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# Effect of heterogeneous radiosensitivity on the optimal fractionation in radiotherapy

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ABSTRACT

*Purpose:* to determine optimal fractionation schedule which provides maximum biologically effective dose (*BED*) in the targeted tumor in the case of heterogeneous radiosensitivity of malignant cells in combination with a spatially varying sparing factor for the organ at risk.

*Methods:* the mathematical framework used in the current study is based on the linear-quadratic (LQ) model with heterogeneous parameters alpha and beta for malignant cells. To determine optimal fractionation, we consider changes in *BED* in the treatment target ($BED_{tar}$) under the condition of fixed *BED* in the affected normal tissue ($BED_{nt}$).

*Results:* we demonstrate both analytically and via numerical calculations that there exists an optimal number of fractions for which biologically effective dose in the uniformly irradiated target is at maximum. It is also shown that dependence of $BED_{tar}$ on number of fractions is generally non-monotonic and is affected by the variances $\sigma_\alpha$ and $\sigma_\beta$ of the alpha and beta radiosensitivities, respectively. In a particular case when $\sigma_\alpha$ and $\sigma_\beta$ are sufficiently small, expression for the optimal target dose which maximizes $BED_{tar}$ was derived analytically.

*Conclusion:* the obtained results demonstrate that in the presence of heterogeneous alpha and beta in the tumor, hypofractionation can either increase or decrease $BED_{tar}$ depending on the variances $\sigma_\alpha$ and $\sigma_\beta$. Consequently, intratumor heterogeneity is an important factor which can affect radiobiological comparison of different fractionation regimens.

## 1. Introduction

In clinical practice, the majority of radiation treatments are performed by using fractionation; i.e., the course of radiotherapy is typically divided into 20–40 fractions delivered over a period of 4–8 weeks. Use of fractionation allows for repair of sublethal damage between fractions which is particularly important for normal tissue [1]. Recent wide adaptation of stereotactic body radiation therapy (e.g., see Refs. [2–4]) has stimulated a number of studies focused on radiobiology of treatments with fewer fractions than standard fractionation (i.e., 1.8–2 Gy per fraction), known as *hypofractionated* regimens. In particular, several investigations [5–7] have described conditions under which hypofractionation can reduce $BED_{nt}$ in the affected organ at risk (OAR) as compared to $BED_{nt}$ achieved with standard fractionation. These results are clinically important because they can help select the optimal fractionation scheme in radiotherapy.

### 1.1. Previous studies

For the purpose of our discussion, it is important to review main conclusions from earlier investigations [5–7]. Suppose that malignant cells in the targeted tumor and normal cells in the OAR have the alpha/beta ratios $(\alpha/\beta)_{tar}$ and $(\alpha/\beta)_{nt}$, respectively. By using the linear-quadratic (LQ) model [8], it was theoretically shown that for a given target dose $D_{tar}$ and maximum dose $D_{\max,nt}$ in the affected, serial organ at risk (e.g., spinal cord), $BED_{nt}$ decreases with decreasing number of fractions if and only if $\frac{D_{\max,nt}}{D_{tar}} < \frac{(\alpha/\beta)_{nt}}{(\alpha/\beta)_{tar}}$ [5–7]. This result clearly indicates that in the absence of tumor cell repopulation the optimal fractionation schedule includes either a single treatment with a large dose or a number of fractions with much smaller dose per fraction. Note that the latter treatment approach is known as *hyperfractionation*.

A limitation of the previous studies [5–7] was the assumption of homogeneous alpha and beta in the tumor. As it was emphasized in several studies, a more accurate model should take into account intratumor heterogeneity in $\alpha$ and $\beta$ [9–11]. In particular, Shultheiss et al [9] and Hawkins [11] listed several mechanisms which can cause greater heterogeneity on the cellular level in malignant tumors as compared to that in normal tissue. These mechanisms include temporal and spatial variations in tumor blood supply which result in existence of acutely or chronically hypoxic cells [12,13]. Another effect which can

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cause intratumor heterogeneity is rapid transitions between different phases of cell cycle in malignant cells [11]. A recent comparison of the LQ model with heterogeneous alpha and beta and several other models with uniform radiosensitivities clearly demonstrated that the former model provided a better fit to the studied tumor control data for almost 3000 patients [10].

### 1.2. Current work

In this investigation we expand the mathematical framework based on the LQ model [5–7] to incorporate intratumor heterogeneity in radiosensitivity. Our main objective is to determine optimal fractionation regimen characterized by the maximum $BED_{tar}$ in the treatment target under the condition of fixed $BED_{nt}$ in the affected OAR. Other important effects elucidated in a recent review [14] (including tumor hypoxia, repair of sublethal damage, repopulation and re-oxygenation) which can affect $BED_{tar}$ achieved with standard fractionation or hypofractionated regimens, are beyond the scope of this study.

Mathematical description and properties of the utilized LQ model with uncorrelated variations in alpha and beta [15] are discussed in Section II. Numerically calculated BEDs in the target for different values of radiobiological and dosimetric parameters are included in Section III. Discussion of the obtained results and conclusions of this work are contained in Sections IV and V, respectively.

## 2. Methods

### 2.1. Distribution of radiosensitivities in the target

In the considered model, probability of cell survival $S$ is described by the well-known LQ equation [8]

$$S = \exp(-\alpha N_f d - \beta N_f d^2), \tag{1}$$

where $N_f$ and $d$ denote number of fractions and dose per fraction, respectively. For malignant cells, we assume that variations in alpha and beta are described by the truncated Gaussian probability distribution function (*pdf*) [16]

$$f(\alpha, \beta) = \begin{cases} \dfrac{\exp\left(-\frac{(\alpha-\lambda)^2}{2a^2} - \frac{(\beta-\mu)^2}{2b^2}\right)}{2\pi ab\Phi\left(\frac{\lambda}{a}\right)\Phi\left(\frac{\mu}{b}\right)}, & \text{if } \alpha \text{ and } \beta > 0 \\ 0, & \text{if } \alpha \leqslant 0 \text{ and/or } \beta \leqslant 0 \end{cases} \tag{2}$$

where $\Phi(t) = \frac{1}{\sqrt{2\pi}}\int_{-\infty}^{t} e^{-\frac{x^2}{2}}dx$ is known as the *cumulative* probability distribution function; $a$, $b$, $\lambda$ and $\mu$ are positive parameters which define first and second moments for either alpha or beta distributions. For example, mean value ($\bar{\alpha}$) and second moment ($\bar{\alpha^2}$) of the alpha distribution are

$$\bar{\alpha} = \lambda + \frac{ae^{-\frac{\lambda^2}{2a^2}}}{\Phi\left(\frac{\lambda}{a}\right)\sqrt{2\pi}} \quad \text{and} \quad \bar{\alpha^2} = \lambda^2 + a^2 + \frac{a\lambda e^{-\frac{\lambda^2}{2a^2}}}{\Phi\left(\frac{\lambda}{a}\right)\sqrt{2\pi}}. \tag{3}$$

To analytically determine optimal target dose which maximizes *BED* in the target (see Section 2.5), we found it more convenient to use variances

$$\sigma_\alpha^2 = \bar{\alpha^2} - \bar{\alpha}^2 \quad \text{and} \quad \sigma_\beta^2 = \bar{\beta^2} - \bar{\beta}^2. \tag{4}$$

instead of the corresponding second moments of the probability distributions of alpha and beta.

The relationships between $\bar{\alpha}$, $\sigma_\alpha$ and parameters $\lambda$ and $a$ described in Eqs. (3) and (4) are shown in Fig. 1a. Similar relationships (not listed here for brevity) exist between $\bar{\beta}$, $\sigma_\beta$ and parameters $\mu$ and $b$.

### 2.2. Average probability of survival and tumor control

In the considered case of heterogeneous alpha and beta, the average probability of cell survival $\bar{S}$ is given by

$$\bar{S} \equiv \int_0^\infty \int_0^\infty S(\alpha, \beta) f(\alpha, \beta) d\alpha d\beta. \tag{5}$$

By substituting expression for $S(\alpha, \beta)$ from Eq. (1) into Eq. (5) and integrating over alpha and beta, we obtain

$$\bar{S} = e^{-\lambda D - \mu d D + \frac{a^2 D^2}{2} + \frac{b^2 d^2 D^2}{2}} \frac{\Phi\left(\frac{\lambda}{a} - aD\right)}{\Phi\left(\frac{\lambda}{a}\right)} \frac{\Phi\left(\frac{\mu}{b} - bdD\right)}{\Phi\left(\frac{\mu}{b}\right)}, \tag{6}$$

where $D = N_f d$ is the total dose given over the course of radiotherapy.

Suppose that the targeted tumor contains $N_0$ cells before the beginning of treatment. If we assume that the number of malignant cells at the end of radiotherapy is Poisson distributed, then tumor control probability (*TCP*) is described by the equation (see Appendix A)

$$TCP = \exp(-N_0 \bar{S}). \tag{7}$$

In the following sections we analytically determine optimal target dose which maximizes *TCP* under the condition of acceptable, fixed probability of normal tissue complications (NTCP). In order to relate NTCP and target dose, we further assume that NTCP is defined by the biologically effective dose in the affected OAR. Since for any $N_0$ maximum *TCP* correspond to the minimum of the average probability of survival, optimal fractionation corresponds to the minimum achievable $\bar{S}$ in Eq. (6). Furthermore, because we find it easier to work with *BED* than $\bar{S}$, we will utilize the former quantity for target dose optimization as described in the following sections.

### 2.3. BED in the treatment target and organ at risk

In the case of homogeneous alpha and beta, biologically effective dose is defined as

$$BED = D\left(1 + \frac{d}{\alpha/\beta}\right). \tag{8}$$

Note that *BED* in Eq.(8) can be interpreted as the equivalent total dose required to give the same log cell kill as the schedule being studied, at an infinitely low dose-rate or with infinitely small fractions well spaced out [17,18]. In the considered case, one can alternatively express *BED* as

$$BED = -\frac{1}{\alpha}\ln S. \tag{9}$$

It is easy to verify that Eq. (8) and Eq. (9) are equivalent. In the presence of tumor heterogeneity, we generalize the definition of *BED* as

$$BED = -\frac{1}{\bar{\alpha}}\ln \bar{S}, \tag{10}$$

where $\bar{S}$ is the average probability of survival [19]. From Eq. (10) it follows that maximum *BED* corresponds to minimum achievable $\bar{S}$.

In the discussion below, subscripts “tar” and “nt” are used to differentiate between the irradiated malignant cells and normal cells, respectively. Note that in contrast to normal cells, malignant cells are assumed to have heterogeneous alpha and beta characterized by the probability distribution in Eq. (2). We also assume that the planning target volume (PTV) is uniformly irradiated with dose per fraction $d_{tar}$, number of fractions $N_f$ and total dose $D_{tar}$. We will focus our discussion on the case of a serial OAR (e.g., spinal cord) for which the effect of radiation is defined by the maximum value of biologically effective dose ($BED_{nt,\max}$) [7,20]. The relationship between maximum dose per fraction in the OAR ($d_{nt,\max}$) and target dose can be expressed as $d_{nt,\max} = \xi d_{tar}$, where $\xi$ is the radiation sparing factor for the OAR. Note that sparing factor depends on several parameters (including separation between PTV and OAR, energy and angles of radiation beams, beam blocking etc.). In the case when separation between PTV and OAR is sufficiently large, it is frequently possible to have $\xi = \frac{d_{nt,\max}}{d_{tar}} << 1$. On

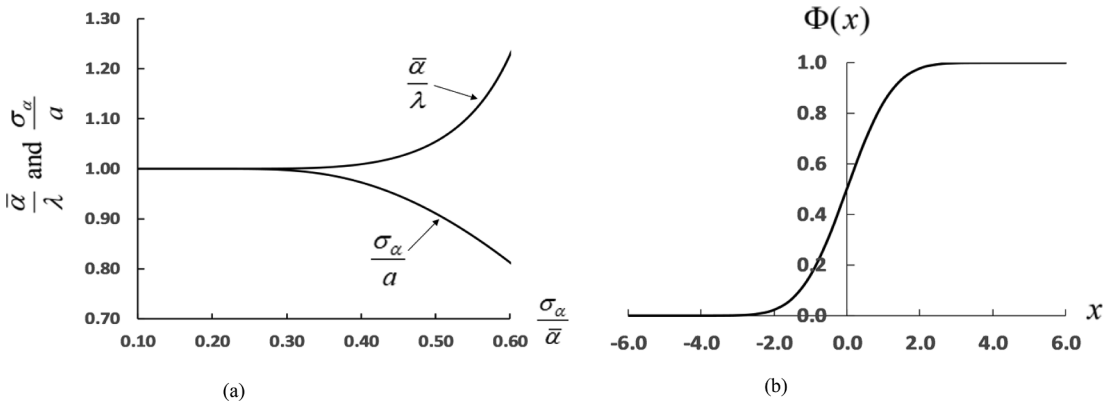


**Fig. 1.** (a) Ratios $\frac{\bar{\alpha}}{\lambda}$ and $\frac{\sigma_\alpha}{a}$ plotted as functions of $\frac{\sigma_\alpha}{\bar{\alpha}}$; (b) $\Phi(x)$ as a function of $x$. Note that $\Phi(t)$ is an integral from negative infinity to $x$ of a univariate Gaussian *pdf* (see Eq. (2)) assuming zero $\lambda$ (or $\mu$) and $a$ (or $b$) of unity.

the other hand, if the separation is small, $\xi$ can be close to unity. In the discussion below, it will be demonstrated that compared to standard fractionation, hypofractionation increases $BED_{tar}$ only under a certain condition which includes $\xi$, alpha and beta of both normal and malignant cells, and variances $\sigma_\alpha^2$ and $\sigma_\beta^2$ for the tumor.

As mentioned above, the radiobiological effect for the affected organ at risk is defined by the biologically effective dose $BED_{nt,\max}$

$$BED_{nt,\max} = N_f d_{nt,\max}\left(1 + \frac{d_{nt,\max}}{(\alpha/\beta)_{nt}}\right) = N_f \xi d_{tar}\left(1 + \frac{\xi d_{tar}}{(\alpha/\beta)_{nt}}\right). \tag{11}$$

On the other hand, cell kill in the treatment target is specified by the quantity $BED_{tar}$ defined in Eq. (10). In the following sections we analytically determine optimal dose which maximizes $BED_{tar}$ under condition of fixed $BED_{nt,\max}$ in the OAR.

### 2.4. Variations in target dose with number of fractions

Eq. (11) indicates that under the condition $BED_{nt,\max} = const$, dose per fraction $d_{tar}$ decreases with increasing number of fractions. Rewriting this equation as

$$BED_{nt,\max} = \xi D_{tar} + \frac{\xi^2 D_{tar}^2}{N_f (\alpha/\beta)_{nt}} = const \tag{12}$$

makes it apparent that total target dose $D_{tar}$ increases with increasing $N_f$. The minimum of $D_{tar}$ is achieved for a single-fraction treatment and is given by

$$D_{tar,\min} = \frac{\left(\alpha/\beta\right)_{nt}}{2\xi}\cdot\left(\sqrt{1 + \frac{4BED_{nt,\max}}{\left(\alpha/\beta\right)_{nt}}} - 1\right). \tag{13}$$

The product of dose per fraction and total dose satisfies equation

$$d_{tar} D_{tar} = \frac{(\alpha/\beta)_{nt}}{\xi^2}(BED_{nt,\max} - \xi D_{tar}). \tag{14}$$

Notice that because $D_{tar}$ increases with increasing number of fractions, $d_{tar} D_{tar}$ decreases with $N_f$. The expression for the product $d_{tar} D_{tar}$ from Eq. (14) will be used in the following section to determine target dose which maximizes $BED_{tar}$.

### 2.5. Small-variance approximation

To analytically determine optimal target dose, we consider the case when variances $\sigma_\alpha^2$ and $\sigma_\beta^2$ for the tumor are sufficiently small so that the following conditions are satisfied:

$$\frac{\sigma_\alpha}{\bar{\alpha}} < 0.3,\ \frac{\sigma_\beta}{\bar{\beta}} < 0.3,\ \frac{\bar{\alpha}}{\sigma_\alpha} - \sigma_\alpha D_{tar} > 2 \text{ and } \frac{\bar{\beta}}{\sigma_\beta} - \sigma_\beta d_{tar} D_{tar} > 2 \tag{15}$$

Under the first two conditions from Eq. (15), we can replace parameters $\lambda$ and $\mu$ with $\bar{\alpha}$ and $\bar{\beta}$, respectively, and replace parameters $a$ and $b$ with $\sigma_\alpha$ and $\sigma_\beta$, respectively (see Fig. 1a). Under the last two conditions from Eq. (15), factor $\frac{\Phi\left(\frac{\lambda}{a} - aD\right)}{\Phi\left(\frac{\lambda}{a}\right)}\frac{\Phi\left(\frac{\mu}{b} - bdD\right)}{\Phi\left(\frac{\mu}{b}\right)}$ in the expression for $\bar{S}$ in Eq. (6) is approximately equal to unity (see Fig. 1b). As a result, equations for the average probability of survival and $BED_{tar}$ (see Eqs. (6) and (10)) become:

$$\bar{S} = e^{-\bar{\alpha}D - \bar{\beta}dD + \frac{\sigma_\alpha^2 D^2}{2} + \frac{\sigma_\beta^2 d^2 D^2}{2}} \tag{16}$$

and

$$BED_{tar} = D_{tar} + \frac{d_{tar} D_{tar}}{(\bar{\alpha}/\bar{\beta})_{tar}} - \frac{\sigma_\alpha^2 D_{tar}^2}{2\bar{\alpha}_{tar}} - \frac{\sigma_\beta^2 d_{tar}^2 D_{tar}^2}{2\bar{\alpha}_{tar}}. \tag{17}$$

The optimum target dose which corresponds to the maximum value of $BED_{tar}$, can be obtained as follows. First, substitute expression for the product $d_{tar} D_{tar}$ from Eq. (14) into Eq. (17). The latter equation then becomes

$$BED_{tar} = D_{tar} + \frac{\eta}{\xi^2}(BED_{nt} - \xi D_{tar}) - \frac{\sigma_\alpha^2 D_{tar}^2}{2\bar{\alpha}_{tar}} - \frac{\sigma_\beta^2 (\alpha/\beta)_{nt}^2 (BED_{nt} - \xi D_{tar})^2}{2\bar{\alpha}_{tar}\xi^4}, \tag{18}$$

where $\eta \equiv \frac{(\alpha/\beta)_{nt}}{(\bar{\alpha}/\bar{\beta})_{tar}}$. Second, find extremum of $BED_{tar}$ specified by the condition that derivative $\frac{dBED_{tar}}{dD_{tar}}$ is zero. It is straightforward to show that the maximum of $BED_{tar}$ is reached at dose $D_{tar} = \widetilde{D}_{tar}$, where $\widetilde{D}_{tar}$ is given by

$$\widetilde{D}_{tar} = \frac{\frac{\sigma_\beta^2 (\alpha/\beta)_{nt}^2}{\xi^3} BED_{nt} + \bar{\alpha}_{tar}\left(1 - \frac{\eta}{\xi}\right)}{\sigma_\alpha^2 + \frac{\sigma_\beta^2 (\alpha/\beta)_{nt}^2}{\xi^2}}. \tag{19}$$

Since the optimum target dose ($D_{tar,opt}$) cannot be smaller than $D_{tar,\min}$ (see Eq. (13)), the expression for $D_{tar,opt}$ is

$$D_{tar,opt} = \begin{cases} \widetilde{D}_{tar}, & \widetilde{D}_{tar} > D_{tar,\min} \\ D_{tar,\min}, & \widetilde{D}_{tar} \leqslant D_{tar,\min} \end{cases} \tag{20}$$

From Eq. (14) and Eq. (12), respectively, it follows that the optimal dose per fraction ($d_{tar,opt}$) and optimal number of fractions ($N_{f,opt}$) are as follows:

$$d_{tar,opt} = \frac{(\alpha/\beta)_{nt}}{\xi^2}\left(\frac{BED_{nt,\max}}{D_{tar,opt}} - \xi\right) \text{ and } N_{f,opt} = \frac{\xi^2 D_{tar,opt}^2}{(\alpha/\beta)_{nt}\cdot(BED_{nt,\max} - \xi D_{tar,opt})} \tag{21}$$

It should be kept in mind that the obtained solution for the optimum fractionation regimen including the derived expression for $D_{tar,opt}$, is

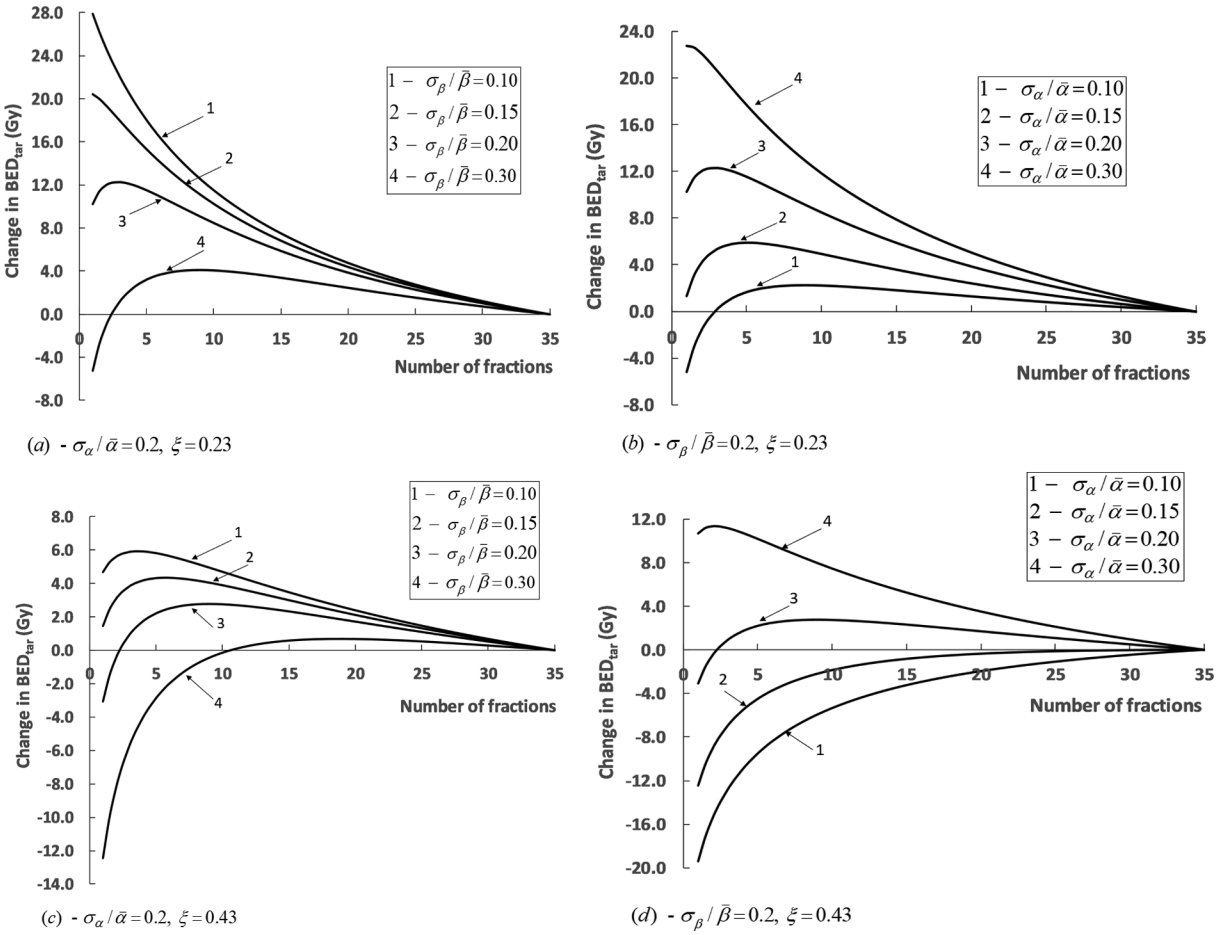


**Fig. 2.** Changes in $BED_{tar}$ with number of fractions for different values of $\sigma_\alpha$, $\sigma_\beta$ and $\xi$. Note that the displayed quantity is the difference between $BED_{tar}$ for varying $N_f$ and the baseline $BED_{tar}$ defined for standard fractionation.

valid for a serial OAR. The case of a parallel-type OAR is considered in Appendix B.

### 2.6. Effect of variable dose per fraction

So far, we have restricted our discussion to the case when each treatment is delivered with the same dose per fraction. Can fractionated regimens with variable dose per fraction be more efficient? It turns out that under the condition $BED_{nt,\max} = const$, the optimal target dose $D_{tar,opt}$ cannot be delivered in fewer than $N_{f,opt}$ fractions. Consequently, the optimal fraction schedule includes $N_{f,opt}$ fractions delivered with the same dose per fraction $d_{tar,opt}$.

To prove the latter statement, let us consider a course of radiotherapy with $N_f$ fractions and varying dose per fraction. In this case total dose is given by

$$D_{tar} = \sum_{i=1}^{N_f} d_{tar,i}, \tag{22}$$

where $d_{tar,i}$ denotes the dose given during the $i^{\text{th}}$ fraction. Note that under the condition of varying fraction size, Eq. (14) is replaced by

$$\sum_{i=1}^{N_f} d_{tar,i}^2 = \frac{(\alpha/\beta)_{nt}}{\xi^2}(BED_{nt,\max} - \xi D_{tar}) \tag{23}$$

while Eq. (18) remains intact. Suppose that radiation is delivered with the optimal total dose $D_{tar,opt}$ by using fewer than $N_{f,opt}$ fractions; i.e., $N_f < N_{f,opt}$. Consequently, we have

$$\sum_{i=1}^{N_f} d_{tar,i}^2 = \frac{(\alpha/\beta)_{nt}}{\xi^2}(BED_{nt,\max} - \xi D_{tar,opt}). \tag{24}$$

Note that under the condition $D_{tar,opt} = \sum_{i=1}^{N_f} d_{tar,i}$, the minimal value of $\sum_{i=1}^{N_f} d_{tar,i}^2$ is achieved for equal fraction sizes; i.e., $d_{tar,i} = \frac{D_{tar,opt}}{N_f}$ (see Ref. [21]). As a result, in the considered case we obtain

$$\min\left(\sum_{i=1}^{N_f} d_{tar,i}^2\right) = \frac{D_{tar,opt}^2}{N_f} > \frac{D_{tar,opt}^2}{N_{f,opt}} = \frac{(\alpha/\beta)_{nt}}{\xi^2}(BED_{nt,\max} - \xi D_{tar,opt}). \tag{25}$$

The apparent contradiction between equations (24) and (25) indicates that $N_f$ cannot be smaller than $N_{f,opt}$.

### 2.7. Numerical calculation of $BED_{tar}$ for different $N_f$

We performed numerical calculations of the change in $BED_{tar}$ with $N_f \leqslant 35$ compared to standard fractionation ($N_f = 35$) for two different cases of lung cancer. In the considered cases the planning target volume was adjacent to the spinal cord. The planned uniform target dose, number of fractions and dose per fraction in each case were 70 Gy, 35 and 2 Gy, respectively. The maximum cord doses were as follows: first case – 16 Gy, second case – 30 Gy. The corresponding sparing factors were 0.23 and 0.43, respectively.

For the considered radiobiological parameters (see next paragraph) and sparing factor, target dose $D_{tar}$ and dose per fraction $d_{tar}$ were determined from equation (12) for different values of $N_f$. Subsequently, $BED_{tar}$ was calculated with the help of equations (3), (4), (6) and (10).

Spinal cord is described as a serial, late-responding structure [20].

**Table 1**
Optimum number of fractions $N_{f,opt}$, $D_{tar,opt}$ and the corresponding change in $BED_{tar}$ for $\xi = 0.43$, $\sigma_\alpha/\alpha = 0.2$ and different values of $\sigma_\beta/\beta$. Data in parenthesis were obtained by using analytical expression for $D_{tar,opt}$.

| $\sigma_\beta/\beta$ | $N_{f,opt}$ | $D_{tar,opt}$ (Gy) | Change *in* $BED_{tar}$ (Gy) |
|---|---|---|---|
| 0.10 | 4 | 38.09 (36.72) | 5.93 |
| 0.15 | 6 | 43.94 (43.09) | 4.34 |
| 0.20 | 9 | 50.10 (49.82) | 2.78 |
| 0.30 | 19 | 61.52 (61.51) | 0.68 |

In the calculations, the ratio $(\alpha/\beta)_{nt} = 3$ Gy was used for the cord. The average alpha and beta radiosensitivities for the tumor were $\bar{\alpha}_{tar} = 0.25\,\text{Gy}$ and $\bar{\beta}_{tar} = 0.025\,\text{Gy}$ with the resulting alpha/beta ratio of 10 Gy. The corresponding value of parameter $\eta = \frac{(\alpha/\beta)_{nt}}{(\bar{\alpha}/\bar{\beta})_{tar}}$ was 0.3.

## 3. Results

Dependence of $BED_{tar}$ on number of fractions under the condition of fixed $BED_{nt,\max}$ in the spinal cord is displayed in Fig. 2. Each plot from this figure shows the difference between $BED_{tar}$ for an arbitrary $N_f \leqslant 35$ and $BED_{tar}$ for standard fractionation (i.e., $D_{tar} = 70$ Gy, $N_f = 35$ and $d_{tar} = 2$ Gy) used as the baseline. Note that calculations were performed for different variances $\sigma_\alpha$ and $\sigma_\beta$. The presented results include two cases defined by different values of sparing factor $\xi$: (a) $\xi < \eta$ – Fig. 2a and b and (b) $\xi > \eta$ – Fig. 2c and d.

Table 1 describes an example of numerically determined optimum number of fractions and target dose which maximize $BED_{tar}$ under the condition of fixed biologically effective dose in the spinal cord. The calculated values of $D_{tar,opt}$ are in good agreement with those obtained by using analytical expression for the optimum target dose (see equations (19) and (20)).

## 4. Discussion

As mentioned previously, several recent studies considered changes in biologically effective dose with number of fractions by using the LQ model with homogeneous alpha and beta [5–7]. In the current work, the radiobiological model used in these studies was extended to incorporate the effect of intratumor heterogeneity. It should be noted that the LQ model with a bivariate normal distribution of alpha and beta radiosensitivites and with a non-zero correlation coefficient was previously studied by Shultheiss et al [9]. In contrast, Shuryak et al [10] considered only heterogeneity in the alpha radiosensitivity. The description of intratumor heterogeneity in the current work differs from studies by Shuryak et al and Schulthiss et al as follows: (a) we use truncated normal distribution for both alpha and beta and (b) we assume that variations in alpha and beta are uncorrelated. The justification for the latter assumption was previously described by Brenner and Hall [15] who noted that the alpha and beta terms in the LQ model depict lethal damage produced on two different levels; i.e., nanometer level for the alpha term and interaction of double-strand breaks on a much greater spatial scale described by the beta term.

According to the developed model, to predict optimum fractionation for individual patients, one needs to know alpha/beta ratios in the target and OAR as well as variances in alpha and beta in the tumor. In a previous study [9], the authors used $\frac{\sigma_\alpha}{\bar{\alpha}} = 0.3$ and $\frac{\sigma_\beta}{\bar{\beta}} = 0.3$ (based on *in-vitro* experiments) which is in line with the values of variances in alpha and beta from the current study. Although this information is not currently available *in-vivo*, estimates of radiosensitivities and their variances can in principle be obtained by analyzing tumor control data in multi-patient studies. For example, a recent study [10] has provided estimates of both $(\bar{\alpha}/\bar{\beta})_{tar}$ and variance in alpha. The author hopes that in the future, information about radiosensitivities and their variations in individual patients becomes available which, in turn, will enable selection of optimal number of fractions and fraction size for hypofractionated regimens.

To elucidate the obtained results, it is important to review two main conclusions from the previous investigations [5–7]. First, under the condition $\xi < \eta$ the optimal fractionation is represented by a single treatment. Second, the optimal treatment regimen in the case $\xi > \eta$ is hyperfractionation with low dose per fraction. Compared to the previous studies, intratumor heterogeneity can affect treatment schedule in several important ways. First, for non-zero variances in alpha and beta, there exists an optimal number of fractions (generally different from unity) which maximizes biologically effective dose in the target. Second, changes in $BED_{tar}$ with varying number of fractions can be non-monotonic; e.g., $BED_{tar}$ can initially increase with decreasing $N_f$ and reach its maximum at certain number of fractions $N_f = N_{f,opt}$. Further decrease in number of fractions causes a reduction in $BED_{tar}$ (see Fig. 2). Third, in the case $\xi < \eta$ the optimal fractionation is not necessarily a single treatment. For example, for a large enough variance $\sigma_\beta$ and/or small $\sigma_\alpha$, regimens with 3–5 fractions can lead to a higher $BED_{tar}$ as compared to that achieved with a single treatment (see Fig. 2a and b). Fourth, in contrast with the conclusions from [5–7], hyperfractionation isn't necessarily advantageous when $\xi > \eta$; e.g., for high enough value of variance in alpha radiosensitivity (e.g., $\sigma_\alpha \geqslant 0.2\bar{\alpha}$), treatment with less than 10 fractions can result in a higher $BED_{tar}$ as compared to that achieved with standard fractionation or hyperfractionation (see Fig. 2c and d).

As mentioned previously, several important mechanisms which can affect tumor response to radiotherapy, are beyond the scope of this study. In particular, accelerated repopulation of malignant cells during treatment can play an important role in radiobiological comparison of different fractionation regimens [22–24]. The author intends to study the effect of repopulation in the LQ model with heterogeneous radiosensitivity in the target in future studies.

It should also be emphasized that the utilized radiobiological framework relies on the LQ model for cell kill. In recent years, the validity of this model for high dose per fraction (e.g., $d > 5 - 10$Gy) was disputed [25,26]. Conversely, the applicability of the LQ model in the case of hypofractionation was defended by several investigators [10,27]. Consequently, it is prudent to currently exercise caution when this model is applied for assessment of clinical cases.

## 5. Conclusions

According to the obtained results, intratumor heterogeneity can be an important factor affecting *BED* in different fractionation regimens. In particular, it has been shown that in the presence of heterogeneous radiosensitivities of malignant cells, hypofractionation can either increase or decrease *BED* in the tumor depending on the variances $\sigma_\alpha$ and $\sigma_\beta$. In a particular case of sufficiently small $\sigma_\alpha$ and $\sigma_\beta$, analytical expression for the optimal target dose which maximizes $BED_{tar}$, was obtained.

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## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

## Appendix A. *TCP* in the case of non-uniform radiosensitivity

Let us first consider the case when malignant cells have uniform radiosensitivity characterized by parameters $\alpha$ and $\beta$. In the LQ model, the fraction of the initial cells which survive the treatment is given by Eq. (1). If $N_0$ denotes the initial number of malignant cells, then the average number of surviving cells is

$$N = N_0 S(\alpha, \beta). \tag{A.1}$$

If we assume that the number of surviving cells is described by a Poisson distribution, then tumor control probability is given by [28]

$$TCP_{uniform} = exp(-N) = \exp(-N_0 S(\alpha, \beta)). \tag{A.2}$$

In the case when alpha and beta are characterized by the probability distribution function $f(\alpha, \beta)$, we can modified Eq. (A.1) as follows. Consider all malignant cells with alpha ranging between $\alpha$ and $\alpha + \Delta\alpha$ and beta ranging between $\beta$ and $\beta + \Delta\beta$. The number of surviving cells with these range of alpha and beta values is

$$\Delta N = N_0 \int_{\beta}^{\beta+\Delta\beta} \int_{\alpha}^{\alpha+\Delta\alpha} S(\alpha, \beta) f(\alpha, \beta) d\alpha d\beta \tag{A.3}$$

The total number of surviving cells is

$$N = N_0 \int_{0}^{\infty} \int_{0}^{\infty} S(\alpha, \beta) f(\alpha, \beta) d\alpha d\beta \tag{A.4}$$

By using the definition of average probability of survival in Eq.(5), we have

$$N = N_0 \bar{S} \tag{A.5}$$

Finally, under the assumption that the number of surviving cells in the case of non-uniform radiosensitivity is Poisson distributed, equation (A.5) leads to the expression for *TCP* in Eq. (7).

## Appendix B. Optimum target dose in the case of a parallel-type OAR

We again assume uniform dose in the target; however, the considered OAR is characterized by a non-uniform dose distribution. Suppose that the OAR is divided into $N_V$ voxels, small enough so that dose per fraction in the $j^{th}$ voxel, $d_{nt,j}$, can be considered uniform. Let $BED_{nt,j}$ denote biologically effective dose in the $j^{th}$ voxel while $<BED_{nt}>$ denotes the average $BED_{nt}$; i.e.,

$$<BED_{nt}> \equiv \frac{1}{N_V} \sum_{j=1}^{N_V} BED_{nt,j}. \tag{B.1}$$

The effect of radiation on a parallel OAR is defined by $<BED_{nt}>$ rather than $BED_{nt,\max}$ [7]. Our objective here is to derive expression for $D_{tar,opt}$ which maximizes $BED_{tar}$ under the condition of fixed $<BED_{nt}>$.

Consider the average sparing factor $<\xi>$ and average squared sparing factor $<\xi^2>$ defined by the dose distribution in the OAR:

$$<\xi> = \frac{1}{N_V} \sum_{j=1}^{N_V} (d_{nt,j}/d_{tar}) \text{ and } <\xi^2> = \frac{1}{N_V} \sum_{j=1}^{N_V} (d_{nt,j}/d_{tar})^2. \tag{B.2}$$

By using parameters $<\xi>$ and $<\xi^2>$, we can rewrite Eq. (12) as

$$<BED_{nt}> = <\xi> D_{tar} + \frac{<\xi^2> D_{tar}^2}{N_f (\alpha/\beta)_{nt}}. \tag{B.3}$$

With the help of Eq. (B.3), the product of dose per fraction $d_{tar} = D_{tar}/N_f$ and total dose $D_{tar}$ can be expressed as (compare with Eq. (14))

$$d_{tar} D_{tar} = \frac{(\alpha/\beta)_{nt}}{<\xi^2>} (BED_{nt,\max} - <\xi> D_{tar}) \tag{B.4}$$

If one substitutes the product $d_{tar} D_{tar}$ from Eq. (B.4) into Eq. (17), the latter equation becomes

$$BED_{tar} = D_{tar} + \frac{\eta}{<\xi^2>} (BED_{nt} - <\xi> D_{tar}) - \frac{\sigma_\alpha^2 D_{tar}^2}{2\bar{\alpha}_{tar}} - \frac{\sigma_\beta^2 (\alpha/\beta)_{nt}^2 (BED_{nt} - <\xi> D_{tar})^2}{2\bar{\alpha}_{tar} (<\xi^2>)^2}. \tag{B.5}$$

By differentiating Eq. (B.5) with respect to $D_{tar}$ and using condition $\frac{dBED_{tar}}{dD_{tar}} = 0$, we obtain the following expression for the optimal dose $\widetilde{D}_{tar,opt}$ that maximizes $BED_{tar}$:

$$\widetilde{D}_{tar,opt} = \frac{\frac{\sigma_\beta^2 (\alpha/\beta)_{nt}^2 <\xi>}{(<\xi^2>)^2} BED_{nt} + \bar{\alpha}_{tar} \left(1 - \frac{\eta <\xi>}{<\xi^2>}\right)}{\sigma_\alpha^2 + \frac{\sigma_\beta^2 (\alpha/\beta)_{nt}^2 (<\xi>)^2}{(<\xi^2>)^2}}. \tag{B.6}$$

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