47(10): 5383-5391.
28. Kuperman VY. Effect of heterogeneous radiosensitivity on the optimal fractionation in radiotherapy. *Phys Med*. 2019;67:185-191.
29. Badri H, Watanabe Y, Leder K. Optimal radiotherapy dose schedules under parametric uncertainty. *Phys Med Biol*. 2016;61(1):338-364.
30. Jones LC, Hoban PW. Treatment plan comparison using equivalent uniform biologically effective dose (EUBED). *Phys Med Biol*. 2000;45(1):159-170.
31. Zhang Q, Tian S, Borasi G. A new definition of biological effective dose: the dose distribution effects. *Phys Medica*. 2015;31(8):1060-1064.
32. Jin J-Y, Kong F-M, Chetty IJ, et al. Impact of fraction size on lung radiation toxicity: hypofractionation may be beneficial in dose escalation of radiotherapy for lung cancers. *Int J Radiat Oncol*. 2010;76(3):782-788.

SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

How to cite this article: Böhlen TT, Germond J-F, Bourhis J, et al. Break-even dose level for hypofractionated treatment schedules. *Med Phys*. 2021;48:7534–7540.
https://doi.org/10.1002/mp.15267