The dependence of optimal fractionation schemes on the spatial dose distribution

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Abstract

We consider the fractionation problem in radiation therapy. Tumor sites in which the dose-limiting organ at risk (OAR) receives a substantially lower dose than the tumor, bear potential for hypofractionation even if the $\alpha/\beta$-ratio of the tumor is larger than the $\alpha/\beta$-ratio of the OAR. In this work, we analyze the interdependence of the optimal fractionation scheme and the spatial dose distribution in the OAR. In particular, we derive a criterion under which a hypofractionation regimen is indicated for both a parallel and a serial OAR. The approach is based on the concept of biologically effective dose (BED). For a hypothetical homogeneously irradiated OAR, it has been shown that hypofractionation is suggested by the BED model if the $\alpha/\beta$-ratio of the OAR is larger than $\alpha/\beta$-ratio of the tumor times the sparing factor, i.e. the ratio of the dose received by tumor and OAR. In this work, we generalize this result to inhomogeneous dose distributions in the OAR. For a parallel OAR, we determine the optimal fractionation scheme by minimizing the integral BED in the OAR for a fixed BED in the tumor. For a serial structure, we minimize the maximum BED in the OAR. This leads to analytical expressions for an effective sparing factor for the OAR, which provides a criterion for hypofractionation. The implications of the model are discussed for lung tumor treatments. It is shown that the model supports hypofractionation for small tumors treated with rotation therapy, i.e. highly conformal techniques where a large volume of lung tissue is exposed to low but nonzero dose. For larger tumors, the model suggests hyperfractionation. We further discuss several non-intuitive
interdependencies between optimal fractionation and the spatial dose distribution. For instance, lowering the dose in lung via proton therapy does not necessarily provide a biological rationale for hypofractionation.

1 Introduction

In radiation therapy, most treatments are delivered in several fractions with a typical fraction dose of two Gray. This is motivated by the fact that many late responding normal tissues have better capabilities to recover between fractions compared to most tumors [4, 12]. In in-vitro cell survival assays, this leads to a shouldered cell survival curve. In clinical data, this becomes manifest in the observation that the total physical dose that is tolerated by an OAR increases with smaller dose per fraction. Both in vitro and in vivo, this is quantified by the \( \alpha/\beta \)-ratio of the tissue.

In radiotherapy planning, we want to determine the fractionation schedule that optimizes the therapeutic ratio, i.e. the optimal number of fractions and the dose per fraction that minimize the complication rate for a given level of tumor control. This can be approached based on the biologically equivalent dose (BED) model [4, 5]. The BED is given by

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

where \( n \) is the number of fractions, \( d \) is the dose per fraction, and \( \alpha/\beta \) is the model parameter. A small \( \alpha/\beta \)-ratio implies that the tissue is sensitive to fractionation, i.e. the BED increases rapidly with increasing dose per fraction. The BED model is widely accepted in the field, even though its validity at very large doses per fractionation must be questioned [2, 8]. To determine fractionation schedules based on BED, it is assumed that a fixed BED corresponds to a given clinical effect, independent of \( n \) and \( d \).

The BED model in (1) corresponds to a uniform fractionation scheme where effects from repopulation, the overall treatment time, and incomplete repair are not included. However, it has been shown that incorporating these effects into the BED model may give rise to optimal non-uniform fractionation schedules [1, 15]. In this paper, using the formulation of BED in (1), we primarily seek to understand circumstances under which hypofractionation is a better alternative to hyperfractionation.

To determine the optimal fractionation schedule, we can minimize the BED in the OAR with respect to \( n \) and \( d \) for a fixed BED in the tumor. Under the assumption that the OAR receives the same dose as the tumor, this approach yields the intuitive result that it is optimal to hypofractionate [13] (i.e. deliver few fractions with high dose per fraction) if the \( \alpha/\beta \)-ratio of the OAR is larger than the \( \alpha/\beta \)-ratio of the tumor. An example of a tumor site where these conditions are fulfilled may be prostate. The rectum as the dose-limiting OAR is directly adjacent to the target volume and receives
in parts the same dose as the tumor. However, there is increasing evidence that the \( \alpha/\beta \)-ratio for prostate carcinoma may be below 2 and therefore lower than the assumed \( \alpha/\beta \) ratio for normal tissue complications [10]. Hence, hypofractionation seems indicated for prostate. However, prostate carcinoma, as slowly proliferating tumors, appears to be an exception in that respect. For the majority of tumors, the \( \alpha/\beta \)-ratio is larger than the \( \alpha/\beta \)-ratio of the dose-limiting OAR. For these treatment sites, hypofractionation can only be motivated in the context of the BED model if the OAR receives a lower dose than the tumor.

To generalize this to the case in which the OAR receives a lower dose than the tumor, we can assume in the first step that the OAR receives a dose of \( \delta d \) Gray per fraction where \( \delta \leq 1 \) is the sparing factor. This yields the result that it is optimal to hypofractionate if the \( \alpha/\beta \)-ratio of the OAR tumor is larger than \( \delta \) times the \( \alpha/\beta \)-ratio of the tumor [11]. This shows two interesting aspects: first, there is potential for hypofractionation even if the OAR is more sensitive to fractionation than the tumor. And second, there is an interdependence between the spatial dose distribution and the optimal fractionation scheme.

In this paper, we address the problem that an OAR is not irradiated with a homogeneous dose. We thus wish to generalize the above case to the situation in which we deliver a homogeneous dose to the tumor and an inhomogeneous dose to the OAR described by a general dose-volume histogram (DVH). For the case of a parallel OAR, we derive an effective sparing factor \( \bar{\delta} \) based on the goal of minimizing the mean BED in the OAR for a fixed tumor BED. The effective sparing factor \( \bar{\delta} \) can be computed from the DVH. The results are discussed in the context of lung tumors. More specifically, it is shown that for small tumors, hypofractionation can be optimal for this model, whereas for larger tumors hyperfractionation is predicted to improve the therapeutic ratio. We further discuss the dependence of the effective sparing factor on the shape of the DVH. It is shown that, counterintuitively, a consistently lower DVH does not necessarily tip the scale more towards a hypofractionated regimen.

## 2 Optimal fractionation based on the BED model

We assume that a treatment plan is given, which yields a uniform dose distribution in the target and a non-uniform dose distribution in the OAR. More specifically, let \( d_T \) denote the uniform dose per fraction in the target and \( d_i \) denote the dose per fraction in OAR voxel \( i \). We define the normalized dose distribution in the OAR via

\[
\delta_i = \frac{d_i}{d_T} \tag{2}
\]

We then let \( \text{BED}_T \) denote the BED in the target, which can be expressed as

\[
\text{BED}_T = nd_T \left( 1 + \frac{d_T}{[\alpha/\beta]_T} \right) \tag{3}
\]
where \([\alpha/\beta]_T\) is the \(\alpha/\beta\)-ratio in the tumor. In the OAR voxel \(i\) we have correspondingly:

\[
\text{BED}_i = n\delta_i d_T \left( 1 + \frac{\delta_i d_T}{[\alpha/\beta]_N} \right),
\]

where \([\alpha/\beta]_N\) is the \(\alpha/\beta\)-ratio in the OAR. To determine the optimal fractionation schedule, we consider a fixed BED in the tumor. We can then rewrite equation (3) as

\[
n d^2_T = [\alpha/\beta]_T \text{BED}_T - [\alpha/\beta]_T n d_T.
\]

By inserting equation (5) into equation (4), we can rewrite the BED in OAR voxel \(i\) as follows:

\[
\text{BED}_i = \left( \frac{1}{\delta_i} - \frac{[\alpha/\beta]_T}{[\alpha/\beta]_N} \right) \delta_i^2 n d_T + \frac{[\alpha/\beta]_T}{[\alpha/\beta]_N} \delta_i^2 \text{BED}_T
\]

\[
= \left( \frac{1}{\bar{\delta}} - \frac{1}{R} \right) \delta_i^2 n d_T + \frac{\delta_i^2}{R} \text{BED}_T
\]

where

\[
R = \frac{[\alpha/\beta]_N}{[\alpha/\beta]_T}
\]

is the ratio of the \(\alpha/\beta\)-ratios in the normal tissue and the tumor.

**A single voxel:** If we consider a single OAR voxel, we see from equation (7) that \(\text{BED}_i\) is a linear function of the total physical dose \(n d_T\) delivered to the tumor. If \((1/\delta_i - 1/R) > 0\) holds, i.e. if \(\delta_i < R\), which is equivalent to the condition \([\alpha/\beta]_N > \delta_i [\alpha/\beta]_T\), we minimize \(\text{BED}_i\) by choosing the physical tumor dose \(n d_T\) as small as possible while fulfilling the constraint of delivering the desired BED to the tumor. This corresponds to the hypofractionation regimen. Conversely, if \(\delta_i > R\), we minimize \(\text{BED}_i\) by choosing the physical tumor dose as large as possible. This corresponds to the hyperfractionation regimen. Figure 1 provides an illustration for these findings. The case for a single OAR dose level is also discussed in detail in [11].

**Parallel OAR:** We now consider the case of a parallel OAR. Assuming a fixed BED in the tumor, we minimize the integral BED in the OAR. Using equation (7) we have

\[
\text{BED}_{\text{OAR}} = \sum_i \text{BED}_i = \left( \sum_i \left( \delta_i - \frac{\delta_i^2}{R} \right) \right) n d_T + \left( \sum_i \frac{\delta_i^2}{R} \right) \text{BED}_T.
\]

We observe that the integral BED in the OAR is also a linear function of the total physical dose in the tumor. We define the effective sparing factor \(\bar{\delta}\) for a parallel OAR as

\[
\bar{\delta} = \frac{\sum_i \delta_i^2}{\sum_i \delta_i}
\]
Figure 1: The red dots show the relation between total physical dose $nd$ and the number of fractions $n$ for fixed BED in the tumor (resulting from equation 3). Parameters in this plot are $R = 0.4$, $[\alpha/\beta]_T = 10\ \text{Gy}$, and $\text{BED}_T = 72\ \text{Gy}$. Assuming $n = 1$ is the minimum and $n = 30$ is the maximum number of fractions, the total physical dose to ensure $\text{BED}_T = 72$ varies between 22.3 Gy and 60 Gy. The black lines show the linear dependence of the BED in the OAR on the total physical dose for different sparing factors $\delta_i$. For $\delta_i = 0.4$, the slope of the line is zero, i.e. hypo and hyperfractionation are equally good. For $\delta_i = 0.2 = R/2$, the slope is maximized, i.e. such voxels benefit most from hypofractionation: the BED decreases from 13.2 Gy for $n = 30$ to 9.43 Gy for $n = 1$. For voxels with $\delta_i = 1$, hyperfractionation is strongly preferable.
and rewrite equation (9) as

$$\text{BED}_{\text{OAR}} = \left( \frac{1}{\delta} - \frac{1}{R} \right) \left( \sum_i \delta_i^2 n d_T \right) + \left( \sum_i \frac{\delta_i^2}{R} \right) \text{BED}_T$$  \hspace{1cm} (11)

In analogy to equation (7), we conclude that we minimize integral BED in the OAR using a hypofractionation regimen if $\bar{\delta} < R$. If instead we have $\bar{\delta} > R$, the model suggests a hyperfractionation regimen. This result was independently derived by Keller in [7].

The effective sparing factor $\bar{\delta}$ can also be directly computed from the differential or the cumulative DVH. Let $f$ denote the differential DVH, i.e. $f(\delta)$ is the differential volume that receives a dose $\delta d_T$. Then the effective sparing factor in equation (10) can be computed as follows:

$$\bar{\delta} = \frac{\int_0^1 \delta^2 f(\delta) d\delta}{\int_0^1 \delta f(\delta) d\delta}$$ \hspace{1cm} (12)

Since the cumulative DVH is far more commonly used in radiation therapy, we also provide the following additional equivalent ways to compute $\bar{\delta}$. Let the standard cumulative DVH curve be given by $G(\delta)$. Also denote the inverse of this function (with the fractional volume axis as the independent variable) by $g(v)$. For this function, we orient the $v$ axis such that $g(v) = \delta$ means that a fractional volume of $v$ receives a dose less than or equal to $\delta d_T$ (note that defined this way, $g(v)$ is a non-decreasing function of $v$). Then we have

$$\bar{\delta} = \frac{2 \int_0^1 \delta G(\delta) d\delta}{\int_0^1 G(\delta) d\delta} = \frac{\int_0^1 g^2(v) dv}{\int_0^1 g(v) dv}$$ \hspace{1cm} (13)

The first of these can be derived directly from equation (12) by following the standard re-expression of mean and other moments of a probability distribution using the cumulative distribution function. The second can be derived using the inverse function theorem but it is more easily obtained as the direct analogy of the discrete version, equation (10).

**Serial OAR:** In case of a serial OAR, we aim at minimizing the maximum BED to the OAR. We first note that the BED in voxel $i$ is an increasing function of $\delta_i$. This can be seen by rewriting equation (7) as

$$\text{BED}_i = \frac{\delta_i^2}{R} (\text{BED}_T - n d_T) + \delta_i n d_T$$

and noting that BED is always larger that the physical dose, i.e. $\text{BED}_T \geq n d_T$. In other words, the OAR voxel with the largest $\delta_i$ receives the largest BED for any fractionation scheme. Thus, we have

$$\max_i (\text{BED}_i) = \left( \frac{1}{\delta_{\text{max}}} - \frac{1}{R} \right) \delta_{\text{max}}^2 n d_T + \frac{\delta_{\text{max}}^2}{R} \text{BED}_T$$
where
\[ \delta_{\text{max}} = \max \delta_i. \] (14)

In analogy to the single voxel case, we conclude that we minimize the maximum BED in the OAR via a hypofractionation regimen if \[ \frac{\alpha}{\beta} \] of the OAR is larger than \[ \delta_{\text{max}} \frac{\alpha}{\beta} \]; otherwise, hyperfractionation is optimal for this model. Thus, for a serial OAR, the optimal fractionation scheme is determined by the part of the OAR that receives the largest dose.

Summary: The decision on whether to hypofractionate or hyperfractionate depends on the ratio of \( \alpha/\beta \)-ratios \( R \) as well as the sparing factor \( \delta \) for the OAR. For a single dose level in the OAR, the transition from hypofractionation to hyperfractionation occurs at \( \delta = R \). In this section, it is shown that this can be generalized to inhomogeneous dose distributions if the sparing factor is replaced by an effective sparing factor \( \bar{\delta} \), resulting in the following rule:

\[
\text{optimal regimen} = \begin{cases} 
\text{hypofractionation,} & \text{if } \bar{\delta} < R \\
\text{hyperfractionation,} & \text{otherwise}
\end{cases}
\] (15)

where the effective sparing factor is obtained from equation (10) and (14) for a parallel and serial OAR, respectively.

3 Application to lung tumors

In this section, we discuss the application of the above model to lung tumor treatments. We assume that the normal lung is the dose limiting normal tissue and represents a parallel organ. We assume \( R = 0.4 \), i.e. an \( \alpha/\beta \)-ratio of 4 in the normal lung [9] and an \( \alpha/\beta \)-ratio of 10 in the tumor. We have extracted DVHs for lung tissue from treatment planning studies found in the literature. Figure 2 shows two sets of DVHs. The red lines (case 2) show DVHs for the total lung extracted from figure 2 in [3] and correspond to a stage 1 lung tumor. It compares a 3D-conformal photon plan (solid line) with a conformal proton plan (dashed line). The blue DVHs (case 1) are extracted from [14] and present a comparison between a 3D-conformal plan (solid line) and a tomotherapy plan (dashed line). Case 3 in (black line) is extracted from a planning study on stereotactic body radiotherapy (SBRT) for early stage lung cancer [6]. We use these examples to discuss the dependence of the effective sparing factor on the shape of the DVH.

We consider the red DVHs (case 2) in Figure 2. The effective sparing factor \( \bar{\delta} \) is 0.64 for the 3D-conformal photon plan and 0.7 for the proton plan. For both plans standard fractionation is superior to hypofractionation assuming \( R = 0.4 \). The interesting observation is that \( \bar{\delta} \) is larger for the proton plan even though the proton DVH is entirely below the photon plan. This can be interpreted as follows: For the proton plan, roughly 80% of the lung receives almost no dose. Regions that receive almost no dose do not
Figure 2: Example DVH curves for the total lung. Case 1a and 1b are from [3, figure 2], case 2a and 2b are from [14], and case 3 is from [6].
contribute to the integral BED in the lung and thus become irrelevant for the optimization of the fractionation scheme. It can be seen from the definition of $\bar{\delta}$ in equation (10) that voxels that receive almost no dose contribute neither to the denominator nor the numerator. Hence, the value of $\bar{\delta}$ for the proton plan is mainly dominated by the high-dose region.

We now consider the blue DVHs (case 1) in Figure 2. The effective sparing factor $\bar{\delta}$ is 0.66 for the 3D-conformal plan and 0.41 for the tomotherapy plan. This suggests standard fractionation for the conformal plan. For the tomotherapy plan, hypofractionation and standard fractionation are almost equally good. For the 3D-conformal plan, a substantial part of the lung is exposed to the prescription dose, whereas roughly half of the lung is spared completely. This leads to a large $\bar{\delta}$. For the tomotherapy plan, the volume of normal lung exposed to high doses is small. Instead, a large volume receives nonzero doses below 40% of the prescription dose. These voxels benefit from hypofractionation and compensate for the adverse effects in the high-dose region. This has also been described in the original publication [14] from which the DVHs have been extracted.

Case 3 in Figure 2 is extracted from a planning study on stereotactic body radiotherapy (SBRT) for early stage lung cancer [6]. The DVH corresponds to a volumetric-modulated arc therapy (VMAT) plan for a small tumor close to the chest wall. The effective sparing factor $\bar{\delta}$ is 0.37 and, therefore, suggests hypofractionation. The original publication shows that very similar lung DVHs are obtained for VMAT when compared to IMRT when a large number of beam directions is used. For both delivery modes, the dose distribution is conformal and the dose to healthy lung tissue is spread out over a large volume. Thus, the value of $\bar{\delta} = 0.37$ confirms the decision of the institution that this patient is eligible for SBRT, i.e. hypofractionation.

4 Discussion

The optimal fractionation scheme depends on the mean OAR dose as well as the dose variation: It has been discussed above that regions of the OAR that receive a very small dose do not shift the fractionation scheme towards hypofractionation as one might intuitively expect. This can also be illustrated by the following consideration: Assuming dose values $\delta_i$ uniformly distributed between 0 and 1, we obtain an average dose value of $\text{mean}(\delta) = \int_0^1 f(\delta) \delta \, d\delta = 1/2$ in the OAR. However, calculating the effective sparing factor via equation (12) yields the value $\bar{\delta} = 2/3$, which is larger than $\text{mean}(\delta)$. This tendency towards hyperfractionation can also be interpreted from another perspective. Using equation (10) we can rewrite $\bar{\delta}$ as

$$\bar{\delta} = \text{mean}(\delta) + \frac{\text{var}(\delta)}{\text{mean}(\delta)}$$

where the numerator in the second term on the right hand side denotes the variation of the dose around the mean lung dose. Because the variation is always positive, $\bar{\delta}$ is
always larger than mean(δ). In addition, we can conclude that for a fixed mean dose, treatment plans with large dose variations in the OAR lean towards hyperfractionation, whereas plans with more uniform dose tend to hypofractionation.

**The BED model supports hypofractionation for small tumors treated with rotation therapy:** Using commonly assumed α/β-ratios, the model supports hypofractionation if $\bar{\delta} \leq 0.4$. To obtain a value this low, the volume of lung exposed to high doses needs to be small, and the treatment plan needs to feature an extended low dose bath that benefits from hypofractionation. This is the case for sufficiently small tumors treated with tomotherapy, arc therapy, or IMRT using a large enough number of beam directions. This can also be understood by considering figure 1: For voxels with large $\delta_i$, hypofractionation is disadvantageous. For a voxel with $\delta_i = 1$, BED increases from 90 Gy for $n = 30$ to 146.6 Gy for $n = 1$. To create a situation in which a hypofractionated regimen minimizes integral BED in the lung, this disadvantage needs to be compensated for by voxels with $\delta_i < 0.4$. It is easy to see that the benefit from hypofractionation is maximized for $\delta_i = R/2 = 0.2$. In the example in 1, the BED decreases from 13.2 Gy for $n = 30$ to 9.43 Gy for $n = 1$. However, the absolute contribution to the integral BED is relatively low, i.e. in this example 15 voxels with $\delta_i = 0.2$ are needed to compensate for one voxel with $\delta_i = 1$. For $\delta_i$ approaching either 0.4 or zero, the benefit of hypofractionation vanishes. Consequently, for hypofractionation to be optimal, a large dose bath in the range $\delta \approx 0.2$ is required.

**Lower doses do not per se favor hypofractionation:** Considering the red DVHs in Figure 2, we note that the proton DVH has a larger $\bar{\delta}$ even though the DVH curve falls completely below the photon DVH. This shows that lower doses do not per se favor hypofractionation. This is also supported by the following consideration. We consider the photon DVH as a reference, and investigate whether $\bar{\delta}$ increases or decreases if we increase the dose in a single voxel. To that end, we calculate the derivative of $\bar{\delta}$ with respect to $\delta_k$ for a single OAR voxel $k$:

$$
\frac{\partial \bar{\delta}}{\partial \delta_k} = \frac{\partial}{\partial \delta_k} \left( \frac{\sum_i \delta_i^2}{\sum_i \delta_i} \right) = \frac{1}{\sum_i \delta_i} (2\delta_k - \bar{\delta}),
$$

thus, for $\delta_k > \frac{1}{2} \bar{\delta}$, we observe a decrease in $\bar{\delta}$ if we lower the dose in voxel $k$. This corresponds to reducing the high dose region. However, for $\delta_k < \frac{1}{2} \bar{\delta}$, lowering the dose in that voxel increases the value of $\bar{\delta}$. This corresponds to lowering the dose in the low dose region, which is typical for proton therapy.

**The BED model does not suggest hypofractionation for proton therapy:** A consequence of the above observation is that hypofractionation for proton therapy is not supported by the BED model. This is because proton therapy reduces the volume of lung that is exposed to low doses, and thus eliminates the dose levels that benefit
from hypofractionation. This does not mean that hypofractionation is not possible for protons. It only means that, within the validity of the BED model, hyperfractionation is expected to be superior. If, however, the mean lung dose is low enough, hypofractionation can still be considered for economical reasons or patient convenience.

5 Conclusion

It is often assumed that more conformal dose distributions justify the use of hypofractionated treatment protocols. In this work, we analyzed the interdependence between the optimal fractionation scheme and the spatial dose distribution in a parallel organ. It turns out that only in specific situations, hypofractionation is expected to be optimal within the validity of the BED model. This is the case for rotation therapy plans (or IMRT plans with a large number of beam direction) for which a large volume of lung is exposed to a small but non-zero dose. In this case, lung tissue in the low-dose bath benefits from hypofractionation, compensating the adverse effects in the high-dose region. For proton therapy, hypofractionation is not necessarily optimal for the BED model even if the dose to normal lung is reduced compared to photon plans. This is because proton plans reduce the low-dose bath and therefore reduce the volume of lung that benefits significantly from hypofractionation. But, current proton techniques do not reduce the volume of lung that is exposed to high doses. As a consequence, standard fractionation is expected to be better, although hypofractionation, desirable from a patient convenience and hospital logistics perspective, may be possible for small tumors if the complication probability is low.

References


