Optimization of Radiation Therapy Fractionation Schedules in the Presence of Tumor Repopulation

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We analyze the effect of tumor repopulation on optimal dose delivery in radiation therapy. We are primarily motivated by accelerated tumor repopulation toward the end of radiation treatment, which is believed to play a role in treatment failure for some tumor sites. A dynamic programming framework is developed to determine an optimal fractionation scheme based on a model of cell kill from radiation and tumor growth in between treatment days. We find that faster tumor growth suggests shorter overall treatment duration. In addition, the presence of accelerated repopulation suggests larger dose fractions later in the treatment to compensate for the increased tumor proliferation. We prove that the optimal dose fractions are increasing over time. Numerical simulations indicate a potential for improvement in treatment effectiveness.

1. Introduction

According to the American Cancer Society, at least 50% of cancer patients undergo radiation therapy over the course of their treatment. Radiation therapy plays an important role in curing early stage cancer, preventing metastatic spread to other areas, and treating symptoms of advanced cancer. For many patients, external beam radiation therapy is one of the best options for cancer treatment. Current therapy procedures involve taking a pretreatment computed tomography (CT) scan of the patient, which provides a geometrical model of the patient that is used to determine incident radiation beam directions and intensities. In current clinical practice, most radiation treatments are fractionated; i.e., the total radiation dose is split into approximately 30 fractions that are delivered over a period of six weeks. Fractionation allows normal tissue to repair sublethal radiation damage between fractions and thereby tolerate a much higher total dose. Currently, the same dose is delivered in all fractions, and temporal dependencies in tumor growth and radiation response are not

taken into account. Biologically based treatment planning, aiming at optimal dose delivery over time, has tremendous potential, as more is being understood about tumor repopulation and reoxygenation, healthy tissue repair, and redistribution of cells.

In this paper, we study the effect of tumor repopulation on optimal fractionation schedules, i.e., on the total number of treatment days and the dose delivered per day. We are primarily motivated by accelerated tumor repopulation toward the end of radiation treatment, which is considered to be an important cause of treatment failure, especially for head and neck tumors (Withers et al. 1988, Withers 1993). Our main conclusion is that accelerated repopulation suggests larger dose fractions later in the treatment to compensate for the increased tumor proliferation.

1.1. Motivation

Radiation therapy treatments are typically fractionated (i.e., distributed over a longer period of time) so that normal tissues have time to recover. However, such time between treatments allows cancer cells to

proliferate and can result in treatment failure (Kim and Tannock 2005). The problem of interest then is the determination of an optimal fractionation schedule to counter the effects of tumor repopulation. Using the biological effective dose (BED) model, a recent paper (Mizuta et al. 2012) mathematically analyzed the fractionation problem in the absence of repopulation. For a fixed number of treatment days, the result states that the optimal fractionation schedule is to deliver either a single dose or an equal dose on each treatment day. The former schedule of a single dose corresponds to a hypo-fractionated regimen, in which treatments are ideally delivered in as few days as possible. The latter schedule of equal dose per day corresponds to a hyperfractionation regimen, in which treatments are delivered in as many days as possible. The work in this paper further develops the mathematical framework in Mizuta et al. (2012) and analyzes the effect of tumor repopulation on optimal fractionation schedules. We are interested in optimizing *nonuniform* (in time) dose schedules, motivated primarily by the phenomenon of accelerated repopulation, i.e., a faster repopulation of surviving tumor cells toward the end of radiation treatment.

1.2. Related Work

There has been prior work on the optimization of nonuniform radiation therapy fractionation schedules (Almquist and Banks 1976; Swan 1981, 1984; Marks and Dewhirst 1991; Yakovlev et al. 1994; Yang and Xing 2005), some of which also includes tumor repopulation effects. However, these works have either not used the BED model or have primarily considered other factors such as tumor reoxygenation. It has been shown that effects such as reoxygenation, redistribution, and sublethal damage repair can result in non-uniform optimal fractionation schemes (Yang and Xing 2005, Bertuzzi et al. 2013). Previous works have considered the case of exponential tumor growth with a constant rate of repopulation (Wheldon et al. 1977, Jones et al. 1995, Armpilia et al. 2004). Other tumor growth models, e.g., Gompertzian and logistic, have also been considered although mostly in the context of constant dose per day (Usher 1980, McAneney and O'Rourke 2007).

There is a significant amount of literature, especially from the mathematical biology community, on the use of control theory and dynamic programming (DP) for optimal cancer therapy. Several of these works (Zietz and Nicolini 2007, Pedreira and Vila 1991, Ledzewicz and Schättler 2004, Salari et al. 2014) have looked into optimization of chemotherapy. For radiation therapy fractionation, some studies (Hethcote and Waltman 1973, Almquist and Banks 1976, Wein et al. 2000) have used the DP approach based on deterministic biological models, as in this

paper. However, these works have not carried out a detailed mathematical analysis of the implications of optimal dose delivery in the presence of accelerated repopulation. Using imaging information obtained between treatment days, dynamic optimization models have been developed to adaptively compensate for past accumulated errors in dose to the tumor (Ferris and Voelker 2004, de la Zerda et al. 2007, Deng and Ferris 2008, Sir et al. 2012). There also has been work on online approaches that adapt the dose and treatment plan based on images obtained immediately prior to treatment (Lu et al. 2008; Chen et al. 2008; Kim et al. 2009, 2012; Kim 2010; Ghate 2011; Ramakrishnan et al. 2012).

Perhaps the closest related work is Wein et al. (2000), which considers both faster tumor proliferation and reoxygenation during the course of treatment. Although a dose intensification strategy is also suggested in Wein et al. (2000), the primary rationale for increasing dose fractions is different: it is concluded that because of the increase in tumor sensitivity from reoxygenation, larger fraction sizes are more effective at the end of treatment. Our work, however, suggests dose intensification (i.e., larger doses over time) as a direct consequence of a model of accelerated tumor repopulation during the course of treatment.

1.3. Overview of Main Contributions

The primary contributions of this paper are the development of a mathematical framework and the analysis of optimal fractionation schedules in the presence of accelerated repopulation. We give qualitative and structural insights on the optimal fractionation scheme, with the hope that it can guide actual practice. Specifically:

1. We formulate a problem that includes general tumor repopulation characteristics and develop a DP approach to solve it. We choose to model accelerated repopulation implicitly by using decelerating tumor growth curves, where a larger number of tumor cells results in slower growth. Thus, faster growth is exhibited toward the end of radiation treatment, when there are fewer cells.

2. We prove that the optimal doses are nondecreasing over time (Theorem 3), because of the decelerating nature of tumor growth curves. This type of result remains valid even when we allow for weekend and holiday breaks (Corollary 1).

3. We analyze the special structure of the problem for the case of Gompertzian tumor growth and show that it is equivalent to maximizing a discounted version of the BED in the tumor (§2.3.2), which results in a simplified DP algorithm.

4. We show that when there is repopulation, the optimal number of dose fractions is finite (Theorem 4).

5. We find through numerical simulations that the optimal fraction sizes are approximately proportional to the instantaneous proliferation rate, suggesting larger dose fractions later in the treatment to compensate for the increased tumor proliferation.

1.4. Organization

In §2, we present the model, formulation, and DP solution approach. We also analyze the special structure of the problem for the case of Gompertzian tumor growth. In §3, we discuss both previously known results and the main results of this paper. Our primary conclusion is that the optimal dose fractions are nondecreasing over time. In §4, we present and discuss numerical results under exponential or Gompertzian growth models. In §5, we provide further remarks about the model under other assumptions and discuss the results in relation to prior work. Finally, in §6, we summarize our main findings and the most important implications.

2. Model, Formulation, and Solution Approach

2.1. Model of Radiation Cell Kill

In this section, we describe the radiation cell kill model without any tumor growth dynamics. We use the linear-quadratic (LQ) model (Fowler 1989) to relate radiation dose and the fraction of surviving cells. This model is supported by observations from irradiating cells in vitro. The LQ model relates the expected survival fraction S (in the absence of tumor growth) after a single delivered dose d, in terms of two tissue parameters α and β, through the relation

$$S = \exp(-(\alpha d + \beta d^2)).$$

Thus, the logarithm of the survival fraction consists of a linear component with coefficient α and a quadratic component β (see the dotted curve in Figure 1). This LQ model assumes two components of cell killing by radiation: one proportional to dose and one to the square of the dose. The respective tissue-specific proportionality constants are given by α and β. It is possible to interpret these two components of killing as they relate to the probability of exchange aberrations in chromosomes (see Hall and Giaccia 2006). We illustrate this cell kill effect by plotting the logarithm of the survival fraction in Figure 1.

For N treatment days with radiation doses $d_0, d_1, \ldots, d_{N-1}$, the resulting survival fractions from each individual dose can be multiplied, assuming independence between dose effects. The resulting relation is

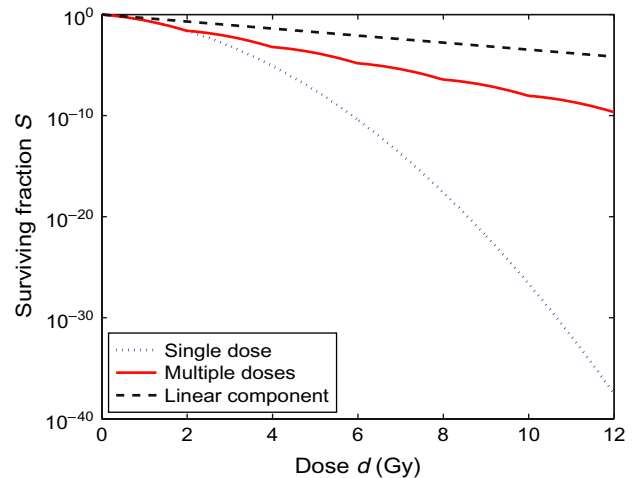$$S = \exp\left(-\sum_{k=0}^{N-1}(\alpha d_k + \beta d_k^2)\right).$$

Figure 1 **(Color online) Illustration of the Fractionation Effect Using the LQ Model**

Notes. The dotted line represents the effect of both the linear and quadratic terms resulting from applying a single total dose of radiation. The solid line corresponds to the effect of the same total dose, if it is divided into multiple individual doses, which results in a much higher survival fraction when the quadratic β term is significant. Finally, the dashed line shows the total effect of the linear term, whether doses are applied as single or multiple individual fractions.

The effect of the quadratic factor β, in the above equation, is that the survival fraction is larger when splitting the total dose into individual dose fractions (Figure 1). Thus, there is an inherent trade-off between delivering large single doses to maximize cell kill in the tumor and fractionating doses to spare normal tissue.

A common quantity that is used alternatively to quantify the effect of the radiation treatment is the BED (Barendsen 1982, Hall and Giaccia 2006, O'Rourke et al. 2009). It is defined by

$$\text{BED}(d) = \frac{1}{\alpha}(\alpha d + \beta d^2) = d\left(1 + \frac{d}{\alpha/\beta}\right), \qquad (1)$$

where α/β is the ratio of the respective tissue parameters. Thus, the BED in the above definition captures the effective biological dose in the same units as physical dose. A small α/β value means that the tissue is sensitive to large doses; the BED in this case grows rapidly with increasing dose per fraction. Note that BED is related to the LQ model by setting $\text{BED} = -\ln(S)/\alpha$. In the BED model, only a single parameter, the α/β value, needs to be estimated; e.g., in Miralbell et al. (2012) the α/β value is estimated for prostate cancer from radiotherapy outcomes of thousands of patients. Whenever nonstandard fractionation schemes are used in a clinical setting, the BED model is typically used to quantify fractionation effects. In this paper, we frequently switch between the cell interpretation in the LQ model and the effective dose interpretation in the BED model, as they

both provide alternative and useful views based on context.

Based on the relation given in Equation (1), we define $\text{BED}_T(d)$ as the BED in a tumor when a dose d is delivered, where $[\alpha/\beta]_T$ is the α/β value of the tumor. We also define the total BED in the tumor from delivering doses $d_0, d_1, \ldots, d_{N-1}$ as

$$\text{BED}_T = \sum_{k=0}^{N-1} \text{BED}_T(d_k) = \sum_{k=0}^{N-1} d_k \left(1 + \frac{d_k}{[\alpha/\beta]_T}\right).$$

In this paper, we consider a single dose-limiting radio-sensitive organ-at-risk (OAR); this assumption is appropriate for some disease sites (e.g., for prostate cancer, the rectum could be taken as the dose-limiting organ). We assume that an OAR receives a fraction of the dose applied to the tumor. Thus, let a dose d be applied to the tumor result in a dose of γd in the OAR, where γ is the fractional constant, also referred to as the normal tissue sparing factor, satisfying $0 < \gamma < 1$. Implicitly, this assumes a spatially homogeneous dose in the tumor and the OAR as in Mizuta et al. (2012). The generalization to a more realistic inhomogeneous OAR dose distribution (Unkelbach et al. 2013), which leaves the main findings of this paper unaffected, is detailed in §5.1. The value of γ will depend on the treatment modality and the disease site. For treatment modalities providing very conformal dose around the tumor and disease sites with the OAR not closely abutting the primary tumor, the OAR will receive less radiation and thus γ would be a smaller. Using γd as the dose in the OAR and $[\alpha/\beta]_O$ as the OAR α/β value, we can define the associated OAR BEDs, $\text{BED}_O(d)$, and BED_O in the same way as was done for the tumor BED:

$$\text{BED}_O = \sum_{k=0}^{N-1} \text{BED}_O(d_k) = \sum_{k=0}^{N-1} \gamma d_k \left(1 + \frac{\gamma d_k}{[\alpha/\beta]_O}\right).$$

2.2. Tumor Growth Model

In this section, we describe tumor growth models that will be used later to formulate a fractionation problem. We model the growth of the tumor through the ordinary differential equation (Wheldon 1988):

$$\frac{1}{x(t)} \frac{dx(t)}{dt} = \phi(x(t)), \qquad (2)$$

with initial condition $x(0) = X_0$, where $x(t)$ is the expected number of tumor cells at time t. In the Equation (2), $\phi(x)$ represents the instantaneous tumor proliferation rate. We assume that $\phi(x)$ is nonincreasing and is continuous in x (for $x > 0$), which implies that the solution to the above differential equation exists and is unique for any $X_0 > 0$. By choosing an appropriate functional form of ϕ, we can describe a variety

0.05
0.04
0.03
0.02
0.01
0

$\phi(x)$ – tumor growth rate (days^{-1})

0   0.2   0.4   0.6   0.8   1.0
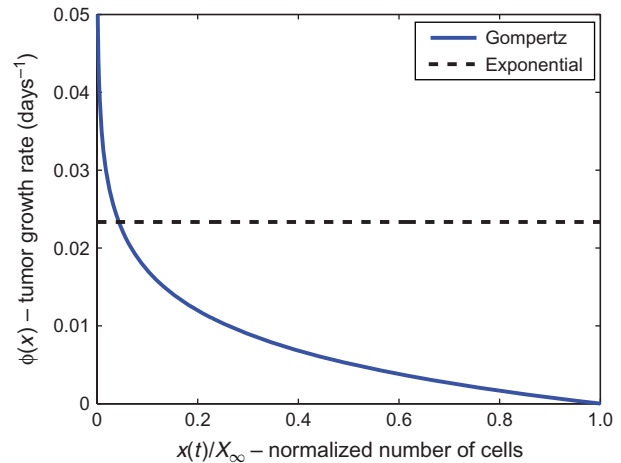$x(t)/X_\infty$ – normalized number of cells

— Gompertz
--- Exponential

Figure 2   (Color online) Tumor Growth Rate vs. Number of Tumor Cells

Note. The Gompertz equation models slower growth for larger number of cells while the exponential model assumes a constant growth rate.

of tumor repopulation characteristics relevant for radiation therapy:

1. We can model *exponential* tumor growth (Wheldon 1988, Yorke et al. 1993) with a constant proliferation rate ρ by choosing $\phi(x) = \rho$. In this case, the solution $x(t)$ of the differential equation with initial condition $x(0) = X_0$ is

$$x(t) = X_0 \exp(\rho t),$$

where X_0 is the initial number of cells and $\rho > 0$ is the proliferation rate.

2. We represent *accelerated* repopulation by choosing $\phi(x)$ to be a decreasing function of x. In this case, the instantaneous tumor proliferation rate increases when, toward the end of treatment, the number of remaining tumor cells decreases. The Gompertz model (Laird 1964, Norton et al. 1976, Norton 1988) is one such decelerating tumor growth curve (Figure 2). For Gompertzian growth, we would simply set

$$\phi(x) = b \ln\left(\frac{X_\infty}{x}\right),$$

where X_0 is the initial number of tumor cells, X_∞ is the carrying capacity or the maximum number of tumor cells, and b is a parameter that controls the rate of growth. The solution to the differential Equation (2), with initial condition $x(0) = X_0$, is

$$x(t) = X_0^{\exp(-bt)} X_\infty^{1-\exp(-bt)}. \qquad (3)$$

This equation models slower repopulation for larger tumor sizes and vice versa (see Figure 2).

2.3. Formulation

In this section, we combine the LQ model from §2.1 and the tumor growth model from §2.2 and formulate

a fractionation problem. The aim of radiation therapy is to maximize the tumor control probability (TCP) subject to an upper limit on the normal tissue complication probability (NTCP) in the OAR (O'Rourke et al. 2009). A significant amount of research has been conducted to determine appropriate and better models of TCP (Brahme and Agren 1987, O'Rourke et al. 2009) and NTCP (Kutcher and Burman 1989, Lyman 1985). A common way to model NTCP is as a sigmoidal function of BED_O (Kutcher et al. 1991). Since a sigmoidal function is monotonic in its argument, it then suffices in our model to impose an upper limit on BED_O. Though some studies have raised concerns (Tucker et al. 1990), TCP has been widely modeled using Poisson statistics (Munro and Gilbert 1961; Porter 1980a, b), under which

$$TCP = \exp(-X_{N-1}^+),$$

where X_{N-1}^+ is the expected number of tumor cells surviving after the last dose of radiation. In this case, maximizing the TCP is equivalent to minimizing X_{N-1}^+. We now define

$$Y_{N-1}^+ = \ln(X_{N-1}^+)/\alpha_T,$$

where α_T is a tumor tissue parameter associated with the linear component of the LQ model. Note that the definition of Y is analogous to the definition of the BED. It has units of radiation dose; thus differences in Y can be interpreted as differences in effective BED delivered to the tumor. We choose to primarily work with this logarithmic version because of this interpretation.

For the rest of the paper, we focus on the equivalent problem of minimizing Y_{N-1}^+ subject to an upper limit on BED_O. The problem is stated mathematically as

$$\underset{\{d_i \geq 0\}}{\text{minimize}} \; Y_{N-1}^+ \quad \text{s.t.} \;\; BED_O \leq c, \tag{4}$$

where c is a prespecified constant. There is no guarantee of the convexity of the objective, and thus, this problem is nonconvex. Note that the feasible region is nonempty because a possible feasible schedule is a dose of zero for all treatment sessions. We claim that the objective function in (4) attains its optimal value on the feasible region. As a function of the dose fractions d_k, it can be seen that Y_{N-1}^+ is continuous. Furthermore, the constraint on BED_O ensures the feasible region is compact. Thus, the extreme value theorem ensures that the objective attains its optimal value on the feasible region.

We now describe the dynamics of the expected number of tumor cells during the course of treatment (Figure 3). We assume that a sequence of N doses $d_0, d_1, \ldots, d_{N-1}$ is delivered at integer times; i.e., time
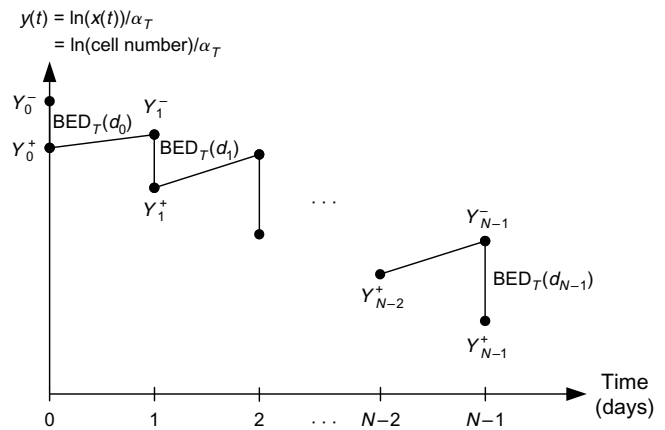

Figure 3   Schematic Illustration of the Expected Number of Tumor Cells Over the Course of Treatment

Note. The effect of radiation dose d is a reduction, proportional to $BED_T(d)$, in the log of the number of cells.

is measured in days. The survival fraction of cells from delivering these radiation doses is described by the LQ model in §2.1. If X_i^- and X_i^+ are the numbers of tumor cells immediately before and after delivering the dose d_i, we will have $X_i^+ = X_i^- \exp(-(\alpha_T d_i + \beta_T d_i^2))$. For the logarithmic versions Y_i^+ and Y_i^-, we have for integer times

$$Y_i^+ = Y_i^- - BED_T(d_i).$$

For noninteger times in $[0, N-1]$, the tumor grows according to the differential Equation (2) with proliferation rate $\phi(x)$, as described in §2.2. For convenience, we denote by $F(\cdot)$ the resulting function that maps Y^- to Y^+ when using the growth differential Equation (2). Thus, we have

$$Y_{i+1}^- = F(Y_i^+)$$

for $i = 0, 1, \ldots, N-2$.

2.3.1.   Exponential Tumor Growth with Constant Proliferation Rate. For the exponential tumor growth model, where $\phi(x) = \rho$, the rate of repopulation ρ does not change with tumor size (see Figure 2). Assuming ρ represents a measure of growth per unit day (or fraction), the number of tumor cells is multiplied by a factor of $\exp(\rho)$ after every fraction. Or, equivalently, a constant factor is added to the logarithmic cell number because of tumor growth in between treatment days. Since there are N dose fractions and $N-1$ days of repopulation in between, it can be seen that the optimization problem (4) simplifies to

$$\underset{\{d_i \geq 0\}}{\text{minimize}} \; \left\{ Y_0 + \frac{1}{\alpha_T}(N-1)\rho - BED_T \right\}$$
$$\text{s.t.} \;\; BED_O \leq c. \tag{5}$$

Here the effect of tumor repopulation is captured in the term $(N-1)\rho/\alpha_T$.

2.3.2. Gompertzian Tumor Growth. For the case of Gompertzian tumor growth, where $\phi(x) = b\ln(X_\infty/x)$, we can also significantly simplify the formulation. As shown in §2.4, this results in a simplified DP approach to determine an optimal fractionation schedule. We will now derive an explicit expression for the expected number of tumor cells at the end of treatment. We claim that

$$Y_i^+ = \frac{1}{\alpha_T}\ln(x(i)) - \sum_{k=0}^{i}\exp[-b(i-k)]\operatorname{BED}_T(d_k), \quad (6)$$

for $i = 0, 1, \ldots, N-1$, where $x(t)$ represents the expected number of tumor cells in the absence of radiation treatment, and which is given by the expression in Equation (3). (In particular, $x(t)$ should not be confused with the number of tumor cells when the tumor is treated.) Equation (6) holds for $i = 0$ because $x(0) = X_0$ and $Y_0^+ = \ln(X_0)/\alpha_T - \operatorname{BED}_T(d_0)$. For the inductive step, suppose that Equation (6) holds true. From the Gompertzian growth Equation (3), and assuming that the time interval between fractions is one day $(t = 1)$, we can write the function F that maps Y_i^+ to Y_{i+1}^- as

$$Y_{i+1}^- = F(Y_i^+) = \exp(-b)Y_i^+ + (1 - \exp(-b))\frac{\ln(X_\infty)}{\alpha_T}.$$

Incorporating the growth and the radiation dose from d_{i+1}, we find

$$\begin{aligned} Y_{i+1}^+ &= F(Y_i^+) - \operatorname{BED}_T(d_{i+1}) \\ &= \frac{1}{\alpha_T}\ln(x(i)^{\exp(-b)}X_\infty^{1-\exp(-b)}) \\ &\quad - \sum_{k=0}^{i+1}\exp[-b(i+1-k)]\operatorname{BED}_T(d_k) \\ &= \frac{1}{\alpha_T}\ln(x(i+1)) - \sum_{k=0}^{i+1}\exp[-b(i+1-k)]\operatorname{BED}_T(d_k), \end{aligned}$$

completing the inductive step. This results in the optimization problem

$$\begin{aligned} \underset{\{d_i \geq 0\}}{\text{minimize}} \quad &\left\{\frac{1}{\alpha_T}\ln(x(N-1)) \right. \\ &\left. - \sum_{k=0}^{N-1}\exp[-b(N-1-k)]\operatorname{BED}_T(d_k)\right\} \end{aligned}$$

$$\text{s.t. } \operatorname{BED}_O \leq c.$$

The interesting aspect of the above optimization problem is that it is essentially a maximization of a discounted sum of the terms $\operatorname{BED}_T(d_k)$. Because the weighting term gives larger weight to later fractions, we can conjecture that the optimal fractionation scheme will result in larger fraction sizes toward the end of treatment. This is in contrast to the exponential tumor growth model for which there is no accelerated repopulation, and the $\operatorname{BED}_T(d_k)$ terms are weighted equally.

2.4. Dynamic Programming Approach

To get from the initial Y_0 to Y_{N-1}^+, one recursively alternates between applying a dose d and the growth function F. That is, Y_{N-1}^+ takes the form

$$\begin{aligned} Y_{N-1}^+ = F(\cdots F(F(Y_0 - \operatorname{BED}_T(d_0)) - \operatorname{BED}(d_1))\cdots) \\ - \operatorname{BED}(d_{N-1}). \end{aligned} \quad (7)$$

Such a recursive formulation lends itself naturally to a DP approach. We can solve the optimization problem by recursively computing an optimal dose backward in time. Note that although nonlinear programming methods can also be used, there is no guarantee of the convexity of (7), and thus, such methods might only provide a local optimum. A global optimum, however, is guaranteed if a DP approach is used.

To determine the dose d_k, we take into account Y_{k-1}^+ and the cumulative BED in the OAR from delivering the prior doses, which we define as

$$z_k = \sum_{i=0}^{k-1}\operatorname{BED}_O(d_i).$$

Here, Y_{k-1}^+ and z_k together represent the state of the system because they are the only relevant pieces of information needed to determine the dose d_k. We do not include a cost per stage; instead, we include Y_{N-1}^+ in a terminal condition. To ensure that the constraint on BED_O is satisfied, we also assign an infinite penalty when the constraint is violated. The Bellman recursion to solve the problem is

$$\begin{aligned} J_N(Y_{N-1}^+, z_N) &= \begin{cases} Y_{N-1}^+, & \text{if } z_N \leq c; \\ \infty, & \text{otherwise,} \end{cases} \\ J_k(Y_{k-1}^+, z_k) &= \min_{d_k \geq 0}\left[J_{k+1}(F(Y_{k-1}^+) - \operatorname{BED}_T(d_k), \right. \\ &\qquad\qquad\left. z_k + \operatorname{BED}_O(d_k))\right], \end{aligned} \quad (8)$$

for $k = N-1, N-2, \ldots, 1$. The initial equation for time 0, given next, is slightly different because there is no prior tumor growth (see Figure 3):

$$J_0(Y_0^-, z_0) = \min_{d_0 \geq 0}\left[J_1(Y_0^- - \operatorname{BED}_T(d_0), z_0 + \operatorname{BED}_O(d_0))\right].$$

For the exponential and Gompertzian growth cases, the DP approach simplifies and only requires the single state z_k. Next, we discuss the approach for the Gompertzian case only; for the exponential case, as will be discussed in §3.1, an optimal fractionation scheme can be characterized in closed form. For simplicity, we use additive costs per stage this time. The simplified algorithm is

$$\begin{aligned} J_N(z_N) &= \begin{cases} (1/\alpha_T)\ln(x(N-1)), & \text{if } z_N \leq c; \\ \infty, & \text{otherwise,} \end{cases} \\ J_k(z_k) &= \min_{d_k \geq 0}\left[-\exp[-b(N-1-k)]\operatorname{BED}_T(d_k) \right. \\ &\qquad\qquad\left. + J_{k+1}(z_k + \operatorname{BED}_O(d_k))\right], \end{aligned} \quad (9)$$

for $k = N-1, N-2, \ldots, 0$. For numerical implementation, the state variables need to be discretized and the tabulated values stored. For evaluating the cost-to-go function J_k at any nondiscretized values, an interpolation of appropriate discretized values can be used for increased accuracy.

3. Properties of an Optimal Fractionation Schedule

In §3.1, we discuss previously known results. These primarily concern the characterization of optimal fractionation schedules in the absence of accelerated repopulation. The purpose of this subsection is to provide the essential results that are scattered in the literature in different papers and formalize them in the framework of this paper. In §3.2, we summarize our main results. The proofs of the results are provided in the online supplement (available as supplemental material at http://dx.doi.org/10.1287/ijoc.2015.0659).

3.1. Previously Known Results

The set of all optimal solutions to the fractionation problem in the absence of repopulation is characterized in the following theorem, published in Mizuta et al. (2012).

Theorem 1. *Let N be fixed. In the absence of repopulation (i.e., $\phi(x) = 0$), an optimal fractionation schedule can be characterized in closed form. If $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$, an optimal solution is to deliver a single dose equal to*

$$d_j^* = \frac{[\alpha/\beta]_O}{2\gamma}\left[\sqrt{1 + \frac{4c}{[\alpha/\beta]_O}} - 1\right] \quad (10)$$

at an arbitrary time j and deliver $d_i = 0$ for all $i \neq j$. This corresponds to a hypofractionation regimen. If $[\alpha/\beta]_O < \gamma[\alpha/\beta]_T$, the unique optimal solution consists of uniform doses given by

$$d_j^* = \frac{[\alpha/\beta]_O}{2\gamma}\left[\sqrt{1 + \frac{4c}{N[\alpha/\beta]_O}} - 1\right], \quad (11)$$

for $j = 0, 1, \ldots, N-1$. This corresponds to a hyperfractionation regimen, i.e., a fractionation schedule that uses as many treatment days as possible.

This theorem states that if $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$, a single radiation dose is optimal; i.e., the optimal number of fractions N^* is 1. However, if $[\alpha/\beta]_O$ is small enough—i.e., the OAR is sensitive to large doses per fraction, so that $[\alpha/\beta]_O < \gamma[\alpha/\beta]_T$—it is optimal to deliver the same dose during the N days of treatment. Because taking larger N only results in extra degrees of freedom, $N^* \to \infty$ in this case. However, this is clearly not realistic and is an artifact of modeling assumptions. We will show that including tumor repopulation results in a finite N^*. In the following remark, we comment on the result and the model assumptions.

Remark 1. Our ultimate goal is to understand the effect of accelerated repopulation over the duration of treatment. Thus, we are primarily interested in the hyperfractionation case, with $[\alpha/\beta]_O < \gamma[\alpha/\beta]_T$, which will hold for most disease sites. The case where $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$ needs careful consideration since the validity of the model may be limited if N is small and the dose per fraction is large. The condition $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$ would be satisfied for the case of an early responding OAR tissue (see §5.4 for further details); however, we have not included repopulation and repair effects into the BED model, which could play an important role for such tissue. Another aspect that requires consideration is whether doses should be fractionated to permit tumor re-oxygenation between treatments. Thus, without extensions to our current model, it may be better to set a minimum number of fractions (e.g., five) in the case where $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$.

In the next remark, we discuss how Theorem 1 can be generalized in the case of exponential tumor growth.

Remark 2. For the problem including exponential tumor growth with $\phi(x) = \rho$, there is only an additive term $(N-1)\rho/\alpha_T$ in objective (5), which is independent of the dose fractions. Thus, for a fixed N, the result from Theorem 1 still holds for the exponential growth case.

It turns out that one can also characterize the optimal number of fractions in closed form for the exponential tumor growth case. The result is consistent with and similar to the work in a few papers (Wheldon et al. 1977, Jones et al. 1995, Armpilia et al. 2004), though we interpret it differently here. Our statement below is a slight generalization in that we do not assume uniform dose per day a priori.

Theorem 2. *The optimal number of fractions N^* for exponential growth with constant proliferation rate ρ (i.e., $\phi(x) = \rho$) is obtained by the following procedure:*
1. *If $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$, then $N^* = 1$.*
2. *If $[\alpha/\beta]_O < \gamma[\alpha/\beta]_T$, then*
   (a) *Compute $N_c = A(\sqrt{(\rho+B)^2/(\rho(\rho+2B))} - 1)$, where $A = 2c/[\alpha/\beta]_O$, $B = (\alpha_T[\alpha/\beta]_O/2\gamma)(1 - [\alpha/\beta]_O/\gamma[\alpha/\beta]_T)$.*
   (b) *If $N_c < 1$, then $N^* = 1$. Otherwise, evaluate the objective at $\lfloor N_c \rfloor$ and $\lceil N_c \rceil$, where $\lfloor \cdot \rfloor$ and $\lceil \cdot \rceil$ are the floor and ceiling operators, respectively, and let the optimum N^* be the one that results in a better objective value.*

This result also makes sense in the limiting cases. When approaching the case of no repopulation—i.e., $\rho \to 0$—we see that $N_c \to \infty$, and the optimum N^* approaches infinity. When $\rho \to \infty$, we see that $N_c \to 0$, meaning that the optimum N^* is a single dose. Recall that if $[\alpha/\beta]_O < \gamma[\alpha/\beta]_T$, $N^* \to \infty$ in the absence of

repopulation. For the case of exponential repopulation with constant but positive rate, the above result shows that the optimum N is finite. Indeed, even for general tumor growth characteristics, we will show nextthat as long as there is some repopulation, the optimal number of fractions will be finite.

3.2. Main Results of This Paper

We begin with two lemmas. The first one simply states that the constraint on BED_O is binding; intuitively, this is because of the assumption that $\phi(x) > 0$ (implying the growth function $F(\cdot)$ is increasing) and the fact that the BED function is monotone in dose.

LEMMA 1. *Assume that $\phi(x) > 0$ for all $x > 0$. Then the constraint on BED_O in (4) will be satisfied with equality.*

LEMMA 2. *Assume that $\phi(x) > 0$ for all $x > 0$ and that $\phi(x)$ is a nonincreasing function of x. Suppose that $i < j$ and that we apply the same sequence of doses $d_{i+1}, \ldots, d_j$, starting with either Y_i^+ or $\tilde{Y}_i^+$. If $Y_i^+ < \tilde{Y}_i^+$, then $Y_j^+ < \tilde{Y}_j^+$ and $\tilde{Y}_j^+ - Y_j^+ \leq \tilde{Y}_i^+ - Y_i^+$.*

Assuming that the same sequence of doses are applied, Lemma 2 states a monotonicity and a contraction type property when mapping the expected number of cells from one point in time to another. Next, we state the main theorem.

THEOREM 3. *Let us fix the number of treatment days N. Assume that there is always some amount of repopulation—i.e., $\phi(x) > 0$ for all $x > 0$—and that the instantaneous tumor growth rate $\phi(x)$ is nonincreasing as a function of the number of cells x. If $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$, then it is optimal to deliver a single dose equal to (10) on the last day of treatment. This corresponds to a hypofractionation regimen. If $[\alpha/\beta]_O < \gamma[\alpha/\beta]_T$, then any optimal sequence of doses is nondecreasing over the course of treatment. That is, these doses will satisfy $d_0^* \leq d_1^* \leq \cdots \leq d_{N-1}^*$.*

For the case where $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$, we take note of Remark 1 again. It is reasonable that an optimal solution uses the most aggressive treatment of a single dose, as this is the case even without repopulation. The next remark gives an intuitive explanation for why in the fixed N case it is optimal to deliver only on the last treatment day and shows the optimal number of fractions N^* is 1 when $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$.

REMARK 3. A single dose delivered on the last treatment day is optimal when $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$ because it is better to let the tumor grow slowly during the course of treatment rather than to stimulate accelerated growth by treating it earlier. However, this does not mean it is optimal to wait too long before treating the patient. Starting with a given initial number of tumor cells, it is clear that treating a single dose with a smaller N results in a better cost. This is because the tumor grows for a shorter time. Thus, it follows

that when $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$, the optimal number of fractions is $N^* = 1$.

When $[\alpha/\beta]_O < \gamma[\alpha/\beta]_T$, the doses must increase over time. Intuitively, because of the decreasing property of $\phi(x)$ as a function of x, the tumor grows faster when its size becomes smaller over the course of treatment; higher doses are then required to counter the increased proliferation. An interchange argument is used to prove the above theorem.

The next theorem states that as long as the repopulation rate cannot decrease to 0, the optimal number of fractions N^* is finite.

THEOREM 4. *Suppose that there exists $r > 0$ such that $\phi(x) > r$ for all $x > 0$. Then there exists a finite optimal number of fractions N^*.*

Typically in a clinical setting, dose fractions are not delivered during weekend and holiday breaks. The following remark explains how such breaks can be included in our formulation.

REMARK 4. We can adjust the fractionation problem by setting N to be the total number of days, including weekend and holiday breaks. For days in which a treatment is not administered, the dose fraction is set to 0. For all other days, the DP algorithm (8) is used as before to determine the optimal fractionation schedule.

Corollary 1 shows that the structure of an optimal solution is still similar to that described in Theorem 3 even when including holidays in the formulation and/or fixing some dose fractions.

COROLLARY 1. *Including breaks and/or fixing the dose in some fractions does not change the structure of the optimized dose fractions as described in Theorem 3. Fix N. Assume that $\phi(x) > 0$ for all $x > 0$ and that $\phi(x)$ is nonincreasing in x. If $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$, then an optimal solution is to deliver a single dose on the last deliverable day that is not a break and not a fixed dose fraction. If $[\alpha/\beta]_O < \gamma[\alpha/\beta]_T$, then an optimal sequence of doses, excluding breaks and fixed dose fractions, is nondecreasing over the course of treatment.*

Thus, according to this corollary, if $[\alpha/\beta]_O < \gamma[\alpha/\beta]_T$ and we introduce weekend breaks, the dose on Monday will in general be larger than the dose on the Friday of the previous week. To understand why this is so, consider what would happen if the Friday dose were in fact larger. The tumor would then be growing at a faster rate over the weekend; then it would make better sense to deliver a higher Monday dose instead. This result is different from the numerical results in Wein et al. (2000). Of course, the model was different in that paper because the primary motivation was to determine the effect of the varying

tumor sensitivity over the course of treatment, not to counter accelerated repopulation.

When we assume an exponential growth model, we can fully characterize the optimal solution, like in Remark 5.

REMARK 5. For the exponential growth model where $\phi(x) = \rho$, if $[\alpha/\beta]_O < \gamma[\alpha/\beta]_T$, we claim that the optimal solution would be to deliver uniform doses at each treatment session, i.e., on days that are not breaks and that do not have fixed dose fractions. Let us adjust the number of days N appropriately and set the dose fractions to 0 for the breaks. Then, for a fixed N, as seen from the objective in (5), the only relevant term that determines the dose fractions is $-\text{BED}_T$. Thus, for a fixed N, the arguments from Theorem 1 hold and uniform doses are optimal. Now we discuss the effect of breaks on the optimal number of fractions. If the number of breaks is simply a fixed number, the optimal number of days N^*, including holiday breaks, would be still given by the expression in Theorem 2. This is because the derivative of the objective given in (5) as a function of N would remain unchanged. If the number of breaks is nondecreasing in the number of treatment days (as would be the case with weekend breaks), the expression for N^* given in Theorem 2 would not necessarily hold. Deriving a closed form formula for N^* for this case appears to be tedious, if not impossible. We suggest, therefore, exhaustively evaluating the objective given in (5) for reasonable values of N to obtain a very good, if not optimal, choice of the number of treatment days. For a given break pattern, we could also optimize the starting day of treatment by appropriately evaluating the objective in (5).

4. Numerical Experiments

In §4.1, we calculate the optimal treatment duration while assuming exponential tumor growth with varying rates of repopulation. In §§4.2 and 4.3, we model accelerated repopulation using Gompertzian growth and numerically calculate the resulting optimal fractionation scheme. Finally, in §4.4, we evaluate the effect of weekend breaks. For all of our numerical simulations, we used MATLAB on a 64-bit Windows machine with 4GB RAM.

4.1. Faster Tumor Growth Suggests Shorter Overall Treatment Duration

We use realistic choices of radiobiological parameters to assess the effect of various rates of tumor growth on the optimal number of treatment days. Here, we assume exponential growth with a constant rate of repopulation. We use $[\alpha/\beta]_T = 10$ Gy, $[\alpha/\beta]_O = 3$ Gy, and $\alpha_T = 0.3$ Gy^{-1} for the tissue parameters; these are appropriate standard values (Guerrero and Li 2003,

Hall and Giaccia 2006). We consider a standard fractionated treatment as reference, i.e., a dose of 60 Gy delivered to the tumor in 30 fractions of 2 Gy. For the above choice of α/β values and $\gamma = 0.7$, this corresponds to an OAR BED of 61.6 Gy, which we use as the normal tissue BED constraint c. To choose appropriate values for the proliferation rate ρ, we relate it to the tumor doubling time τ_d. Since τ_d represents the time it takes for the tumor to double in size, we set $\exp(\rho t) = 2^{t/\tau_d}$, resulting in the following relation:

$$\rho = \frac{\ln(2)}{\tau_d}.$$

For human tumors, the doubling time can range from days to months (Withers et al. 1988, Kim and Tannock 2005), depending on the particular disease site. We observe that for the parameters assumed above, the optimal number of treatment days is smaller for faster growing tumors (Figure 4).

The objective value plotted in Figure 4 is

$$\text{BED}_T - \frac{1}{\alpha_T}(N-1)\rho.$$

For the reference treatment ($N = 30$) and $\alpha_T = 0.3$, the decrease in the tumor BED from the second term $(N-1)\rho/\alpha_T$ evaluates to about 1.3 Gy for a slowly proliferating tumor with doubling time $\tau_d = 50$. This is small compared to $\text{BED}_T = 72$. For a fast proliferating tumor with doubling time $\tau_d = 5$, the correction $(N-1)\rho/\alpha_T$ is about 13.4 Gy and becomes more important. Thus, smaller values of N are suggested for faster proliferating tumors.

4.2. Accelerated Repopulation Suggests Increasing Doses Toward the End of Treatment

One way to model accelerated repopulation is to use decreasing tumor growth curves (see Figure 2). We model this behavior using the Gompertzian tumor growth model and solve the fractionation problem by using the simplified DP Equation (9). For numerical implementation of the DP algorithm, we discretize the state into 500 points for each time period. When evaluating the cost-to-go function for values in between discretization points, we use linear interpolation. We illustrate optimal fractionation schemes for both slow and fast proliferating tumors. For a slowly proliferating tumor, we choose the parameters $X_0 = 4 \times 10^6$, $X_\infty = 5 \times 10^{12}$, and $b = \exp(-6.92)$ by fixing X_∞ (to be on the order of the value given in Norton (1988) for breast cancer) and manually varying X_0 and b so that the doubling time for the reference treatment starts at 50 days in the beginning and decreases to 20 days at the end of treatment. For a fast proliferating tumor, we adjust the parameters accordingly so that the doubling time goes from 50 to 5 days: $X_0 = 6 \times 10^{11}$,
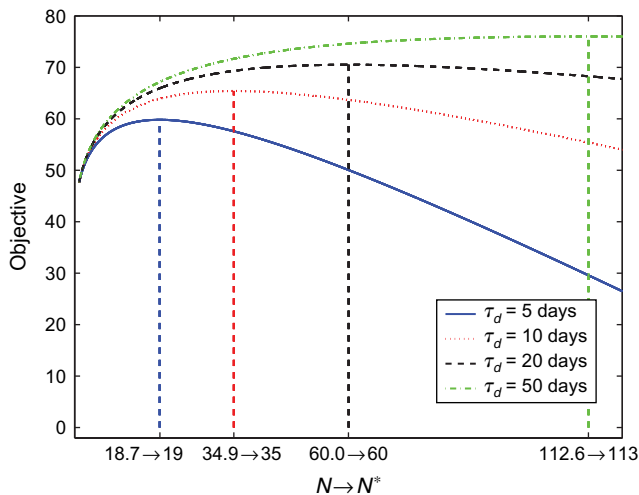
Figure 4   (Color online) Dependence of the Optimal Value of the Objective Function for Different Choices of the Number of Fractions, Assuming Exponential Tumor Growth

Notes. The optimal number of treatment days is smaller for faster growing tumors. The expression in Theorem 2 was used to generate this plot. The objective was evaluated at the floor and ceiling of the continuous optimum N to obtain the actual optimum N^*.

$X_\infty = 5 \times 10^{12}$, and $b = \exp(-5.03)$. Such fast growth is not atypical; clinical data on squamous cell carcinomas of the head and neck show that it is possible for the doubling time to decrease from 60 days to four days, although there could be an initial lag period of constant repopulation (Withers et al. 1988). As before, we use the parameters $[\alpha/\beta]_T = 10$ Gy, $[\alpha/\beta]_O = 3$ Gy, $\alpha_T = 0.3$ Gy^{-1}, $c = 61.6$ Gy, and $\gamma = 0.7$.

As shown in Figure 5, for a fast proliferating tumor, the sequence of radiation doses increases from 1 Gy to 3 Gy, which is a significant difference from the standard treatment of 2 Gy per day for 30 days. For a slow proliferating tumor, the doses closely resemble standard treatment and only increase slightly over the course of treatment. Note that the optimal fractionation scheme distributes the doses so that they are approximately proportional to the instantaneous proliferation rate $\phi(x)$. The plotted $\phi(x)$ in Figure 5 is the resulting instantaneous proliferation rate after the delivery of each dose fraction. For the reference treatment of 2 Gy per day with $N = 30$, in the case of a fast proliferating tumor, the objective Y_{N-1}^+ is 26.03. The objective Y_{N-1}^+ for the optimal fractionation scheme in plot (b) of Figure 5 is 25.41. This is a change of about 2.4% in Y_{N-1}^+ and 17.0% change in X_{N-1}^+ in comparison to the reference treatment. It is not straightforward to make a meaningful statement about the improvement in tumor control simply based on these values. However, we can say that even a small improvement in tumor control for a specific disease site can make a significant impact because of the large number of patients treated with radiation therapy every year.

In principle, running the DP algorithm for every possible value of N would give us the optimal number of fractions. We choose to run the algorithm for $N = 1, 2, \ldots, 100$. For each run of the DP algorithm for a fixed N, it takes on average about 7 seconds using MATLAB on a 64-bit Windows machine with 4GB RAM and an Intel i7 2.90 GHz chip. We find $N = 79$ results in the best cost for the slowly proliferating tumor and $N = 38$ for the fast proliferating tumor. For the slowly proliferating tumor, a very small fraction of the tumor's cells remains, regardless of whether $N = 79$ or $N = 30$; for the fast proliferating tumor, setting $N = 30$ instead of $N = 38$ results only in a change of 0.7% in Y_{N-1}^+. Thus, for practical purposes, it is reasonable to set $N = 30$ because more dose fractions could mean, among other factors, patient inconvenience and further cost.

4.3. Smaller α/β Value of the Tumor Results in Larger Changes in the Fractionation Schedule

We use a smaller value for the α/β value of the tumor and rerun the calculations from the previous subsection. The parameters of the Gompertzian growth remain the same for the slow and fast proliferating tumor. As before, we use the parameters $[\alpha/\beta]_O = 3$ Gy, $\alpha_T = 0.3$ Gy^{-1}, $c = 61.6$ Gy, and $\gamma = 0.7$, with the only change being that $[\alpha/\beta]_T = 5.7$ Gy. Note that the condition $[\alpha/\beta]_O = 3 < \gamma[\alpha/\beta]_T = 4$ is satisfied, meaning that hypofractionation is not optimal (see Theorem 3). We run the DP algorithm for $N = 1, 2, \ldots, 100$, and find $N = 42$ and $N = 17$ result in the best cost for the slowly and fast proliferating tumors, respectively. However, for practical purposes, we again set the maximum number of fractions as 30 for the slowly proliferating tumor because a very small fraction of the tumor's cells remains, regardless of whether $N = 42$ or $N = 30$, and there is a change of only 0.7% in Y_{N-1}^+. As seen in part (b) of Figure 6, for the fast proliferating tumor, the sequence of radiation doses ranges from approximately 1 Gy to 5.5 Gy for the 17 days of treatment. This change in the fractionation schedule results in the objective Y_{N-1}^+ being 15.42, compared to 17.78 for the reference treatment of 2 Gy per day for 30 days. This is a significant change of 13.3% in Y_{N-1}^+ and about 50.7% change in X_{N-1}^+ in comparison to the reference treatment. Similar to §4.2, the fraction doses are approximately proportional to the instantaneous proliferation rate.

We can infer that a smaller α/β value of the tumor suggests using larger changes in the fraction sizes and shorter overall treatment duration; this results in larger gains in the objective value and hence in overall tumor control. Low values of α/β have been observed for disease sites such as prostate cancer (Miralbell et al. 2012). Numerical experiments also indicate a similar effect when varying the normal
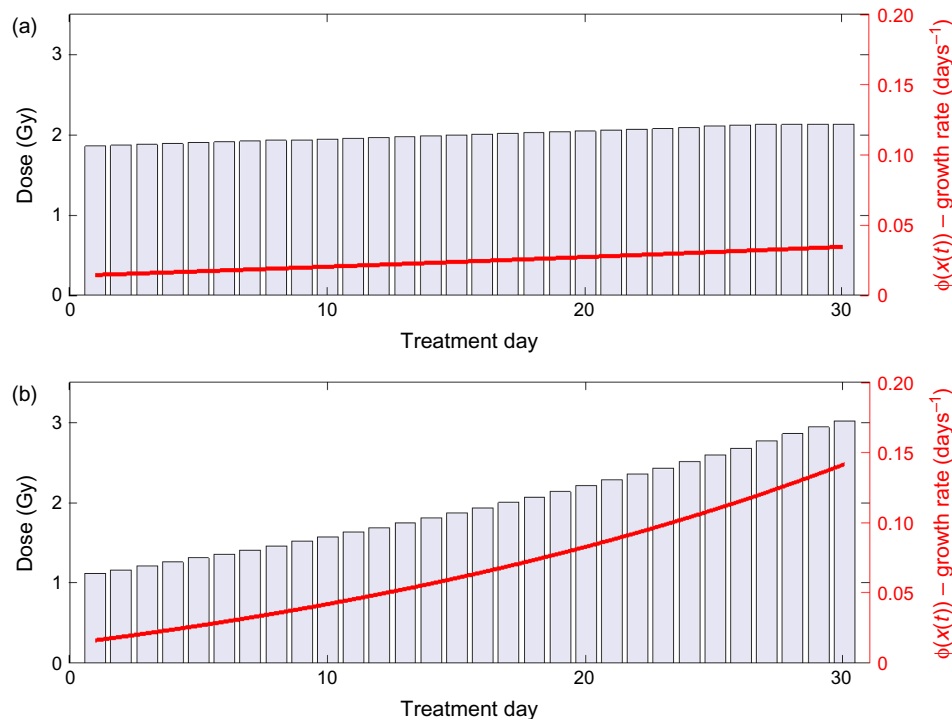
Figure 5   **(Color online) Optimal Fractionation for Accelerated Repopulation**

Notes. Plot (a) shows the optimal fractionation schedule for a slowly proliferating tumor and plot (b) for a fast one. The doubling time for the reference treatment begins at $\tau_d = 50$ days and decreases approximately to (a) 20 and (b) 5 days, respectively, at the end of treatment. The plotted $\phi(x)$ is the resulting instantaneous proliferation rate after the delivery of each dose fraction.

tissue sparing factor γ. That is, a smaller γ results in larger changes in the fractionation schedule. Intuitively, this is because better sparing of normal tissue allows a more aggressive treatment with higher tumor control. Of course, if the α/β value or sparing factor γ is very small, hypofractionation would be optimal (see Theorem 3).

4.4. Effect of Weekend Breaks
We simulate the effect of weekend breaks using 30 treatment sessions (starting Monday and ending Friday) with appropriately inserted weekend days, resulting in $N = 40$ days (6 weeks, 5 weekends). We set $[\alpha/\beta]_T = 10$ and assume a fast proliferating tumor, with Gompertzian growth parameters given in §4.2. Thus, the parameters are the same as those used in part (b) of Figure 5, with the only difference being the inclusion of weekend breaks. The optimal fractionation scheme in this case is shown in Figure 7. Note that the dose fractions range from approximately 0.9 Gy in the first fraction to 3.5 Gy in the last fraction. The dose increase toward the end of treatment is larger than in Figure 5 part (b), which can probably be attributed to the lengthened overall treatment time from weekend breaks. Note that $\phi(x)$ is slightly decreasing during the weekend interval; this

is because a growing tumor results in a smaller proliferation rate. In this numerical example, the decrease in $\phi(x)$ is small so that the dose fractions remain approximately proportional to $\phi(x)$.

5. Discussion and Further Remarks

5.1. Nonuniform Irradiation of the OAR
Although we have assumed throughout the paper that a dose d results in a homogeneous dose γd to the OAR, in reality the OAR receives nonuniform irradiation. The tumor, however, is generally treated homogeneously. In Unkelbach et al. (2013) and Keller et al. (2013), the basic result stated in Theorem 1 is generalized to arbitrary inhomogeneous doses in the OAR. The arguments in Unkelbach et al. (2013) are also applicable to the case of repopulation as considered in this paper. We can define an effective sparing factor γ_{eff} and an effective upper limit c_{eff} on the BED_O, and the results in this paper will still hold.

The results differ for the case of parallel OAR and serial OAR. A parallel organ could remain functional even with damaged parts; a serial OAR, in contrast, remains functional only when all of its parts remain functional. For the case of a parallel OAR (e.g., lung), assuming that $\gamma_i d$ represents the dose in the ith voxel
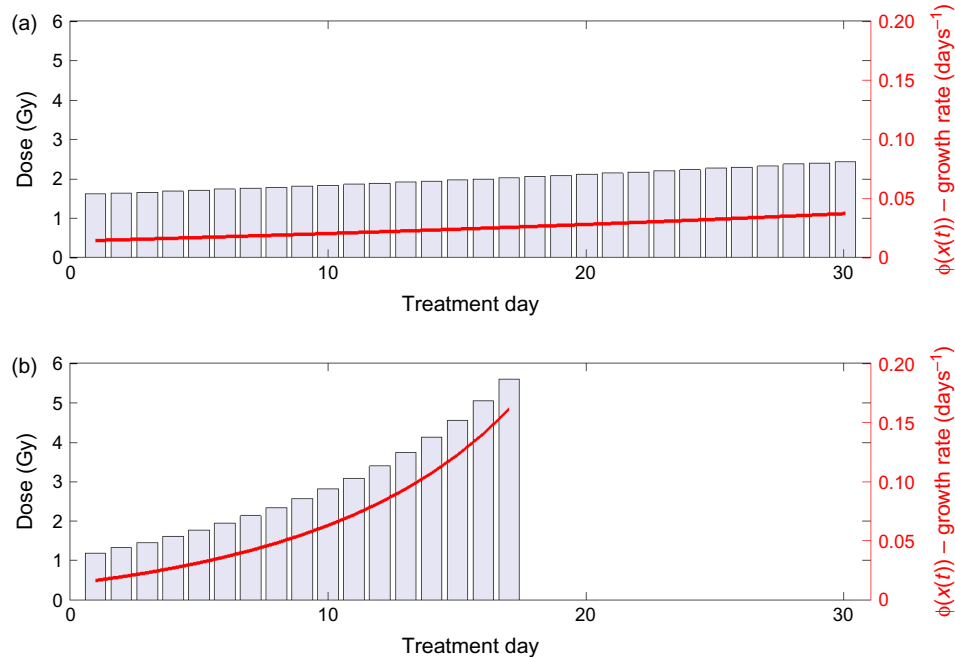
Figure 6 (Color online) Optimal Fractionation for Accelerated Repopulation in the Case of $[\alpha/\beta]_T = 5.7$ **Gy**

Notes. Plot (a) shows the optimal fractionation schedule for a slowly proliferating tumor and plot (b) for a fast one. The doubling time for the reference treatment begins at $\tau_d = 50$ days and decreases approximately to (a) 20 and (b) 5 days, respectively.
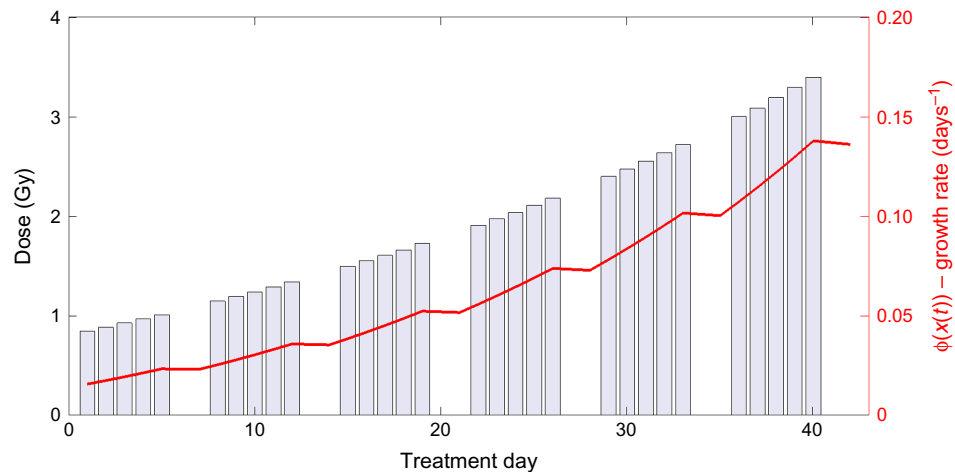

Figure 7 (Color online) Effect of Weekend Breaks on Optimal Fractionation

Note. We use 30 treatment sessions and $[\alpha/\beta]_T = 10$ Gy. The doubling time for the reference treatment begins at $\tau_d = 50$ days and decreases approximately to 5 days.

(or spatial point) in the OAR, the integral BED in the OAR is given by

$$\text{BED}_O = \sum_{k=0}^{N-1} \sum_i \gamma_i d_k \left(1 + \frac{\gamma_i d_k}{[\alpha/\beta]_O}\right).$$

After some algebraic manipulations, we obtain the same form for the normal tissue constraint as in this paper:

$$\sum_{k=0}^{N-1} \gamma_{\text{eff}} d_k \left(1 + \frac{\gamma_{\text{eff}} d_k}{[\alpha/\beta]_O}\right) = c_{\text{eff}},$$

where $\gamma_{\text{eff}} = \sum_i \gamma_i^2 / \sum_i \gamma_i$ and $c_{\text{eff}} = c \gamma_{\text{eff}} / \sum_i \gamma_i$. For the serial case (e.g., spinal cord), only the maximum dose to the OAR matters, resulting in $\gamma_{\text{eff}} = \max_i \gamma_i$ and $c_{\text{eff}} = c$. Additional details can be found in Unkelbach et al. (2013). When the OAR is neither completely parallel nor completely serial, a good approximation of the BED may, e.g., be a weighted combination of the BED for the parallel and serial cases.

5.2. Evolution of Instantaneous Proliferation Rate
In this work, we modeled accelerated repopulation as Gompertzian growth. For the numerical examples

provided in §4, this leads to steadily increasing instantaneous proliferation rates over the course of treatment (see Figures 5 and 7). For a smaller α/β value and a fast proliferating tumor, we even observed rapid increases in the instantaneous proliferation rate—see Figure 6, panel (b). However, more work is needed to estimate the temporal evolution of the repopulation rate $\phi(x)$ during treatment for specific disease sites.

There are alternative tumor growth models, such as the logistic and the Gomp-ex curve (Wheldon 1988) that we did not consider. However, the framework in this paper can also model these patterns of tumor growth.

There are some studies that indicate accelerated repopulation begins only after a lag period, e.g., for head and neck cancer (Brenner 1993). We did not include such a lag period in our numerical experiments. But it can be modeled in our framework by using an appropriate form for $\phi(x)$. We expect a constant dose per fraction during this initial period of constant proliferation rate.

5.3. Variable Time Intervals
The models in this paper are applicable for variable time intervals (e.g., weekends, holidays), as long as each radiation treatment is delivered in a short period of time and the time interval between doses is comparatively long. However, our formulation is not applicable for very short time intervals (on the order of hours) between doses; in such cases, we would need to include biological effects such as incomplete repair of sublethal damage. For optimal fractionation schemes that result from including these sublethal damage repair effects, see Bertuzzi et al. (2013).

5.4. Early and Late Responding Normal Tissue, and Multiple OARs
In the context of fractionation, two types of tissue are typically distinguished in the literature: early responding and late responding. Tumor tissue and some types of healthy tissue such as the skin are typically early responding. That is, they have a relatively large α/β value (e.g., 10), and they start proliferating within a few weeks of the start of radiation treatment (Hall and Giaccia 2006). In contrast, late responding tissue typically has a low α/β value. In this paper, we considered a BED constraint for a single OAR and focused on the situation where $[\alpha/\beta]_O < \gamma[\alpha/\beta]_T$. This describes the situation in which a single late responding tissue is dose limiting and needs to be spared via fractionation. This situation is expected to be most common.

For the case where $[\alpha/\beta]_O \geq \gamma[\alpha/\beta]_T$, our model suggests a hypofractionation regimen. This condition can be fulfilled for early responding tissues that may exhibit a large enough $[\alpha/\beta]_O$ value. However, this case requires careful consideration and possibly an extension of the model. For early responding tissue, the complication probability depends not only on the dose per fraction (as described via the $[\alpha/\beta]_O$ value) but also the overall treatment time. This is currently not explicitly included in our model.

In this paper, we have considered the case where a single OAR is dose-limiting. This is reasonable for some disease sites (e.g., in prostate cancer, the rectum is a single dose-limiting OAR). In the situation where multiple OARs are dose limiting, additional BED constraints and therefore more states in the DP model would be required. This could be computationally intensive even with a few OARs; future research may address this situation. See also Saberian et al. (2014, 2015) for some recent studies on optimal fractionation with multiple OARs.

5.5. Comparison with Prior Work
There have been studies that suggest dose escalation uniformly in time, to counter accelerated repopulation (see, for example, Wang and Li 2005 for prostate cancer and Huang et al. 2012 for cervical cancer). However, our paper primarily suggests dose intensification over time to counter the increased repopulation toward the end of treatment. Dose intensification has now been recommended by many studies, though in other contexts. The Norton-Simon hypothesis (Norton and Simon 1977, 1986) suggests increasing the dose intensity over the course of chemotherapy because of a Gompertzian tumor growth assumption. This work, however, dealt with chemotherapy and thus did not make use of the LQ model. Other studies suggest dose intensification to capitalize on the increased sensitivity of the tumor to radiation toward the end of treatment (Hethcote and Waltman 1973, Almquist and Banks 1976, Marks and Dewhirst 1991, Wein et al. 2000). In Marks and Dewhirst (1991) and Wein et al. (2000), a spherical tumor model consisting of a hypoxic core and an outer rim of well-nourished cells was used to analyze alternative fractionation schemes. The effect of radiation response, e.g., tumor shrinkage, here led to accelerated growth of the tumor toward the end of treatment. Our approach differs from these studies in that accelerated repopulation is modeled by letting the rate of repopulation depend directly on the number of cells in the tumor volume. A few studies indicate the effectiveness of concomitant boost therapy for head and neck cancers (Harari 1992, Ang and Peters 1992), where increased radiation is delivered at the end of treatment. These results seem to be consistent with the analysis in this paper.

The dose intensification strategy presented in this paper has the potential to improve treatment outcomes for certain disease sites that exhibit significant

accelerated repopulation, as long as the objective in our optimization model represents to some degree the actual objectives of the treatment. We note that current practice may actually result in the opposite of the suggested intensification strategy. The initial uniform doses prescribed are sometimes changed to reduced doses at the end of treatment to mitigate patient side effects. Intuitively, however, it is more beneficial to wait until the tumor is aggressive at the end of treatment and only then deliver a high dose, which may result in reduced side effects experienced at that time. Further studies investigating the clinical benefit of dose intensification to counter accelerated repopulation for specific disease sites would be useful.

With technological advances such as functional and molecular imaging, there is potential to track previously unobservable biological processes such as the tumor proliferation rate during the course of therapy (Bading and Shields 2008). The opportunity to then adapt the treatment to the observed data, rather than relying on a model, becomes a possibility. Although previous works have investigated using imaging technology to select dose fractions (Lu et al. 2008, Chen et al. 2008, Kim et al. 2009, Kim 2010, Ghate 2011, Ramakrishnan et al. 2012), they have not done so to counter accelerated repopulation. The problem in this paper can be seen as a special case of the general one presented in Kim et al. (2012), but the effect of tumor proliferation, which is our main focus, was not analyzed therein. Prior works have also considered optimizing the number of treatment days (Kim 2010) but, again, have not done so for general tumor repopulation characteristics, including the case of accelerated repopulation. The insights from this paper suggest that the increases in doses are approximately proportional to the proliferation rate $\phi(x)$. This suggests the importance of further advancement of biological imaging technologies that can accurately measure quantities such as tumor proliferation rates during the course of treatment. An interesting approach worth investigating would then be the use of such imaging techniques to guide therapy.

6. Conclusions

There are multiple ways to model accelerated repopulation. One approach could be to increase the tumor proliferation rate with already delivered dose or BED. In this paper, we chose instead to model accelerated repopulation implicitly by using a decelerating tumor growth curve, e.g., Gompertzian growth, with a proliferation rate $\phi(x)$ that is dependent on the number of tumor cells. This resulted in accelerated growth toward the end of the treatment because fewer cells remained after initial radiation treatment. We developed a DP framework to solve the optimal fractionation problem with repopulation for general tumor growth characteristics described by $\phi(x)$. We proved that the optimal dose fractions are nondecreasing over time, and showed the optimal number of fractions is finite. We derived the special structure of the problem when assuming Gompertzian tumor growth. This resulted in maximizing a discounted version of BED_T, which placed a higher weight on later treatment days, because of increased tumor proliferation. In this paper, we arrived at three main conclusions:

• Faster tumor growth suggested shorter overall treatment duration.

• Accelerated repopulation suggested larger dose fractions later in the treatment to compensate for the increased tumor proliferation. Numerical results indicated that the optimal fraction sizes were approximately proportional to the instantaneous proliferation rate.

• The optimal fractionation scheme used more aggressive increases in dose fractions with a shorter overall treatment duration when the α/β value of the tumor was smaller; in this case, there were larger gains in tumor control.

The advantage of the methods presented in this paper is that a change in the fractionation schedule can be readily implementable in a clinical setting, without technological barriers. However, the results presented in this paper are for illustrative purposes and should not be taken as immediate recommendations for a change in clinical practice. Clinical trials that compare standard approaches with intensified dose at the end of treatment would be needed to quantify the benefit for specific disease sites. We also realize that actual tumor dynamics are more complex than presented in this paper. The tumor volume may consist of a heterogeneous set of cells each with varying division rates. Effects such as re-oxygenation and incomplete repair have not been taken into account. Yet we have avoided incorporating all of these aspects in a single model to primarily focus on the effect of accelerated repopulation. We hope that this analysis can provide useful insights and a basis for further research.

References

Almquist KJ, Banks HT (1976) A theoretical and computational method for determining optimal treatment schedules in fractionated radiation therapy. *Math. Biosciences* 29:159–179.

Ang KK, Peters LJ (1992) Concomitant boost radiotherapy in the treatment of head and neck cancers. *Seminars Radiation Oncology* 2:31–33.

Armpilia CI, Dale RG, Jones B (2004) Determination of the optimum dose per fraction in fractionated radiotherapy when there is delayed onset of tumour repopulation during treatment. *British J. Radiology* 77:765–767.

Bading JR, Shields AF (2008) Imaging of cell proliferation: Status and prospects. *J. Nucl. Med.* 49:64S–80S.

Barendsen GW (1982) Dose fractionation, dose rate and iso-effect relationships for normal tissue responses. *Internat. J. Radiation Oncology Biol. Phys.* 8:1981–1997.

Bertuzzi A, Bruni C, Papa F, Sinisgalli C (2013) Optimal solution for a cancer radiotherapy problem. *J. Math. Biol.* 66:311–349.

Brahme A, Agren AK (1987) Optimal dose distribution for eradication of heterogeneous tumors. *Acta Oncology* 26:1–9.

Brenner DJ (1993) Accelerated repopulation during radiotherapy: Quantitative evidence for delayed onset. *Radiation Oncology Investigations* 1:167–172.

Chen M, Lu W, Chen Q, Ruchala K, Olivera G (2008) Adaptive fractionation therapy: II. Biological effective dose. *Phys. Med. Biol.* 53:5513–5525.

de la Zerda A, Armbruster B, Xing L (2007) Formulating adaptive radiation therapy (ART) treatment planning into a closed-loop control framework. *Phys. Med. Biol.* 52:4137–4153.

Deng G, Ferris MC (2008) Neuro-dynamic programming for fractionated radiotherapy planning. *Springer Optim. Its Appl.* 12:47–70.

Ferris MC, Voelker MM (2004) Fractionation in radiation treatment planning. *Math. Programming* 101:387–413.

Fowler JF (1989) The linear-quadratic formula and progress in fractionated radiotherapy. *British J. Radiology* 62:679–694.

Ghate A (2011) Dynamic optimization in radiotherapy. Geunes J, ed. *TutORials in Operations Research: Transforming Research into Action* (INFORMS, Catonsville, MD), 60–74.

Guerrero M, Li XA (2003) Analysis of a large number of clinical studies for breast cancer radiotherapy: Estimation of radiobiological parameters for treatment planning. *Phys. Med. Biol.* 48:3307–3326.

Hall EJ, Giaccia AJ (2006) *Radiobiology for the Radiologist* (Lippincott Williams & Wilkins, Philadelphia).

Harari PM (1992) Adding dose escalation to accelerated hyperfractionation for head and neck cancer: 76 Gy in 5 weeks. *Seminars Radiation Oncology* 2:58–61.

Hethcote HW, Waltman P (1973) Theoretical determination of optimal treatment schedules for radiation therapy. *Radiation Res.* 56:150–161.

Huang Z, Mayr NA, Gao M, Lo SS, Wang JZ, Jia G, Yuh WTC (2012) Onset time of tumor repopulation for cervical cancer: First evidence from clinical data. *Internat. J. Radiation Oncology Biol. Phys.* 84:478–484.

Jones B, Tan LT, Dale RG (1995) Derivation of the optimum dose per fraction from the linear quadratic model. *British J. Radiology* 68:894–902.

Keller H, Hope A, Meier G, Davison M (2013) A novel dose-volume metric for optimizing therapeutic ratio through fractionation: Retrospective analysis of lung cancer treatments. *Med. Phys.* 40:084101-1–084101-10.

Kim JJ, Tannock IF (2005) Repopulation of cancer cells during therapy: An important cause of treatment failure. *Nature* 5:516–525.

Kim M (2010) A mathematical framework for spatiotemporal optimality in radiation therapy. Unpublished doctoral dissertation, University of Washington, Seattle.

Kim M, Ghate A, Phillips MH (2009) A Markov decision process approach to temporal modulation of dose fractions in radiation therapy planning. *Phys. Med. Biol.* 54:4455–4476.

Kim M, Ghate A, Phillips MH (2012) A stochastic control formalism for dynamic biologically conformal radiation therapy. *Eur. J. Oper. Res.* 219:541–556.

Kutcher GJ, Burman C (1989) Calculation of complication probability factors for nonuniform normal tissue irradiation: The effective volume method. *Internat. J. Radiation Oncology Biol. Phys.* 16:1623–1630.

Kutcher GJ, Burman C, Brewster L, Goitein M, Mohan R (1991) Histogram reduction method for calculating complication probabilities for three-dimensional treatment planning evaluations. *Internat. J. Radiation Oncology Biol. Phys.* 21:137–146.

Laird AK (1964) Dynamics of tumor growth. *British J. Cancer* 18:490–502.

Ledzewicz U, Schättler H (2004) Application of control theory in modelling cancer chemotherapy. *Internat. Conf. Control, Automation, Systems, Bangkok, Thailand*.

Lu W, Chen M, Chen Q, Ruchala K, Olivera G (2008) Adaptive fractionation therapy: I. Basic concept and strategy. *Phys. Med. Biol.* 53:5495–5511.

Lyman JT (1985) Complication probability as assessed from dose-volume histograms. *Radiation Res. Suppl.* 8:S13–S19.

Marks LB, Dewhirst M (1991) Accelerated repopulation: Friend or foe? Exploiting changes in tumor growth characteristics to improve the "efficiency" of radiotherapy. *Internat. J. Radiation Oncology Biol. Phys.* 21:1377–1383.

McAneney H, O'Rourke SFC (2007) Investigation of various growth mechanisms of solid tumour growth within the linear-quadratic model for radiotherapy. *Phys. Med. Biol.* 52:1039–1054.

Miralbell R, Roberts SA, Zubizarreta E, Hendry JH (2012) Dose-fractionation sensitivity of prostate cancer deduced from radiotherapy outcomes of 5,969 patients in seven international institutional data sets: $\alpha/\beta = 1.4$ (0.9–2.2) Gy. *Internat. J. Radiation Oncology Biol. Phys.* 82:e17–e24.

Mizuta M, Takao S, Date H, Kishimoto N, Sutherland KL, Onimaru R, Shirato H (2012) A mathematical study to select fractionation regimen based on physical dose distribution and the linear-quadratic model. *Internat. J. Radiation Oncology Biol. Phys.* 84:829–833.

Munro TR, Gilbert CW (1961) The relation between tumour lethal doses and the radiosensitivity of tumour cells. *British J. Radiology* 34:246–251.

Norton L (1988) A Gompertzian model of human breast cancer growth. *Cancer Res.* 48:7067–7071.

Norton L, Simon R (1977) Tumor size, sensitivity to therapy, and design of treatment schedules. *Cancer Treatment Rep.* 61:1307–1317.

Norton L, Simon R (1986) The Norton-Simon hypothesis revisited. *Cancer Treatment Rep.* 70:163–169.

Norton L, Simon R, Brereton HD, Bogden AE (1976) Predicting the course of Gompertzian growth. *Nature* 264:542–545.

O'Rourke S, McAneney H, Hillen T (2009) Linear quadratic and tumour control probability modelling in external beam radiotherapy. *J. Math. Biol.* 58:799–817.

Pedreira CE, Vila VB (1991) Optimal schedule for cancer chemotherapy. *Math. Programming* 52:11–17.

Porter EH (1980a) The statistics of dose/cure relationships for irradiated tumours. Part I. *British J. Radiology* 53:210–227.

Porter EH (1980b) The statistics of dose/cure relationships for irradiated tumours. Part II. *British J. Radiology* 53:336–345.

Ramakrishnan J, Craft D, Bortfeld T, Tsitsiklis JN (2012) A dynamic programming approach to adaptive fractionation. *Phys. Med. Biol.* 57:1203–1216.

Saberian F, Ghate A, Kim M (2014) Optimal fractionation in radiotherapy with multiple normal tissues. Accessed November 2014, http://ssrn.com/abstract=2478481.

Saberian F, Ghate A, Kim M (2015) A two-variable linear program solves the standard linear-quadratic formulation of the fractionation problem in cancer radiotherapy. *Oper. Res. Lett.* 43:254–258.

Salari E, Unkelbach J, Bortfeld T (2014) A mathematical programming approach to the fractionation problem in chemoradiotherapy. Accessed November 2014, http://arxiv.org/abs/1312.5657.

Sir MY, Epelman MA, Pollock SM (2012) Stochastic programming for off-line adaptive radiotherapy. *Ann. Oper. Res.* 496: 767–797.

Swan GW (1981) *Optimization of Human Cancer Radiotherapy* (Springer, New York).

Swan GW (1984) *Applications of Optimal Control Theory in Biomedicine* (CRC Press, Boca Raton, FL).

Tucker SL, Thames HD, Taylor JMG (1990) How well is the probability of tumor cure after fractionated irradiation described by Poisson statistics? *Radiation Res.* 124:273–282.

Unkelbach J, Craft D, Salari E, Ramakrishnan J, Bortfeld T (2013) The dependence of optimal fractionation schemes on the spatial distribution. *Phys. Med. Biol.* 58:159–167.

Usher JR (1980) Mathematical derivation of optimal uniform treatment schedules for the fractionated irradiation of human tumors. *Math. Biosciences* 49:157–184.

Wang JZ, Li XA (2005) Impact of tumor repopulation on radiotherapy planning. *Internat. J. Radiation Oncology Biol. Phys.* 61: 220–227.

Wein LM, Cohen JE, Wu JT (2000) Dynamic optimization of a linear-quadratic model with incomplete repair and volume-dependent sensitivity and repopulation. *Internat. J. Radiation Oncology Biol. Phys.* 47:1073–1083.

Wheldon TE (1988) *Mathematical Models in Cancer Research* (IOP Publishing Ltd., Bristol, UK).

Wheldon TE, Kirk J, Orr JS (1977) Optimal radiotherapy of tumour cells following exponential-quadratic survival curves and exponential repopulation kinetics. *British J. Radiology* 50: 681–682.

Withers HR (1993) Treatment-induced accelerated human tumor growth. *Seminars Radiation Oncology* 3:135–143.

Withers HR, Taylor JMG, Maciejewski B (1988) The hazard of accelerated tumor clonogen repopulation during radiotherapy. *Acta Oncologica* 27:131–146.

Yakovlev AY, Pavlova L, Hanin LG (1994) *Biomathematical Problems in Optimization of Cancer Radiotherapy* (CRC Press, Boca Raton, FL).

Yang Y, Xing L (2005) Optimization of radiotherapy dose-time fractionation with consideration of tumor specific biology. *Med. Phys.* 32:3666–3677.

Yorke ED, Fuks Z, Norton L, Whitmore W, Ling CC (1993) Modeling the development of metastasis from primary and locally recurrent tumors: Comparison with clinical data base for prostate cancer. *Cancer Res.* 53:2987–2993.

Zietz S, Nicolini C (2007) Mathematical approaches to optimization of cancer chemotherapy. *Phys. Med. Biol.* 52:4137–4153.