Robust optimization of dose schedules in radiotherapy

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Abstract

A major difficulty of choosing an optimal radiation schedule is the uncertainty of model parameters due to geometric and patient specific uncertainties. This paper proposes a method for determining the optimal fractionation schedule in the Linear Quadratic (LQ) model with multiple normal tissue toxicity constraints in the presence of uncertainties in model parameters. To this end, we assumed uncertainty in the LQ model can take two forms: (i) estimation errors for parameters of constant but unknown value, and (ii) stochasticity of random variables. For the unknown parameters, we formulated our problem as a conservative model whose solution is immune to the parameter drifts. When the underlying distributions of uncertain parameters are known, we developed a model which required the decision maker to specify a probability that determined the feasibility of normal tissues constraints and risk factor in the objective function. We proved that our problem can be solved efficiently through a decision variable transformation with a few nonlinear constraints and implementing several iterative optimization algorithms. We performed substantial numerical experiments for head-and-neck tumor including six normal tissues, spinal cord, brain stem, skin, oral cavity, mandible and larynx to reveal the effect of parameter uncertainty on optimal schedules.

Keywords: Robust Optimization, Radiotherapy, Nonlinear Programming, Linear-Quadratic Model

1 Introduction

The building block for virtually all mathematical models of radiation response is the linear-quadratic model (LQ), which matches well with experimental data across a wide range of clinically relevant radiation doses and fractionation schemes ([17] and [8]). The basic model states that if a collection of cells is exposed to $N$ fractions of radiation, $d_i$ Gy (SI derived unit of ionizing radiation) in $i^{th}$ fraction, the reproductively viable fraction of cells after the exposure is given by $e^{-\sum_{i=1}^{N} \alpha d_i + \beta d_i^2}$. The two parameters $\alpha$ and $\beta$ depend on the specific tissue that is being irradiated. The parameter $\alpha$ represents killing of cells from a single track of radiation, and $\beta$ represents the killing of a cell via two independent tracks of radiation [21]. There are several mathematical extensions to the LQ framework to incorporate additional biological phenomena such as repopulation of the tumor population between fractions, re-oxygenation of the tumor (this is required for some radiation therapy to be effective), the effectiveness of DNA repair mechanisms between fractions, and the redistribution of tumor cells within the cell cycle. Taken together these four extensions are often referred to as the ‘4Rs’ and there have been several works based on these extensions [46].
When radiotherapy is used in the clinical setting, it is necessary to ensure that the treatment avoid excessive toxicity in normal tissues in the vicinity of the tumor. Therefore it is necessary to ensure that the radiation absorbed by the surrounding normal tissue falls within desired constraints. Hence the ultimate goal in radiotherapy is maximizing tumor damage while ensuring that the level of normal structures toxicity does not exceed a given threshold. The standard method for measuring tumor damage and tissue toxicity are done via linear quadratic model and the biologically equivalent dose (BED), respectively ([17] and [18]).

Most radiation treatments is currently administered in equal fractions five days a week, for 6 weeks total. Over the past decades there have been several mathematical works that have studied the survival benefit of various fractionation schedules for a wide range of cancers. In [9], the relationship between the LQ formalism and other radiobiological models in terms of their predicted time-dose relationships is studied. They use the LQ model in combination with Lea-Catcheside time factor, which takes into account dose protraction or fractionation and DNA repair between fractions. Yang and Xing ([48]) explore the influence of the '4Rs' of radiobiology on external beam radiotherapy for fast and slowly proliferating tumors and conclude that considering the effects of the BED model may give rise to optimal non-uniform fractionation schedules. Mizuta et al. ([31]) present a mathematical model that minimizes the radiation effect on late responding normal tissues while keeping the effect of radiation on the tumor constant. They show that the multi-fractionated irradiation with a constant dose is better if the ratio of $\frac{2}{3}$ for the normal tissue and the tumor is less than the ratio of the dose for the normal tissue and the tumor, while Hypo-Fractionated irradiation is better otherwise. Unkelbach et al. ([45]) study the interdependence of the optimal fractionation scheme and the spatial dose distribution in the normal tissues. In particular, they derive a criterion under which a Hypo-Fractionation regimen is indicated for both a parallel and a serial organ at risk. In a very recent work ([39]), a formulation of the optimal fractionation problem that includes multiple normal tissues has been considered. They establish sufficient conditions under which equal-dosage or single-dosage fractionation is optimal. In recent work ([27]) the authors investigated optimal fractionation for a mouse model of glioblastoma, in this work they found that non-standard fractionation schedules lead to improved survival times; a finding that was verified in experimental studies. In [1] this work was extended to include a richer set of toxicity constraints.

The existing works do not explicitly describe precisely how the optimal fractionation doses in the presence of multiple normal tissues could be discovered. Most of them find the optimal schedule with respect to a single normal tissue. However in practice, there are at least two healthy structures in the vicinity of tumor. Saberian et al. consider several normal tissues in their study, however they were unable to find the closed form solution to the problem for all possible cases and they only discuss the sufficient conditions under which equal-dosage fractionation is optimal ([39]). In [1] two simultaneous normal tissue toxicity constraints were implemented. As we were finalizing our manuscript the work ([40]) was published online. To the best of our knowledge, our current work and [40] are the only works to find the closed form solution to the problem of optimal fractionation while maintaining multiple simultaneous normal tissue constraints without considering any presumptions about the configuration of optimal solution.

The parameters in the linear quadratic model have a significant impact on the performance of radiotherapy fractionation schedules. An important result emerging from recent work is that the fraction of the dose that normal tissues absorb and the magnitude of the $\alpha/\beta$ ratio for both normal tissues and the tumor determine the optimal radiation scheme ([1], [31] and [45]). Therefore the optimal fractionation schedule is acutely sensitive to perturbations in these parameters. One
consequence of this sensitivity is the following: an optimal fractionation schedule will have been derived for a fixed set of parameter values (called the nominal values), but for a specific patient with a distinctly different set of parameter values this schedule is no longer optimal, and in fact may have poor performance. The uncertainties in radiotherapy treatment can be categorized into two groups, geometric and patient specific uncertainties. Target volumes take account of geometric uncertainties such as organ motion, inaccuracies or variations in treatment set-up, patient positioning errors and fluctuations in machine output. Several studies addressed these uncertainties using different techniques. Stroom et al [42] developed a method for calculation of clinical target volume to planning target volume margins based on the geometric uncertainties requiring that the clinical target volume should be adequately irradiated with a high probability. As an alternative approach, Chu et al [12] used the robust optimization method to find the optimal schedules in IMRT treatment plans while considering patient motion and setup uncertainties. The patient specific uncertainties are due to inter-patient variations in patient-specific variables such as the sensitivity of their normal tissues and tumor to radiation, and the tumor growth rate. In several cancers there have been multiple subtypes discovered driven by distinct genetic pathways and having distinct phenotypic behaviors such as growth parameters and response to therapy (e.g. glioblastoma [32], breast cancer [33], head and neck cancer [14], melanoma [30] and many others). A distinct possibility is that there is still significant patient variability within these subtypes, and that this inter patient heterogeneity is a large reason for the pursuit of personalized medicine [22]. Given current technologies it is difficult to measure tumor response parameters $\alpha$ and $\beta$ during treatment due to confounding effects such as protracted cell death [16], cell cycle arrest [6], and radiotherapy mediated immune response [26]. Furthermore, toxicity effects often do not show up until several months or even years after conclusion of therapy, and it is therefore not possible to learn the tumor response properties of normal tissues during treatment. Therefore we are interested in finding schedules which minimizes tumor cell populations while maintaining acceptable levels of normal tissue damage under any possible realization of model parameters. To the best of our knowledge, the present study is the first to address this uncertainty generated by inter patient heterogeneity.

Two common paradigms for addressing such optimization problems in the presence of uncertainty are stochastic programming and robust optimization. In this study, robust optimization will be utilized in order to find the optimal schedule when model parameters are uncertain. Robust optimization which was introduced and made popular by Ben-Tal, Nemirovski ([3], [4] and [5]) and by El Ghaoui et al. ([19] and [20]) is used to deal with optimization problems with uncertain parameters. In these models, decision-maker seeks two objectives. First, the optimal solution is constructed to insure that all constraints are satisfied under any possible realization of the parameters and second, it protects the solution against the worst case within the uncertainty set. Thus, the robust formulation provides a worst-case guarantee on the quality of the solution, for any possible realization of model parameters. We refer the interested reader to textbook by Ben-Tal et al. [2]. Another method which has been used widely in optimization problem facing uncertainty is stochastic programming, see [24] [25] for application of these ideas in radiotherapy. There are several advantages in using robust optimization compared to stochastic programming approach. First stochastic programming assumes an ability to learn something about the tumor state during the course of the therapy, however as described in the previous paragraph there are several confounding factors that make this extremely difficult given current technology. Second, the robust approach is generally more computationally tractable than stochastic programming. Finally, robust approach allows us to control the level of flexibility between robustness and performance of the optimal schedule by choosing the probabilistic protection that provides a notion of a budget of uncertainty [7].
We present a mathematical formulation of the optimal fractionation problem in the presence of multiple normal tissues incorporating uncertainties in model parameters based on the LQ model adjusted for tumor proliferation with a time lag. This formulation allows for the parametric uncertainty to take two forms. First a minimal underlying stochastic model of the uncertain parameters is assumed to be known and every parameter, independently of other entries, takes values in a given interval. We formulate our problem as a model whose solution must be feasible for all realizations of the parameters, and even a small violation of the constraints cannot be tolerated. This method may lead to an overly pessimistic solution, therefore we develop additional models where we assume that the uncertain parameters are characterized by a probability distribution and we reformulate our optimization problem to now insure that our constraints are satisfied with a given probability, and that our objective function achieves a desired level with a given probability. We study our optimization problems in two different scenarios, in the presence and absence of tumor proliferation. We simplify our problem through a variable transformation and obtain necessary and sufficient conditions for the feasibility of optimal doses with respect to a given number of radiation fractions. Then we propose several algorithms to find the optimal solution of the simplified problem in different models and we introduce a method to retrieve the optimal doses and number of fractions based on the solution of the simplified problems.

The organization of the remainder of the paper is as follows. In section two we describe the problem formulation in the setting of fixed parameters (the nominal setting), and then formulate the robust counterpart of this nominal problem for various uncertainty sets. In the next section we describe our solution methods for the problems presented in section two. In section four we solve our optimization problems for the specific case of head and neck carcinomas. In section five we summarize our results and discuss the implications of our findings.

2 Model of uncertainty and robust formulation

In this section, we first define an objective function derived from the standard linear-quadratic model of radiotherapy response. We next discuss the constraints that are present in our optimization problem, these are derived by maintaining a fixed level of normal tissue damage for a variety of tissue types. Finally we incorporate parameter uncertainty by formulating a robust version of our optimization problem.

2.1 The nominal formulation

We now consider the problem of finding fractionation schedules that lead to maximal tumor reduction while maintaining acceptable levels of normal tissue damage. The basic linear quadratic (LQ) model states that if a collection of tumor cells are exposed to \( N \) fractions of radiation with \( d_j \) Gy (SI derived unit of ionizing radiation) in \( j^{th} \) fraction, the reproductively viable fraction of cells is given by \( e^{-\sum_{j=1}^{N} \alpha d_j + \beta d_j^2} \). However, reproductively viable tumor cells will eventually begin to reproduce, and thus the total surviving fraction of surviving cells is often adjusted to take into account the reproduction. A common way to model the repopulation effect is to assume an exponential repopulation process, see e.g., [43]. Thus the net surviving fraction \((S)\) due to combined effects of radiation and repopulation after the conclusion of a fractionated radiotherapy treatment is given by

\[
S = e^{-\sum_{j=1}^{N} \alpha d_j + \beta d_j^2} e^{\ln(2)(T_r - T_k) / \ln(4)}
\]
where $T_r$, $T_e$ and $T_k$ are respectively radiation delivery duration, effective cellular doubling time and kick-off time (or lag before exponential growth begins). The expression $(T_r - T_k)^+$ is defined as $\max(0, T_r - T_k)$. Throughout this paper, we made two important assumptions. First in order to consider the impact of working hour constraints on the objective function, we assume that working hour constraints require that radiation can only be delivered hourly between 8 am and 8 pm and five days per week. Second, we assume for every schedule there exist $n$ daily fractions with equal elapse between consecutive fractions. If we define $a$ and $r$ as the quotient and remainder of $\frac{N}{n}$, respectively, and $a'$ and $r'$ as the quotient and remainder of $\frac{a}{5}$, respectively, we can compute $T_r$ as

$$T_r = \begin{cases} 7a' + r', & r = 0, r' \neq 0 \\ 7(a' - 1) + 5, & r = 0, r' = 0 \\ 7a' + r' + \frac{8 + 12 r' - 1}{24}, & r \geq 1, r' \neq 0 \\ 7(a' - 1) + 5 + \frac{8 + 12 r' - 1}{24}, & r \geq 1, r' = 0 \end{cases} \quad (2.1)$$

A natural risk associated with radiotherapy is damage to normal tissue near the tumor. Thus an important constraint when constructing fractionation schedules is to insure that normal tissue damage is kept at a sufficiently low level. When modeling normal tissue toxicity from radiation it is common to use the LQ model to keep track of normal tissue damage. In particular, assume that for a specific normal tissue of interest there radio response is characterized by parameters $\alpha_{NT}$ and $\beta_{NT}$, furthermore assume that this tissue is exposed to $N$ fractions of sizes $\{d_1, \ldots, d_N\}$ respectively, and lastly assume that for fraction $j$ normal tissue is only exposed to $\delta d_j$ Gy of radiation for a sparing factor $\delta \in (0, 1]$. Then a common measure of toxicity for this tissue is the $BED$,

$$\sum_{j=1}^{N} (\delta d_j + \frac{\beta_{NT}}{\alpha_{NT}} \delta^2 d_j^2).$$

Note that the $BED$ follows from the LQ model after some simple algebraic manipulations. A common method of avoiding excessive normal tissue damage is to require that the normal tissue BED is below a specified level which is determined by previous experiments and clinical experience.

However, a further complication to the above toxicity discussion is that in any radiotherapy treatment there are often a large number of possible normal tissues exposed to radiotherapy. In addition to the existence of a large number of normal parenchymal cells in the clinical target volume of the respective organ, all tumor volume contains various stromal tissues (e.g. blood vessels and normal connective tissue). In all these normal cells and structures, radiation side-effects may be different. The volume and fundamental elements or characteristics of tissue irradiated can be important determinants of clinical tolerance. In organs with a parallel structure, such as the liver, functional subunits (FSU) function independently. Hence, a clinical radiation effect is observed only if the number of surviving FSUs is too low to keep the physiological organ function \[37\]. In contrast, in organs with a serial structure, such as spinal cord, intestine and oesophagus, the function of the entire organ depends on the function of each individual FSU. In these organs, damage of only one FSU results in clinical side-effects in the whole organ. In these organs, the minimum of maximum tolerated BED by each voxel in organ should remain within the maximum admissible levels. Finally in reality, there are normal tissues, named as dose-volume organs, that cannot be categorized as purely parallel or serial organs, such as kidney and lung \[23\]. These organs can endure the loss of more than half their total mass without significant loss of function. In particular in these organs,
no more than a specified volume fraction of normal tissue voxels can receive a dose more than maximum allowable dose. Thus in order to insure sufficiently low normal tissue toxicity we need a multitude of toxicity constraints \[39\], i.e.,

\[
\sum_{j=1}^{N} \left( \delta_i d_j + \frac{\beta_i}{\alpha_i} \delta_i^2 d_j^2 \right) \leq BED_i \quad \text{for } 1 \leq i \leq M,
\]

(2.2)

where \(M\) is the number of different normal tissues under consideration and \(BED_i\) is the total toxicity for normal tissue type \(i\).

By taking the natural logarithm of objective function and using (2.2) to model acceptable normal tissue damage, the nominal problem of finding fractionation schedules that lead to maximum tumor damage while maintaining acceptable levels of normal tissue damage can be modeled as

\[
\max_{d_j, N} \sum_{j=1}^{N} \alpha d_j + \beta d_j^2 - g(N)
\]

subject to

\[
\sum_{j=1}^{N} \left( \delta_i d_j + \frac{\beta_i}{\alpha_i} \delta_i^2 d_j^2 \right) \leq BED_i, \quad i = 1, \ldots, M
\]

\(d_j \geq 0, \quad N \geq 0, \text{ integer}\)

where \(g(N) = \frac{\ln(2)|T_r - T_k|}{T_c}\).

### 2.2 Modeling uncertainty in radiobiologic parameters

In order to solve the optimization problem (2.3) it is vital to know the parameters \(\alpha, \beta, \beta_i/\alpha_i, \) and \(\delta_i\) since the optimal fractionation schedule will depend on their value (11, 31 and 45). However, it is quite difficult to obtain accurate measurements of these parameters in a clinical setting and precise estimates of these values are very difficult to find. Furthermore, due to inter-patient heterogeneity it is possible that a wide range of parameter values are possible across the patient population. For example in several cancers there are a multitude of possible mutational pathways responsible for the creation of the tumor, e.g., breast, glioblastoma, and head & neck. As a result of this situation we are investigate the effect of parametric uncertainty on the solution to problem (2.3).

We assume uncertainties presented in LQ model can take two forms: (i) estimation errors for parameters of constant but unknown value, and (ii) stochasticity of random variables. In the first case only the range forecasts for the uncertain parameters are known, specifically, we assume parameter \(a\) belongs to a symmetric interval \([\bar{a} - l_a, \bar{a} + l_a]\) centered at \(\bar{a}\) and for the second scenario we consider \(a\) as a continuous random variables with probability density function \(f(a)\). In the second case, we are interested in finding the optimized scheduled break-up of a radiotherapy treatment based on two principles: first the nominal values of sensitive parameters are inaccurate and should be replace by range forecast and second, using the range forecasts alone may lead to an excessively high level of conservativeness and the the objective function may suffer as a result.
2.2.1 Non-probabilistic robust formulation

As mentioned above the parameters $\alpha$, $\beta$, $\{\delta_i\}_{i=1}^M$ and $\{\beta_i/\alpha_i\}_{i=1}^M$ are subject to uncertainty and are may vary amongst patients. For example the general values of 0.33Gy and 0.10Gy for the ratio $\beta/\alpha$ for late effects and tumors, respectively, should be considered as a rough estimate. There is little evidence [23] to show that these values can be generalized across a wide range of human normal-tissue endpoints and tumor histologies. Therefore, calculations using these values may be seen as simply exploring the behavior of the model, but they are detached from the clinical reality.

Here our aim is to construct a robust formulation to (2.3) that is immune to realizations of the uncertain parameters so long as they lie within certain sets. This approach may be the only reasonable alternative when the parameter uncertainty is uniformly distributed, or if no distributional information is available. First we consider the case that we know that $\beta_i/\alpha_i \in [\bar{\beta}_i/\alpha_i - l_i, \bar{\beta}_i/\alpha_i + l_i]$, $i \in \{1, \ldots, M\}$. (2.4)

That is we assume that the values of parameters $\alpha$ and $\beta$ are known and we only know that the parameters $\{\beta_i/\alpha_i\}_{i=1}^M$ lie in given intervals.

In the non-probabilistic robust formulation we do not allow any violation of the normal tissue constraints for any parameters taking values in the sets (2.4). Therefore the robust counterpart of (2.3) associated with uncertainty sets defined in (2.4) is found by solving

$$\max_{d_j,N} \sum_{j=1}^N \alpha d_j + \beta d_j^2 - g(N)$$

Subject to

$$\sup \left\{ \sum_{j=1}^N (\delta_i d_j + \delta_i^2 \beta_i d_j^2) \big| \frac{\beta_i}{\alpha_i} \in [\bar{\beta}_i/\alpha_i - l_i, \bar{\beta}_i/\alpha_i + l_i] \right\} \leq BED_i \ \forall i$$

$$d_j \geq 0, \ N \geq 0, \ \text{integer}$$

Since all parameters in (2.4) take positive values, we can simplify above formulation as (2.5)

$$\max_{d_j,N} \sum_{j=1}^N \alpha d_j + \beta d_j^2 - g(N)$$

subject to

$$\sum_{j=1}^N (\delta_i d_j + \delta_i^2 (\frac{\beta_i}{\alpha_i} + l_i) d_j^2) \leq BED_i \ i = 1, \ldots, M$$

$$d_j \geq 0, \ N \geq 0, \ \text{integer}$$

The optimization problem in (2.5) does not address uncertainty in the parameters $\{\delta_i\}_{i=1}^M$; however, these are naturally very important parameters since they specify the amount of radiation that sensitive normal tissues receive. There has been a significant amount of effort dedicated to improving the accuracy and precision of radiation therapy delivery in the past decades. However there exist some sources of uncertainty which make it impossible to achieve full precision in estimating parameters associated with organ movements in radiotherapy. Machine precision, motion and deformation of the patient or of the inner organs during, or between, the treatment fractions, as well
as any positioning uncertainties are among these factors. These uncertainty sources can have a detrimental effect on configurations or feasibility of optimal schedules. In this paper, we assume a fixed amount of radiation are delivered to tumor, however the fraction of radiation absorbed by normal tissues is subject to uncertainty. First let’s assume for $i^{th}$ normal tissue, $\delta_i$ is modeled as a symmetric and bounded random variable that take value in $[\bar{\delta}_i - l\delta_i, \bar{\delta}_i + l\delta_i]$. By using the same approach described earlier to obtain (2.5), we can easily show that the robust formulation when $\delta_i$ are subject to uncertainty, is as follows:

$$\max_{d_j, N} \sum_{j=1}^{N} \alpha d_j + \beta d_j^2 - g(N) \quad (2.6)$$

subject to

$$\sum_{j=1}^{N} ((\bar{\delta}_i + l\delta_i)d_j + (\bar{\delta}_i + l\delta_i)^2 \frac{\beta_i}{\alpha_i} d_j^2) \leq BED_i \quad i = 1, \ldots, M$$

$$d_j \geq 0, \; N \geq 0, \text{integer}$$

### 2.2.2 Probabilistic robust optimization models

Next we view $\alpha$ and $\beta$ as continuous random variables with joint probability density function $f(\alpha, \beta)$ and also we assume that the cdf of $\frac{\beta_i}{\alpha_i}$ in $i^{th}$ normal tissue is $F_i$. We will require that BED in $i^{th}$ does not exceed some level with a high probability. This desire can be naturally expressed by requiring that the BED in $i^{th}$ normal tissue exceeds the maximum allowable BED, $BED_i$, with probability at most $1 - p_i$, where $p_i$ is some constant close to 1, e.g., 0.95. Written mathematically we have

$$P\left(\sum_{j=1}^{N} (\delta_i d_j + \delta_i^2 \frac{\beta_i}{\alpha_i} d_j^2) \leq B E D_i \left| \frac{\beta_i}{\alpha_i} \geq 0 \right.\right) \geq p_i \quad \forall i$$

Furthermore we require that optimized schedules obtained by our robust formulation result in an objective value which exceed level $z$, with probability more than or equal to $p_z$, or equivalently we can say

$$P\left(\sum_{j=1}^{N} (\alpha d_j + \beta d_j^2) \geq z \left| \alpha \geq 0, \beta \geq 0 \right.\right) \geq p_z$$

Note that from a biological point of view, it is impossible for $\frac{\beta_i}{\alpha_i}$, $\alpha$ and $\beta$ to take negative values, and since in literature it is often assumed that these parameters are normally distributed, we need to add the non-negatively conditions to above constraints. Computing the above probabilities, we can derive the new formulation as:

$$\max_{d_j, N, z} z - g(N) \quad (2.7)$$

subject to
\[ \int_0^{\sum_{j=1}^N d_j} \int_0^{\sum_{j=1}^N d_j} f(\alpha, \beta) d\beta d\alpha \leq (1 - p_z) P(\alpha \geq 0, \beta \geq 0) \]

\[ \sum_{j=1}^N \left( \delta_i d_j + \delta_i^2 F_i^{-1} \left(1 - F_i(0) (1 - p_i)\right) d_j^2 \right) \leq BED_i \quad i = 1, \ldots, M \]

\[ d_j \geq 0, \quad N \geq 0, \text{integer} \]

We next consider randomness in the parameters \( \{\delta_i\}_{i=1}^M \). In spite of the fact that (2.6) provides the highest protection against infeasible solutions, it is also the most conservative solution in practice and supplies an objective function value which is worse than objective value of nominal formulation. To address this excessive conservativeness, we control the level of flexibility between robustness and performance of the optimal schedule by again using a probabilistic formulation that provides a notion of a budget of uncertainty. We assume that \( \delta_j \) is a continuous random variable with cdf \( G_j \), then we require that

\[ P \left( \sum_{j=1}^N (\delta_i d_j + \delta_i^2 \frac{\beta_i}{\alpha_i} d_j^2) \leq BED_i \bigg| \delta_i \geq 0 \right) \geq p_i \quad \forall i \]

or equivalently

\[ P \left( \delta_i \leq \frac{\alpha_i BED_i}{\beta_i \sum_{j=1}^N d_j^2} + \frac{\alpha_i^2 (\sum_{j=1}^N d_j)^2}{4 \beta_i (\sum_{j=1}^N d_j)^2} - \frac{\alpha_i \sum_{j=1}^N d_j}{2 \beta_i \sum_{j=1}^N d_j^2} \right) \geq 1 - (1 - p_i) P(\delta_i \geq 0) \quad \forall i. \]

So that we can derive the robust counterpart of (2.3) considering trade-off between objective function value and uncertainty in sparing factor of healthy tissues as (2.8)

\[ \max_{d_j, N} \sum_{j=1}^N \alpha d_j + \beta d_j^2 - g(N) \quad (2.8) \]

subject to

\[ G_i^{-1} \left(1 - (1 - p_i) G_i(0)\right) \sum_{j=1}^N d_j + G_i^{-1} \left(1 - (1 - p_i) G_i(0)\right) \frac{\beta_i}{\alpha_i} \sum_{j=1}^N d_j^2 \leq BED_i, \quad i = 1, \ldots, M \]

\[ d_j \geq 0, \quad N \geq 0, \text{integer}. \]

### 3 Solution approach

We now turn our attention to the solution of the optimization problems presented in the previous section. Note that for any fixed \( N \), the feasible region of models described in Section 2 are compact sets and their objective value are continuous. Therefore by the extreme value theorem of Weierstrass \[35\], optima exist.
In this section, we first show how the optimal solutions for problems posed in (2.3), (2.5), (2.6), (2.7) and (2.8) can be found when the tumor proliferation term \( g(N) \) is disregarded. Then we describe how the feature of optimality conditions established by removing \( g(N) \) term, provides additional insights about the optimal solution of these formulations in the presence of tumor proliferation. It enables us to model (for a fixed \( N \)) (2.3), (2.5), (2.6) and (2.8) as convex formulations with linear objective functions and linear constraints and (2.7) as a non-convex formulation. Finally we end this section by introducing a brute-force algorithm to locate the optimum fractional doses and total number of fractions in the presence of tumor proliferation.

3.1 Optimal fractionation in the absence of tumor proliferation

The correction proposed for tumor proliferation in (2.3) is a crude approximation and is not included in the basic LQ model [21]. For tumors with large effective cellular doubling time \( (T_e) \) or kick-off time \( (T_k) \), the effect of tumor reproduction, \( g(N) \), is negligible. By removing the tumor proliferation term and related constraints associated with \( N \), we can significantly simplify the formulations in section 2. A further simplification is to introduce the variables

\[
X = \sum_{j=1}^{N} d_j, \quad Y = \sum_{j=1}^{N} d_j^2.
\]  

(3.9)

Using these new variables we consider a two-dimensional version of (2.3), (2.5), (2.6), and (2.8) without the \( g(N) \) term. We provide the simplified version of these problems in Appendix as (6.20), (6.21), (6.22) and (6.23) respectively.

For (2.7) a more specialized approach is required. The new formulation of (2.7) is

\[
\max_{X,Y,z} z \quad \text{subject to}
\]

\[
\int_{0}^{X} \int_{0}^{z-X} f(\alpha, \beta)d\beta d\alpha \leq (1 - p_z)P(\alpha \geq 0, \beta \geq 0)
\]  

(3.11)

\[
\delta_i X + \delta_i^2 F_i^{-1} \left(1 - \bar{F}_i(0)(1 - p_i)\right) Y \leq BED_i \quad i = 1, \ldots, M
\]  

(3.12)

\[
X, Y \geq 0.
\]  

(3.13)

These novel formulations based on the new decision variables are appealing since the problem now can be solved easily in lower dimension. However two issues remain unanswered, first how the optimal values of \( d_i \) and \( N \) can be retrieved from optimal values of \( X \) and \( Y \) and second, how the model described in (3.10) can be solved in lower dimension. We will first present a method for solving (3.10), and then discuss how we can use the optimal \( X \) and \( Y \) to find the optimal radiation doses using (3.9).

Let be given a constrained optimization problem as

\[
\max f(x), \ x \in \mathbb{R}^n,
\]

subject to \( g_i(x) \leq 0, \ i = \ldots, m \)

then we define the \( i^{th} \) constraint to be active (at a solution \( y \)) if \( g_i(y) = 0 \). We will now show that in optimality, (3.11) is active and optimal solution always lie on the most restrictive constraint(s), the constraint(s) that impose the largest restriction on the dose that can be delivered to the tumor.
Lemma 1. The optimal \( X^* \) and \( Y^* \) in (3.10) lies on the feasible boundaries of (3.12) and furthermore constraint (3.11) is active in optimality.

We provide the proof of this result in the Appendix.

The conditions (3.12) specify that the feasible pairs of \((X,Y)\) lie in a convex polygon. For each feasible pair we can find the unique value of \( \hat{z}(X,Y) \) that gives equality in (3.11). From the above Lemma we know that the optimal pair \((X^*,Y^*)\) lie along the boundary of the polygon, and is the pair that maximizes the function \( \hat{z}(X,Y) \). Therefore in order to solve the optimization problem (3.10) we need to specify the polygon defined by the inequalities in (3.12). In the Appendix, Algorithm 3 describes how to construct the corners of the of the polygon \( \mathcal{C} = \{(X_1,Y_1), \ldots, (X_k,Y_k)\} \).

Note that point \((X_i,Y_i)\) is only connected to the points \((X_{i-1},Y_{i-1})\) and \((X_{i+1},Y_{i+1})\), where \((X_0,Y_0) \equiv (X_k,Y_k)\) and \((X_{k+1},Y_{k+1}) \equiv (X_1,Y_1)\).

In order to solve problem (3.10) we can find \( \hat{z}_i = \hat{z}(X_i,Y_i) \) for each \( 1 \leq i \leq k \), and then look at \( \max\{\hat{z}_i : 1 \leq i \leq k\} \). This process will tell us the optimal corner, but it does not necessarily tell us the optimal pair \((X^*,Y^*)\). In order to find the optimal pair it is necessary to consider the edges of the polygon. We therefore define the vector valued function for \( 1 \leq i \leq k \)

\[
(X_i(t),Y_i(t)) = (tX_i + (1-t)X_{i+1}, tY_i + (1-t)Y_{i+1}), \quad 0 \leq t \leq 1,
\]

and the inverse function

\[
z_i(t) = \{z | \int_0^{X_i(t)} \int_0^{z-X_i(t)} f(\alpha,\beta) d\beta d\alpha = (1-p_z)P(\alpha \geq 0, \beta \geq 0)\}.
\]

If there is very little chance of \( \alpha \) or \( \beta \) being negative we can work with the simpler function

\[
\tilde{z}_i(t) = \{z | \int_0^{X_i(t)} \int_0^{z-X_i(t)} f(\alpha,\beta) d\beta d\alpha = (1-p_z)\}.
\]

Note that the function \( z_i \) is continuously differentiable by the inverse function theorem and that for every \( t \), the value of \( z_i(t) \) can be computed using bisection method. We now show an interesting feature of \( z_i(t) \) for three common distributions.

Lemma 2. The function \( z_i(t) \) is concave at its critical points in the following two scenarios:

- \( \alpha \) and \( \beta \) are distributed according to two independent exponential distributions
- \( \alpha \) and \( \beta \) are distributed according to two independent distributions with the following densities \( c_1 \) and \( c_2 \) are two positive constants and \( k_1 \) and \( k_2 \) are two positive integers:

\[
f(\alpha) = c_1 \alpha^{k_1}, 0 \leq \alpha \leq 1, \quad g(\beta) = c_2 \beta^{k_2}, 0 \leq \beta \leq 1
\]

- If \( \alpha \) and \( \beta \) are distributed according to two independent normal distributions and \( p_z \geq 0.5 \) then \( \tilde{z}_i \) is concave at its critical points.

The proof of this lemma is provided in the Appendix. This lemma motivates Algorithm 2 presented in the appendix, to find the optimal solution of (3.10) when \( z_i(t) \) is a concave function. We can use Algorithm 3 in appendix which is designed based on the branch and bound approach to find the optimal solution of (3.10) when \( z_i(t) \) is not necessarily a concave function at its critical points.
The previous result shows how the solution \((X^*, Y^*)\) to the problem \((3.10)\) can be found. The solution to the problems posed in \((6.20), (6.21), (6.22)\) and \((6.23)\) can be easily found using general mathematical solution technique for solving linear programming problems such as simplex algorithm or interior point method. We now consider the problem of extracting optimal fraction sizes from the pair \((X^*, Y^*)\). In order to do this, it is necessary to introduce the maximum number of radiation fractions we are willing to administer in the course of radiation therapy, \(N_{\text{max}}\). If we have that

\[
X = \sum_{i=1}^{N} d_i \quad \text{and} \quad Y = \sum_{i=1}^{N} d_i^2
\]

for some \(N \in \{1, \ldots, N_{\text{max}}\}\) then by the Cauchy-Schwarz inequality

\[
X^2 = \left( \sum_{i=1}^{N} d_i \right)^2 \leq \left( \sum_{i=1}^{N} d_i^2 \right) \left( \sum_{i=1}^{N} 1 \right) = NY
\]

and since \(d_i \geq 0\), we also have

\[
X^2 = \left( \sum_{i=1}^{N} d_i \right)^2 \geq \left( \sum_{i=1}^{N} d_i^2 \right) = Y
\]

In particular, if \((X^*)^2 > N_{\text{max}} Y^*\) or \((X^*)^2 < Y^*\) then there is no feasible assignment of fraction sizes for the pair \((X^*, Y^*)\). In the first case it is necessary to use a larger number of fractions; however, increasing the fraction number may lead to further complications due to smaller inter-fraction times and thus the necessity to model repair effects. In the next section we introduce an optimization problem that avoids this issue.

The result below discusses how to find optimal dose sizes when \((X^*)^2 \leq N_{\text{max}} Y^*\) and \((X^*)^2 \geq Y^*\).

**Theorem 3.** If \(N_{\text{max}} \geq \frac{X^*}{Y^*} \) and \((X^*)^2 \geq Y^*\) then the optimal solution to problems \((6.20), (6.21), (6.22), (3.10)\) and \((6.23)\) takes one of the following two forms.

1. \(NY^* = (X^*)^2\) for some \(N \in \{1, \ldots, N_{\text{max}}\}\). In this case optimal schedule is given by \(d_i^* = X^*/N\) for \(i = 1, \ldots, N\). Note that if \(N = 1\) then the schedule is hypo-fractionated, and if \(N > 1\) then the schedule is hyper-fractionated.

2. \((X^*)^2/Y^*\) is not an integer: In this case, the optimal solution given by the following. Choose a positive integer \(j\) less than \((X^*)^2/Y^*\) and a positive integer \((X^*)^2/Y^* < N \leq N_{\text{max}}\), and set

\[
d_1^* = \cdots = d_j^* = \frac{jX^* + \sqrt{(N-j)(jNY^* - jX^*)^2)}}{jN}, \quad d_{j+1}^* = \cdots = d_{N^*}^* = \frac{X^* - jd_1^*}{N-j}. \quad (3.15)
\]

**Proof.** To establish the result in case 1, we can easily check that equation \((3.9)\) holds for \(d_1, \ldots, d_N = X/N\) if \(NY^* = (X^*)^2\).

In the second scenario, from straightforward calculations, we observe that there is always a solution to our problem in following form:

\[
d_1^* = \cdots = d_j^* = d, \quad d_{j+1}^* = \cdots = d_N^* = w.
\]
We can now solve for \( w \) and \( d \) in (3.9), and establish that
\[
w = \frac{X^* - jd}{N - j}
\]
and
\[
d = \frac{jX^* + \sqrt{j^2(X^*)^2 - jN((X^*)^2 - (N - j)Y^*)}}{jN} = \frac{jX^* + \sqrt{(N - j)(jNY^* - j(X^*)^2)}}{jN}.
\]
It then remains to establish that \( d \) and \( w \) are non-negative real numbers. First observe that we require that \( j \leq (X^*)^2/Y^* \leq N \). It follows from this that \( d \) is a positive real number, and thus \( w \) is a real number as well. It then remains to establish that \( w \) is non-negative. This is of course equivalent to showing that \( X^* - jd > 0 \). Note that
\[
X^* - jd = \frac{1}{N} \left[ (N - j)X^* - \sqrt{j(N - j)(jNY^* - (X^*)^2)} \right]
\]
and therefore
\[
X^* - jd > 0 \iff \frac{(X^*)^2}{Y^*} > j.
\]
The result then follows from our conditions on the integer \( j \).

Observe that without proliferation any feasible \( N \) (i.e., \( (X^*)^2/Y^* < N \leq N_{max} \)) is optimal since \( N \) does not appear in the problems (6.20), (6.21), (6.22), (3.10) and (6.23). In the next section we will see how we can use Theorem 3 to identify the optimal number of fractions in the presence of proliferation.

### 3.2 Optimal fractionation in the presence of tumor proliferation

If we retain \( g(N) \) in the objective function of the models described in Section 2, we can observe that these formulations become nonlinear mixed integer problems. Subsequently the exact solution of these optimization problems becomes computationally challenging.

As a result of Theorem 3, it can be observed that if there exists an \( N \in \left[ \frac{(X^*)^2}{Y^*}, N_{max} \right] \) and a feasible \( n \) defined in (2.1), such that satisfies the condition \( T_r \leq T_k \), then tumor regrowth during the course of radiation will be zero, \( g(N) = 0 \). In this case the optimal schedule obtained by solving the model in the absence of tumor repopulation is the same as the optimal schedule obtained by solving the model in the presence of tumor proliferation. We expect that these conditions hold in many common situations by manipulating parameters \( N_{max} \) and \( n \) in (2.1), however when this condition is violated and tumor regrowth term is not negligible, we implement Algorithm 4 to find the optimal radiation doses and total number of fractions.

When \( N \) is fixed, we can use the results of Theorem 3 and conclude that there is a feasible solution for (3.9) as (3.15) if and only if \( X^2 \leq NY \) and \( X^2 \geq Y \). As a consequence, by adding these constraints we guarantee that solution of adjusted formulations are optimal for a fixed \( N \) and also \( d_i^* \) can be derived by solving (3.9) using Theorem 3. We can transform mathematical models in (2.3), (2.5), (2.6) and (2.8) to problems with linear objective function and quadratic...
and linear constraints using (3.16). Note that \( c_i, a_i \) and \( b_i \) represent equivalent coefficients in each formulation.

\[
\max_{X,Y,W} \quad c_1X + c_2Y - W \tag{3.16}
\]

subject to

\[
a_iX + b_iY \leq BED_i, \quad i = 1, \ldots, M
\]

\[
X^2 \leq NY
\]

\[
X^2 \geq Y
\]

\[
W \geq \frac{\ln(2)}{T_e} (T_r - T_k)
\]

\[
X, Y, W \geq 0
\]

and we get (3.17) as the modified formulation of (3.10):

\[
\max_{X,Y,z} \quad z - W \tag{3.17}
\]

subject to

\[
\int_0^{\bar{z}} \int_0^{z-x} f(\alpha, \beta) d\beta d\alpha \leq (1 - p_z)P(\alpha \geq 0, \beta \geq 0)
\]

\[
X^2 \leq NY
\]

\[
X^2 \geq Y
\]

\[
W \geq \frac{\ln(2)}{T_e} (T_r - T_k)
\]

\[
\delta_iX + \delta_i^2F_i^{-1} (1 - \bar{F}_i(0)(1 - p_i)) Y \leq BED_i \quad i = 1, \ldots, M
\]

\[
X, Y, W \geq 0
\]

Note that for a fixed \( N \) and given \( n, T_r \) can be computed using (2.1). We use the result of Theorem 3 and design Algorithm 4 for solving problems posed in (3.16) and (3.17).

Note that the optimization problem defined in (3.16) is not convex. However by using the result of Lemma 4 we can replace \( X^2 \geq Y \) by a linear constraint and formulate (3.16) as a convex model. Therefore it can be easily solved using commercial solvers such as CPLEX or CVX. For formulation posed in (3.17), first note that the result of lemma 1 still holds. Also since the optimal value of \( W \) for each \( N \) is independent from \( X \) and \( Y \) (equal to \( \max \left( 0, \frac{\ln(2)}{T_e} (T_r - T_k) \right) \)), therefore we can still solve (3.17) by optimizing it with respect to \( X \) and \( Y \) in 2D. Now we discuss the impact of adding \( X^2 \leq NY \) and \( X^2 \geq Y \) on optimal solutions of (3.16) and (3.17).

**Lemma 4.** At the optimal solution to (3.16) and (3.17), the constraints \( X^2 \leq NY \) and \( X^2 \geq Y \) are either inactive or the optimal solution occurs at the feasible corner defined by the intersection of \( X^2 = NY \) or \( X^2 = Y \) and one of the equations \( a_iX + b_iY = BED_i \quad i = 1, \ldots, M \) (Note that \( a_i \) and \( b_i \) represent equivalent coefficients in each formulation).
Proof. Note that the feasible region $\mathcal{C}$ for (3.16) and (3.17) is defined by following,

$$\mathcal{C} = \{(X,Y)|X^2 \leq NY, \ X^2 \geq Y, \ a_iX + b_iY = BED_i, \ i = 1,\ldots,M\}.$$ 

For a fixed $N$, the optimal solution of (3.16) lies on the boundary of feasible region defined by $\mathcal{C}$. Furthermore based on lemma 1, the optimal solution of (3.17) lies on the feasible boundaries of $\mathcal{C}$ too. If $X^2 \leq NY$ and $X^2 \geq Y$ are redundant constraints ($(X^*,Y^*)$ obtained by ignoring these constraints satisfy these constraints), then $X^2 \leq NY$ and $X^2 \geq Y$ are inactive in optimality.

For the other case, first define the collection of points $(X^{(q)}_i,Y^{(q)}_i), \ 1 \leq i \leq M$ obtained by solving the equations

$$X^2 = NY$$

$$a_iX + b_iY = BED_i,$$

and find the minimal point

$$q = \arg\min_{1\leq i\leq M} Y^{(q)}_i.$$

Next define collection of points $(X^{(p)}_i,Y^{(p)}_i), \ 1 \leq i \leq M$ obtained by solving the equations

$$X^2 = Y$$

$$a_iX + b_iY = BED_i,$$

and find the minimal point

$$p = \arg\min_{1\leq i\leq M} X^{(p)}_i.$$

Consider the three corners $p_1 = (0,0), \ p_2 = (X_q,Y_q)$ and $p_3 = (X_p,Y_p)$. As we move from $p_1$ toward $p_2$ or from $p_1$ toward $p_3$, we can increase both $X$ and $Y$. At the end of two line segments $\overrightarrow{p_0p_1}$ and $\overrightarrow{p_0p_2}$, we are at a feasible solution ($p_2$ or $p_3$) with maximum $X$ and $Y$, and since objective functions in (3.16) and (3.17) are increasing functions in both $X$ and $Y$, we see that the maximal value of $z$ is obtained at either $p_1$ or $p_2$. 

By using the result of Lemma 1, we can replace the quadratic constraints $X^2 \geq Y$ and $X^2 \leq NY$ by linear constraints $Y \leq \frac{Y_p}{X_p}X$ and $Y \geq \frac{Y_q}{X_q}X$ respectively and model (3.16) and a convex formulation and also use Algorithm 3 to find the optimal solution of (3.17).

4 Application to head and neck tumors

In this section, we discuss the application of nominal and robust formulations discussed in section 2 to treatment of head and neck tumors via radiotherapy. We first describe the data set and parameters that were used in our numerical experiments, then the solution to the nominal and robust optimum dosing schedules will be explored. We then comment on the effect of parameter uncertainty on the optimal schedule. At the end of the section the sensitivity of the optimal solution to model parameters is studied.

In order to estimate head and neck tumor radiobiologic parameters, we use the data set in [36]. To improve estimation accuracy, trials with same properties such as total dose administered, number of fractions and treatment duration were merged. Model fit is carried out by minimizing the weighted error between the model predictions of survival probability and the observed values.
of survival probabilities in trials associated with different schedules. In particular, the results of $K$ trials have been considered. The trial outputs are survival fraction for each trial $f_1, \ldots, f_K$. We assume that the tumor cell population regrows exponentially after irradiation with a time lag of $T_k$ and rate $\gamma$. Then following fractionated radiotherapy with $X = \sum_{i=1}^{N} d_i$ and $Y = \sum_{i=1}^{N} d_i^2$, the population of tumor cells $T$ units of time after start of therapy (which lasts $T_r$ units of time) in the absence of tumor repopulation during treatment is given by

$$N(T) = N(0) \exp[-\alpha X - \beta Y] \exp[\gamma(T - T_r - T_k)^+]$$

(4.18)

and in the presence of tumor repopulation during therapy is given by

$$N(T) = N(0) \exp[-\alpha X - \beta Y] \exp[\gamma(T - T_k)^+]$$

(4.19)

As a simplification we say that recurrence is only detectable if $N(T)/N(0) \geq 1$, i.e., if the tumor is bigger than its size at the start of therapy. There are $K$ total trials and the total radiation in trial $i$ is $X_i$ and the sum of the doses squared in trial $i$ is $Y_i$, and that the radiotherapy lasted for $T_{ri}$ days. Then from (4.18) and (4.19) we want to choose the distribution of $\alpha$ and $\beta$ such that for each $1 \leq i \leq K$

$$P(N(T)/N(0) \leq 1) = f_i$$

Assume that the distributions of $\alpha$ and $\beta$ are characterized by the joint density $f(x; y; \theta)$ where $\theta$ is a parameter that specifies the distribution. We define the probability that $(\alpha, \beta)$ take values in some set as (with the $\theta$ dependence explicit)

$$P_{\theta}(a_1 \leq \alpha \leq a_2, b_1 \leq \beta \leq b_2) = \int_{a_1}^{a_2} \int_{b_1}^{b_2} f(x, y; \theta) dx dy.$$

We assume that $\theta$ takes values in the space $\Theta$. For each trial $1 \leq i \leq K$ we define function

$$\phi_i(\theta) = P_{\theta}(\exp[-\alpha X_i - \beta Y_i] \exp[\gamma(T - T_{ri} - T_k)] \leq 1)$$

when ignoring tumor proliferation during treatment in the model and

$$\phi_i(\theta) = P_{\theta}(\exp[-\alpha X_i - \beta Y_i] \exp[\gamma(T - T_k)] \leq 1)$$

when considering tumor proliferation during treatment. Then our procedure for finding the best parameter set is to solve the minimization problem

$$\min_{\theta \in \Theta} \sum_{i=1}^{K} n_i(\phi_i(\theta) - f_i)^2$$

where $n_i$ is the number of patients in $i^{th}$ trial. Simulated annealing algorithm is utilized to find the optimal values of above model. We assume that the radiosensitivity parameters of LQ model, $\alpha$ and $\beta$ are distributed based on two independent normal distributions with means $\mu_\alpha$ and $\mu_\beta$ and standard deviations $\sigma_\alpha$ and $\sigma_\beta$, respectively. The reproduction rate $\gamma = \ln(2)/T_e$ for head and neck was selected to be 0.003 per day [36]. Kick-off time, $T_k$ and $p_z$ were selected from the set $\{0, 21, 28\}$ days and $\{50\%, 60\%, 70\%, 80\%\}$ percent respectively. The parameter $T$ was set to be 5 years and the nominal values of $\alpha$ and $\beta$ were set to be equal $\mu_\alpha$ and $\mu_\beta$. All parameters are summarized in Table 1.
We consider 6 different normal tissues involved in the treatment of head and neck carcinomas ([11] and [41]). The nominal values and confidence intervals for $\beta/\alpha$ for various normal tissues were extracted from [38], [44], [13], [29], [34] and [28] and are listed in Table 2. We assume that the ratio of $\{\beta_i/\alpha_i\}_{i=1}^{M}$ for normal tissues are distributed based on normal distributions with means $\mu_i$ and standard deviations $\sigma_i$. The values of means $\mu_i$ were set to the average of lower bound and upper bound of confidence intervals reported in above references. Also the standard deviation of $\{\beta_i/\alpha_i\}_{i=1}^{M}$ associated with different normal tissues were computed based on their confidence intervals given in references. Uniform distributions with parameters $U([a_i, b_i])$ are considered for $\{\delta_i\}_{i=1}^{M}$. Mandible and spinal cord are considered as serial structures and the data reported in [15] is utilized to compute their distribution parameters. Brain stem is assumed to be a serial tissue and its parameters are estimated from data reported in [41]. In these papers, average and standard deviation of dose absorbed by a normal tissue for a given dose radiated to the tumor are reported. We use these values to compute the mean ($\mu_i$) and standard deviation ($\sigma_i$) of sparing factors and then the values of $a_i$ and $b_i$ are computed using these equations:

$$a_i = b_i - \sqrt{12}\sigma_i \quad \text{and} \quad b_i = \mu_i + \frac{\sqrt{12}}{2}\sigma_i.$$ 

In [11], the values for planned dose, actually delivered dose and re-planned dose have been reported. We used these values to obtain a range for sparing factors for oral cavity, larynx and skin. Oral cavity, skin and larynx have been considered as serial structures. Nominal values of $\{\beta_i/\alpha_i\}_{i=1}^{M}$ and sparing factors are set to the $\mu_i$ and $\mu_i$, respectively. The values for $p_i$ associated with different normal tissues were selected from the set $\{50\%, 60\%, 70\%, 80\%\}$. We use the BED of the standard scheme ($2 \text{ Gys/day} \times 35$) computed based on the nominal values of $\{\beta_i/\alpha_i\}_{i=1}^{M}$ and $\{\mu_i\}_{i=1}^{M}$ as the maximum limit of BED for each normal tissues, $BED_i$.

We assume that patients may be treated at most in seven weeks and they visit the clinics three times a day, $n = 3$, however the sensitivity of optimal solution with respect to $n$ is studied later in this section. By considering 5 working days every week, we can compute the maximum number of allowable fractions as $N_{max} = 7 \times 5 \times n$.

Tables 3 to 13 display the optimum schedule for different models (optimal $d_i$ can be calculated from Theorem 3 and Algorithm 4). The optimum total dose ($X^*$) for different models is robust to uncertainty presented in parameters of head and neck tumors and does not change significantly in different models ($X^* \in [67 \text{ GY}, 73 \text{ GY}]$). However the presence of uncertainty in model parameters highly affects the optimal value of dose distribution $Y^*$. In fact, it is observed in the numerical results that it is preferable to deliver the radiation in more fractions when there is uncertainty in model parameters, e.g. see $N_{max}^*$ in Tables 6 and 7 or 8. Also as the amount of uncertainty increases, the optimal number of fractions tends to increase, for example compare the optimal values of number of fractions in Table 6 with 9 or Table 10 with 11. In some cases, there exist multiple optimal solutions with the same $X$ and $Y$ but different number of fractions which adds a lot of flexibility to the creation of treatment schedules. As expected, the value of objective function $z^*$ is decreasing in the probability of having the actual tumor BED less than optimal value of $z^*$ (See the $z^*$ in Tables 6 to 9 or Tables 10 to 13).

Figure 1 plots $\frac{BED_i-BED_{os_i}}{BED_i}$ for individual normal tissues as functions of $N_{max}$ for models (2.3), (2.5) and (2.6) modified in form of model (3.16) where $BED_{os_i}$ is the BED of $i^{th}$ normal tissue computed based on the optimal schedule. The Figure 1(a) shows that the limiting normal tissue is the Larynx normal tissue for $N_{max} \leq 35$. When $N_{max} > 35$, the optimal solution occurs at a degenerate corner where all normal tissue constraints are active. The reason for this degeneracy is
that for all normal tissues, \(BED_i\) are computed based on the standard schedule. The Figure 1(b) shows that the limiting normal tissue switches from the Mandible to the oral cavity as the number of fractions varies from 1 to 105. Figure 1(c) reveals that for shorter schedules, \(N_{max} \leq 67\), the most limiting constraint is Mandible and for longer schedules, \(N_{max} \in [68, 105]\), the most constrictive normal tissues are both Mandible and Skin.

Figure 2 plots the tumor BED versus \(N_{max}\) for different values of \(\gamma\). We observed that for schedules having fewer than 48 fractions, the outcome will be same since the proliferation effect \(W\) is negligible, \(g(N) \approx 0\). However for cases that treatments duration is longer than 62 fractions, shorter treatments result in better outcome in the fast growing tumors.

Figure 3 displays the tumor BED with \(N_{max}\) for different values of \(T_k\). It is apparent that tumor BED is an increasing function in tumor kick off time, however the difference between the BED of tumor for different values of \(T_k\) is negligible for short treatments and this difference becomes more evident as the \(N_{max}\) increases. Also for schedules lasting less than seven weeks, longer treatments result in higher BED on tumor.

Figure 4 displays the tumor BED with maximum number of allowable treatment duration (days) for different values of daily fractions. We observed that tumor BED is an increasing function in \(n\), and is highly sensitive to this parameter. For schedules delivering 3 fractions per day, we can improve the BED on tumor by more than 20% compared to schedules delivering only 1 fraction per day.

5 Conclusion

In this work, we have analyzed the problem of finding optimum radiation administration schedules considering various types of normal tissues in the presence of model parameter uncertainty. In particular, we aimed to identify the optimized total dose, number of fractions, dose per fraction and treatment duration for a variety of formulations considering different kinds of uncertainties. We used the traditional linear quadratic model including tumor proliferation to investigate the dynamics of radiation response considering two uncertainty sets. First we assumed that only the range forecasts for the uncertain parameters, \(\alpha\) and \(\beta\) and sparing factors for normal tissues, are known and we presented robust formulations of our optimization problem that are immune to realizations of the uncertain parameters so long as they lie within certain sets. Since using the range forecasts alone may lead to an excessively high level of conservativeness, in the second phase, we adjusted our formulations for the cases that uncertain parameters are distributed based on continuous random variables with known probability density function. Here we imposed the risk aversion factors in the objective function and the feasibility of constraints using some pre-defined probabilities.

We split our problem into two models, the first one ignores the repopulation effect in the tumor BED and the second one finds the optimized schedule in the presence of tumor proliferation. In the first case, we have shown that by defining the total radiation as \(X\) and sum of the doses square as \(Y\), our problem can be significantly simplified and easily solved in two dimensions when uncertainty in model parameters is linear or stochasticity of random variables only exists in sparing factors of normal tissues. When \(\alpha\) and \(\beta\) of tumor are considered to be continuous random variables, the problem becomes more challenging. In this case, first we have shown that the optimal value occurs at the boundary of feasible region defined by normal tissues BED constraints and then for several distributions we have proved that the objective function defined between two vertices of feasible region is concave. We also designed a branch and bound algorithm to find the optimal solution in the case that objective function is not a concave function. Using the variable transformation
for total dose and sum of the doses squared, we obtained necessary and sufficient conditions for the feasibility of our problem for a fixed number of fractions, $X^2 \leq N_{\text{max}} Y$ and $X^2 \geq Y$. If these conditions hold, we can use the solution of the simplified problems $(X^*, Y^*)$ to extract the optimal dose per fraction $d_i^*$ in the original formulation. When the tumor proliferation is not negligible or the necessary and sufficient conditions for optimal solution are not satisfied, we included these necessary and sufficient conditions in the constraint sets and introduced a brute force algorithm to find the optimal solution in the presence of tumor proliferation. The solution is always feasible in this case and thus the optimal value of radiation doses is guaranteed to be retrieved from the solution of simplified formulations $(X^*, Y^*)$.

Using data gathered previously [36], we parametrized the uncertainty in $\alpha$ and $\beta$ to investigate the behavior of optimal schedules for the head and neck tumors. For the numerical results, we assume that cancer site includes six normal tissues, spinal cord, brain stem, skin, oral cavity, mandible and larynx. The uncertainties in normal tissues have been estimated based on various data sets in the literature. The theoretical optimum total dose is observed to be robust to the uncertainties presented in model parameters and we found that for the parameters we considered, there is only a minor change in the optimal total dose for different schedules. Our numerical results for head and neck tumors support delivering radiation doses in longer schedules for more unknown parameters. It is been found that various types and number of normal tissues can be identified as the most restrictive constraints in optimality. However for our example, the most restrictive normal tissues were mandible, larynx or oral cavity for short treatments and skin for longer schedules. We saw that as the tumor regrowth rate increases, shorter treatment should be preferred. Interestingly we found that for the head and neck tumors, delivering radiation in small doses but more fractions can significantly increase the treatment performance.

There are several possible extensions to this work that we plan to consider in the future. For example, this work does not incorporate spatial structure of the tumor, including possible spatial heterogeneities in the parameters $\alpha$ and $\beta$. Another possible extension is the incorporation of repair effects, this would be useful if we wanted to consider shorter inter fraction periods. Lastly, it would be interesting to incorporate immune response and how inter-patient heterogeneity in immune response could impact the design of optimal fractionation schedules (see [26]).
6 Appendices

6.1 Simplified formulations of problems posed in Section 2

6.1.1 The model (2.3)

\[
\max_{X,Y} \alpha X + \beta Y \tag{6.20}
\]

subject to

\[
\delta_i X + \frac{\beta_i}{\alpha_i} \delta_i^2 Y \leq BED_i, \quad i = 1, \ldots, M
\]

\[X, Y \geq 0\]

6.1.2 The model (2.5)

\[
\max_{X,Y} \alpha X + \beta Y \tag{6.21}
\]

subject to

\[
\delta_i X + \delta_i^2 \left( \frac{\beta_i}{\alpha_i} + l_i \right) Y \leq BED_i, \quad i = 1, \ldots, M
\]

\[X, Y \geq 0\]

6.1.3 The model (2.6)

\[
\max_{X,Y} \sum_{j=1}^{N} \alpha X + \beta Y \tag{6.22}
\]

subject to

\[
(\delta_i + l_{\delta_i}) X + (\delta_i + l_{\delta_i})^2 \frac{\beta_i}{\alpha_i} Y \leq BED_i, \quad i = 1, \ldots, M
\]

\[X, Y \geq 0\]

6.1.4 The model (2.8)

\[
\max_{X,Y} \alpha X + \beta Y \tag{6.23}
\]

subject to

\[
G_i^{-1} \left( 1 - (1 - p_i) \bar{G}_i(0) \right) X + G_i^{-1} \left( 1 - (1 - p_i) \bar{G}_i(0) \right)^2 \frac{\beta_i}{\alpha_i} Y \leq BED_i, \quad i = 1, \ldots, M
\]

\[X, Y \geq 0\]

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6.2 Proof of technical Lemma

Proof. Assume $z^*, X^*$ and $Y^*$ are optimal solutions to (3.10). If $X^*$ and $Y^*$ lie in the interior of (3.12), then there exist $\Delta X^*$ and $\Delta Y^*$ such that $X^* + \Delta X^*$ and $Y^* + \Delta Y^*$ remain feasible. The left hand side of (3.11) is a decreasing function in $X$ and $Y$, therefore we can increase $z$ without violating feasibility constraints. Therefore there exists a feasible $z$ which is strictly greater than $z^*$ and it contradicts the assumption that $z^*$ is an optimal solution to our problem. Therefore the optima must lie on the feasible boundaries of (3.12). Also if (3.11) is not active in optimality, we have

$$\int_0^{\hat{X}} \int_0^{\frac{z-\alpha X}{1-\alpha X}} f(\alpha, \beta) d\beta d\alpha < (1 - p_z) P(\alpha \geq 0, \beta \geq 0)$$

and we can increase $z$ without leaving feasible region which contradicts the optimality assumption.

\[\Box\]
6.3 Algorithms

6.3.1 Finding the corners of the feasible region polygon

For ease of notation we use the following

\[ a_i = \delta_i, \]
\[ b_i = \delta^2 F_i^{-1} (1 - F_i(0)(1 - p_i)) \]
\[ c_i = BED_i \]

Algorithm 1 Constructing the corners of the polygon defined by feasible region

1: Set \((X_1, Y_1) = (0, 0)\).
2: Set \(\ell = 2\).
3: Set \(exit = 0\).
4: Do While \(exit == 0\)
  5: \( \ell = \ell + 1 \)
  6: For \(j = 1 : M, j \neq i_2, \ldots, i_{\ell-1} \)
  7: Solve for \((X_{i_\ell,j}, Y_{i_\ell,j})\) that solve this system
     \[ a_i X + b_i Y = c_i \]
     \[ a_j X + b_j Y = c_j \]
  8: Set \( j_* = \arg \min_j X_{i_\ell,j} \).
  9: Set \( X_{i_\ell}^{(1)} = X_{i_\ell,j_*} \) and \( X_{i_\ell}^{(2)} = c_i/a_i \).
10: If \( \min(X_{i_\ell}^{(1)}, X_{i_\ell}^{(2)}) = X_{i_\ell}^{(2)} \) then:
    11: Set \( exit = 1 \).
    12: Set \((X_, Y_\ell) = (X_{i_\ell}^{(2)}), 0)\).
    13: Else:
    14: Set \((X_\ell, Y_\ell) = (X_{i_\ell,j_*}, Y_{i_\ell,j_*})\).
15: End For Loop.
16: End While Loop.

6.3.2 Maximization of \((3.10)\)

Algorithm 2 Maximization of \((3.10)\) via searching boundaries of feasible region when \(z_i(t)\) is a concave function

1: Compute the complete set of corners, \(\mathcal{C} = \{(X_1, Y_1), \ldots, (X_k, Y_k)\}\) defined by \((3.12)\) and \((3.13)\).
2: For each \((X_i, Y_i) \in \mathcal{C}\), compute \(\hat{z}_i(1)\) and set \(z_i^* = \hat{z}_i(1)\) and \((X_i^*, Y_i^*) = (X_j(1), Y_j(1))\) where \(j = \arg \max_i \hat{z}_i(1)\).
3: Compute \(\frac{\partial z_i(t)}{\partial t} |_{t = 0, \delta_i} \) using \((6.24)\) for \(i \in \{1, \ldots, k\}\).
4: For \(i\) such that \(\frac{\partial z_i(t)}{\partial t} |_{t = 0, \delta_i} < 0\), compute \(t'_i\) such that \(\frac{\partial z_i(t)}{\partial t} |_{t = t'_i} = 0\) and compute \(\tilde{z}_i = z_i(t'_i)\). For all other \(i\) set \(\tilde{z}_i = -\infty\).
5: Define \(z_i^* = \tilde{z}_i(t'_i)\) and \((X_i^*, Y_i^*) = (X_j(t'_i), Y_j(t'_i))\), where \(j = \arg \max_i \tilde{z}_i(t'_i)\).
6: Return \((X_i^*, Y_i^*)\), where \(\ell = \arg \max \{z_1^*, z_2^*\}\).

Remark 1. Algorithm 2 converges in finite time to the optimal \(X\) and \(Y\) and it is computationally tractable for practical \(M\).

The bisection method can be used to find \(\hat{z}_1, \hat{z}_i\) and \(t'_i\) in steps 2 and 4 of Algorithm 1. Note that the left hand side of \((3.11)\) is an increasing function of \(z\), therefore bisection method guarantees to return the \(z_i(t)\) in finite steps for a given accuracy. The number of iterations needed, \(n\), to achieve
a given error , \( \epsilon \), using bisection algorithm is given by \( n = \log_2 \left( \frac{2\epsilon}{\epsilon_0} \right) \), where \( \epsilon_0 \) is the initial bracket interval \( [10] \). Since \( 0 < p_z < 1 \), there are \( \alpha_{\text{max}} \) and \( \beta_{\text{max}} \) such that

\[
\int_0^{\alpha_{\text{max}}} \int_0^{\beta_{\text{max}}} f(\alpha, \beta) d\beta d\alpha > (1 - p_z) P(\alpha \geq 0, \beta \geq 0)
\]

and if we define \( X_{\text{max}} = \max_{1 \leq j \leq k} X_j \) and \( Y_{\text{max}} = \max_{1 \leq j \leq k} Y_j \), then by choosing \( z = \alpha_{\text{max}} X_{\text{max}} + \beta_{\text{max}} Y_{\text{max}} \), we always have

\[
\int_0^{\alpha_{\text{max}}} \int_0^{\beta_{\text{max}}} f(\alpha, \beta) d\beta d\alpha \geq \int_0^{\alpha_{\text{max}}} \int_0^{\beta_{\text{max}}} f(\alpha, \beta) d\beta d\alpha > (1 - p_z) P(\alpha \geq 0, \beta \geq 0).
\]

On the other hand, for each \( (X_j, Y_j) \in C \) we have \( \hat{z}_j \geq 0 \). Therefore we can choose \( \epsilon_1 = \alpha_{\text{max}} X_{\text{max}} + \beta_{\text{max}} Y_{\text{max}} \) for finding \( \hat{z}_j \) and \( \epsilon_2 = 1 \) for finding \( t'_j \) in steps 2 and 5 of Algorithm 2. It is obvious that Algorithm 2 terminates finitely. In practice, there is an upper bound on the number of normal tissues that can be considered for a specific tumor based on clinical considerations. Generally \( M \) is at most several dozen. Since \( M \) is a small integer number, therefore not only does Algorithm 2 terminate in finite steps but also it is computationally tractable for practical \( M \).

### 6.3.3 Branch and bound algorithm

**Algorithm 3** Maximization of (3.10) via searching boundaries of feasible region when \( z_i(t) \) is not a concave function

1. Compute the complete set of corners, \( C = \{ (X_1, Y_1), \ldots, (X_k, Y_k) \} \) defined by (3.12) and (3.13).
2. For each \( (X_j, Y_j) \in C \), compute \( z_i(1) \) and set \( z^* = z_i(1) \) and \( (X^*, Y^*) = (X_j, Y_j) \) where \( j = \arg \max_i z_i \).
3. For \( t = 1 \) to \( t = n \) Do:
   4. \( i \leftarrow 1 \).
   5. \( lb_i(i) \leftarrow 0, ub_i(i) \leftarrow 1 \).
   6. \( lb_i(i) = \max\{z(X_{i}(0), Y_{i}(0)), z(X_{i}(1), Y_{i}(1))\}, ub_i(i) = z(\max\{X_{i}(0), X_{i}(1)\}, \max\{Y_{i}(0), Y_{i}(1)\}) \).
   7. \( a(i) \leftarrow 1 \).
   8. While \( \sum_i a(i) > 0 \) Do:
      9. \( \text{ind} = \text{find}(i | a(i) > 0) \).
      10. For \( j = 1: \text{length}(\text{ind}) \) Do:
          11. \( i \leftarrow i + 1 \).
          12. \( lb_i(i) = (lb_i(\text{ind}(j)) + ub_i(\text{ind}(j)))/2, ub_i(i) = ub_i(\text{ind}(j)) \).
          13. Compute
              \[
              lb_z(i) = \max\{z(X_i(lb_i(i)), Y_i(lb_i(i))), z(X_i(ub_i(i)), Y_i(ub_i(i)))\}, ub_z(i) = z(\max\{X_i(lb_i(i)), X_i(ub_i(i))\}, \max\{Y_i(lb_i(i)), Y_i(ub_i(i))\}) \).
   14. \( \text{if} \ (ub_z(i) - lb_z(i) > \epsilon) \ \text{then} \ a(i) \leftarrow 0, \text{else} \ a(i) \leftarrow 0 \).
   15. \( lb_i(\text{ind}(j)) = lb_i(\text{ind}(j)), ub_i(\text{ind}(j)) = (lb_i(\text{ind}(j)) + ub_i(\text{ind}(j)))/2 \).
   16. Repeat steps 13 and 14 with \( \text{ind}(j) \) instead of \( i \).
   17. Update \( z^* \) and \( (X^*, Y^*) \) for any \( lb_z(j) > z^* \).
18. End For Loop.
19. For every \( j \) such that \( ub_z(j) < z^* \), \( a(j) \leftarrow 0 \).
20. Sort \( \{lb_z(:, ), ub_z(:, ), lb_z(:, ), ub_z(:, )\} \) column-wise based on \( lb_z(i) \).
21. End While Loop.
22. End For Loop.

Note that for every line segment defined by two points \( (X_1, Y_1) \) and \( (X_2, Y_2) \), we can compute the lower bound using

\[
\Phi_{lb} = \max\{z_1(0), z_1(1)\}
\]
and compute the upper bound using
\[ \Phi_{ub} = \{ z \mid \int_0^x \int_0^{x-\alpha} f(\alpha, \beta) d\beta d\alpha = (1-p_z) P(\alpha \geq 0, \beta \geq 0), X = \max(X_1, X_2), Y = \max(Y_1, Y_2) \}. \]

On each edge, the branching variable is \( t \in [0, 1] \). At node \( i \), we store the lower bound and upper bound of \( t \) as \( lb_t(i) \) and \( ub_t(i) \). Similarly lower and upper bounds of optimal solution at node \( i \) are stored in \( lb_z(i) \) and \( ub_z(i) \). Note that \( a(i) = \{0, 1\} \) indicates the state of the node in our optimization tree, if \( a(i) = 1 \) then our node is considered as active node and further partitioning can be proceeded through that branch, otherwise we consider that node as an inactive node. Branching in node \( i \) continues in this manner until there are no active nodes in that branch or \( ub_z(i) - lb_z(i) < \epsilon \), where \( \epsilon \) is the given accuracy for optimal value. Since the objective value of an optimal solution cannot be smaller than a lower bound, active nodes with upper bounds smaller than an existing lower bound can be safely deleted (step 19).

**Remark 2.** Algorithm 3 converges and terminates with certificate proving \( \epsilon \)-suboptimality.

Number of line segments in partition \( L_k \) is \( k \). Note that total length of these line segments is \( L(\Omega_{initial}) \), so
\[ \min_{\Omega \in L_k} L(\Omega) \leq \frac{L(\Omega_{initial})}{k} \]
and hence for big \( k \), at least one line segment has small length and having small length will imply that \( ub_z(k) - lb_z(k) \) is small.

### 6.3.4 Optimization algorithm in the presence of tumor proliferation

**Algorithm 4** Maximization of modified formulations via brute-force search method

1: Set \( i \leftarrow 1 \) and \( o^* \leftarrow -\infty \).
2: While \( i \leq N_{max} \) Do:
3: \quad Compute \( (X_i, Y_i, o_i) \) by setting \( N = i \) and solving (3.16) or (3.17) \( (o_i \) is the value of objective function in optimality).
4: \quad If \( o_i > o^* \) then do \( N^* \leftarrow i, o^* \leftarrow o_i, X^* \leftarrow X_i \) and \( Y^* \leftarrow Y_i \).
5: \quad \( i \leftarrow i + 1 \), Go to step 2.
6: End While Loop.
7: For any arbitrary integer \( j \in (0, \lceil \frac{(X^*)^2}{N^*} \rceil) \), compute optimal \( d_j^* \) as follows:
\[ d_1^* = \cdots = d_j^* = \frac{jX^* + \sqrt{(N^* - j)(jN^*Y^* - j(X^*)^2)}}{jN^*}, \quad d_{j+1}^* = \cdots = d_N^* = \frac{X^* - jd}{N^* - j}. \]

Algorithm 4 is guaranteed to terminate after \( N_{max} \) steps and each step is a direct result based on straightforward procedures. Hence we see that as long as \( N_{max} \) is not too large, this is a feasible algorithm. On the other hand it is clear that maximum number of treatment sessions in radiotherapy, even for large total radiation dose, does not exceed orders of hundred for each patient; that is, the above algorithm terminates finitely and is computationally tractable for pratical \( N_{max} \).
6.4 Proofs of concavity of $z_i(t)$ for various distributions

Define

$$
\phi(z_i(t), t) = \int_0^{\frac{z_i(t)}{1-tX_i+Y_i+1}} \int_0^{\frac{z_i(t)-\alpha(tX_i+(1-t)X_{i+1})}{1-tY_i+Y_i+1}} f(\alpha, \beta) \, d\beta \, d\alpha.
$$

Then we have

$$
\frac{\partial}{\partial t} \phi(z_i(t), t) = \frac{\partial \phi(z_i(t), t)}{\partial z_i(t)} \frac{\partial z_i(t)}{\partial t} + \frac{\partial \phi(z_i(t), t)}{\partial t} = 0
$$

and we can compute that

$$
\frac{\partial z_i(t)}{\partial t} = -\frac{\frac{\partial \phi(z_i(t), t)}{\partial \phi(z_i(t), t)}}{\partial z_i(t)}.
$$

In order to compute $\frac{\partial \phi(z_i(t), t)}{\partial t}$, first define

$$
H(t, \alpha) = \int_0^{\frac{z_i(t)}{1-tX_i+Y_i+1}} \int_0^{\frac{z_i(t)}{1-tX_i+Y_i+1}} f(\alpha, \beta) \, d\beta
$$

then consider that

$$
\frac{\partial \phi(z_i(t), t)}{\partial t} = \frac{\partial}{\partial t} \left( \int_0^{\frac{z_i(t)}{1-tX_i+Y_i+1}} H(t, \alpha) \, d\alpha \right) = \int_0^{\frac{z_i(t)}{1-tX_i+Y_i+1}} \frac{\partial}{\partial t} H(t, \alpha) \, d\alpha.
$$

On the other hand, we have:

$$
\frac{\partial}{\partial t} H(t, \alpha) = \frac{z_i'(t)(tY_i + (1-t)Y_{i+1}) + \alpha(X_{i+1}Y_i - X_iY_{i+1}) + z_i(t)(Y_{i+1} + Y_i)}{(tY_i + (1-t)Y_{i+1})^2} f(\alpha, \frac{z_i(t) - \alpha(tX_i + (1-t)X_{i+1})}{tY_i + (1-t)Y_{i+1}})
$$

therefore we can compute $\frac{\partial \phi(z_i(t), t)}{\partial t}$ as

$$
\int_0^{\frac{z_i(t)}{1-tX_i+Y_i+1}} \frac{z_i'(t)(tY_i + (1-t)Y_{i+1}) + \alpha(X_{i+1}Y_i - X_iY_{i+1}) + z_i(t)(Y_{i+1} + Y_i)}{(tY_i + (1-t)Y_{i+1})^2} f(\alpha, \frac{z_i(t) - \alpha(tX_i + (1-t)X_{i+1})}{tY_i + (1-t)Y_{i+1}}) \, d\alpha
$$

Our next task is computing $\frac{\partial \phi(z_i(t), \alpha)}{\partial z_i(t)}$. Let’s define $L(z_i(t), \alpha)$ as

$$
\int_0^{\frac{z_i(t)}{1-tX_i+Y_i+1}} f(\alpha, \beta) \, d\beta
$$

then we have:

$$
\frac{\partial \phi(z_i(t), \alpha)}{\partial z_i(t)} = \int_0^{\frac{z_i(t)}{1-tX_i+Y_i+1}} \frac{\partial}{\partial z_i(t)} L(z_i(t), \alpha) \, d\alpha
$$

and

$$
\frac{\partial}{\partial z_i(t)} L(z_i(t), \alpha) = \frac{1}{tY_i + (1-t)Y_{i+1}} f(\alpha, \frac{z_i(t) - \alpha(tX_i + (1-t)X_{i+1})}{tY_i + (1-t)Y_{i+1}})
$$

thus we can conclude that

$$
\frac{\partial \phi(z_i(t), t)}{\partial z_i(t)} = \int_0^{\frac{z_i(t)}{1-tX_i+Y_i+1}} \frac{1}{tY_i + (1-t)Y_{i+1}} f(\alpha, \frac{z_i(t) - \alpha(tX_i + (1-t)X_{i+1})}{tY_i + (1-t)Y_{i+1}}) \, d\alpha
$$
and finally compute $\frac{\partial z_i(t)}{\partial t}$ as

$$\int_0^{\lambda X_i \gamma_i (1-t) X_i+1} z_i(t)(\gamma_i+(1-t)Y_{i+1})+\alpha(X_i+1 Y_i-X_i Y_i+1)+z_i(t)(Y_i+1-X_i) f(\alpha, z_i(t)-\alpha(X_i+1-t)X_{i+1}) \, d\alpha - \int_0^{\lambda X_i \gamma_i (1-t) X_i+1} z_i(t)(\gamma_i+(1-t)Y_{i+1})+\alpha(X_i+1 Y_i-X_i Y_i+1)+z_i(t)(Y_i+1-X_i) f(\alpha, z_i(t)-\alpha(X_i+1-t)X_{i+1}) \, d\alpha$$

$$= -\frac{1}{2(Y_i+1-t)Y_{i+1}} \left( z_i(t)(Y_{i+1}-Y_i) + (X_{i+1} Y_i - X_i Y_i+1) \int_0^{\lambda X_i \gamma_i (1-t) X_i+1} f(\alpha, z_i(t)-\alpha(X_i+1-t)X_{i+1}) \, d\alpha \right)$$

To establish concavity of function $z_i(t)$ at its critical points, we require to show that $\frac{\partial^2 z_i(t)}{\partial t^2} < 0$ when $\frac{\partial z_i(t)}{\partial t} = 0$.

$$\frac{\partial^2 z_i(t)}{\partial t^2} = -\frac{(Y_{i+1}-Y_i)}{(Y_i+1-t)Y_{i+1}} \frac{\partial z_i(t)}{\partial t}$$

$$= -\frac{(X_{i+1} Y_i - X_i Y_i+1)}{(Y_i+1-t)Y_{i+1}} \frac{\partial z_i(t)}{\partial t}$$

$$(X_{i+1} Y_i - X_i Y_i+1)/(2(Y_i+1-t)Y_{i+1})$$

is negative, therefore in order to show the concavity of above function it is enough to show that

$$\frac{\partial}{\partial t} \left( f(\alpha, z_i(t)-\alpha(X_i+1-t)X_{i+1}) \right)$$

is positive. We now prove the concavity of $z_i(t)$ for several distributions as follows:

### Exponential Distribution

Assume $f(\alpha) = \mu_1 e^{-\mu_1 \alpha}$ and $g(\beta) = \mu_2 e^{-\mu_2 \beta}$. Therefore we can compute (6.25) as

$$\partial \left( \int_0^{\lambda X_i \gamma_i (1-t) X_i+1} f(\alpha, z_i(t)-\alpha(X_i+1-t)X_{i+1}) \, d\alpha \right)$$

$$= \partial \left( \int_0^{\lambda X_i \gamma_i (1-t) X_i+1} e^{-\alpha(X_i+1-t)X_{i+1}} \, d\alpha \right)$$

$$= \partial \left( \int_0^{\lambda X_i \gamma_i (1-t) X_i+1} e^{-\alpha(X_i+1-t)X_{i+1}} \, d\alpha \right)$$

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Define $\frac{z_i(t)}{X_i + (1 - t)X_{i+1}} = u$ and $\mu_1 + \mu_2 \frac{tX_i + (1 - t)X_{i+1}}{Y_i + (1 - t)Y_{i+1}} = v$, then we can simplify above equation as follows

$$\frac{\partial}{\partial t} \left( \frac{1 - (1 + uv)e^{-uv}}{v(1-e^{-uv})} \right) = \frac{uv(u'v + uv')e^{-uv}v(1-e^{-uv}) - (1 - (1 + uv)e^{-uv})(v' - (1-e^{-uv}) + v(u'v + uv')e^{-uv})}{(v(1-e^{-uv}))^2}$$

$$= \frac{(uv^3 + v^2e^{-uv} - v^2)u'v^{-uv} + (u^2v^2e^{-uv} - 1 + 2e^{-uv} - e^{-2uv})v'}{(v(1-e^{-uv}))^2}.$$ 

Therefore we need to show that $(uv^3 + v^2e^{-uv} - v^2)u'v^{-uv} + (u^2v^2e^{-uv} - 1 + 2e^{-uv} - e^{-2uv})v'$ is positive, note that

$$u' = \frac{z_i'(t)(tX_i + (1 - t)X_{i+1}) + (X_{i+1} - X_i)z_i(t)}{(tX_i + (1 - t)X_{i+1})^2}$$

$$v' = \frac{(X_i - X_{i+1})(tY_i + (1 - t)Y_{i+1}) + (Y_{i+1} - Y_i)(tX_i + (1 - t)X_{i+1})}{(tY_i + (1 - t)Y_{i+1})^2} = \frac{X_iY_{i+1} - X_{i+1}Y_i}{(tY_i + (1 - t)Y_{i+1})^2}$$

$$uv = \frac{\mu_1 z_i(t)}{tX_i + (1 - t)X_{i+1}} + \frac{\mu_2 z_i(t)}{tY_i + (1 - t)Y_{i+1}}$$

In critical points of $z_i(t)$ we have $z_i'(t) = 0$, hence $u'$ and $uv$ are positive and $v'$ is negative. Define $w = uv$, obviously $u, v, w > 0$ and we can simplify $(uv^3 + v^2e^{-uv} - v^2)u'v^{-uv} + (u^2v^2e^{-uv} - 1 + 2e^{-uv} - e^{-2uv})v'$ as

$$(w + e^{-w} - 1)w^2u'v^{-uv} + (w^2v^2e^{-uv} - 1 + 2e^{-uv} - e^{-2uv})v'$$

(6.26)

Note that $w + e^{-w} - 1 \geq 0$ and $w^2 + 2 - e^{-w} - e^{-w} \leq 0$ for $w \geq 0$, therefore (6.26) is always positive.

### 6.4.2 Normal Distribution without positivity conditions on $\alpha$ and $\beta$

If we ignore the positivity conditions of $\alpha$ and $\beta$, $z_i(t)$ can be simplified as

$$z_i(t) = \{z | P(\alpha X_i(t) + \beta Y_i(t) \leq z) = (1 - p_z), 0 \leq t \leq 1 \}$$

or equivalently

$$P \left( N \leq \frac{z_i(t) - X_i(t)\mu_\alpha - Y_i(t)\mu_\beta}{\sqrt{\sigma_\alpha^2 X_i(t)^2 + \sigma_\beta^2 Y_i(t)^2}} \right) = (1 - p_z).$$

Hence $z_i(t)$ can be computed as

$$z_i(t) = \Phi^{-1} (1 - p_z) \frac{\sqrt{\sigma_\alpha^2 X_i(t)^2 + \sigma_\beta^2 Y_i(t)^2 + X_i(t)\mu_\alpha + Y_i(t)\mu_\beta}}$$

or

$$z_i(t) = c \sqrt{u(t)} + L(t)$$

where $c = \Phi^{-1} (1 - p_z), u(t) = \sigma_\alpha^2 X_i(t)^2 + \sigma_\beta^2 Y_i(t)^2$ and $L(t) = X_i(t)\mu_\alpha + Y_i(t)\mu_\beta$ is a linear function of $t$. Note that $L(t)$ is both convex and concave, therefore in order to establish the concavity of $z_i(t)$, it is enough to show the concavity of $c \sqrt{u(t)}$. Note that

$$\frac{\partial^2}{\partial u(t)} \sqrt{u(t)} = \frac{1}{2} u''(t)u(t)^{-\frac{1}{4}} - \frac{1}{4} (u'(t))^2 u(t)^{-\frac{3}{4}} = \frac{1}{2} (2\sigma_\alpha^2 (X_i - X_{i+1})^2 + 2\sigma_\beta^2 Y_i(t)^2) (\sigma_\alpha^2 (X_i + (1 - t) X_{i+1})^2 + \sigma_\beta^2 (Y_i + (1 - t) Y_{i+1})^2)^{-\frac{1}{4}}$$

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\(-\frac{1}{4}(2\sigma^2_\alpha(X_i - X_{i+1})(tX_i + (1-t)X_{i+1}) + 2\sigma^2_\beta(Y_i - Y_{i+1})(tY_i + (1-t)Y_{i+1}))^2(\sigma^2_\alpha(tX_i + (1-t)X_{i+1})^2 + \sigma^2_\beta(tY_i + (1-t)Y_{i+1})^2)\)

Multiplying the above equation by \((\sigma^2_\alpha(tX_i + (1-t)X_{i+1})^2 + \sigma^2_\beta(tY_i + (1-t)Y_{i+1})^2)\), will not affect the sign of above equation, therefore we can simplify it to

\[
(\sigma^2_\alpha(X_i - X_{i+1})^2 + \sigma^2_\beta(Y_i - Y_{i+1})^2)(\sigma^2_\alpha(tX_i + (1-t)X_{i+1})^2 + \sigma^2_\beta(tY_i + (1-t)Y_{i+1})^2) - (\sigma^2_\alpha(X_i - X_{i+1})(tY_i + (1-t)Y_{i+1}))^2 \geq 0.
\]

Therefore \(z_i(t)\) is convex when \(c = \Phi^{-1}(1 - p_z)\) is positive \((p_z < 0.5)\) and concave when \(c = \Phi^{-1}(1 - p_z)\) is negative \((p_z > 0.5)\).

### 6.4.3 Generalization of uniform distribution

Assume \(f(\alpha) = c_1\alpha^{k_1}\) and \(g(\beta) = c_2\beta^{k_2}\), for \(0 \leq \alpha \leq 1\) and \(0 \leq \beta \leq 1\), respectively. Therefore we can compute \((6.25)\) as follows:

\[
\frac{\partial}{\partial t} \left( \int_0^{tX_i+(1-t)X_{i+1}} \frac{z_i(t)}{tX_i+(1-t)X_{i+1}} \alpha^{k_1+1} \left( \frac{z_i(t) - \alpha(tX_i + (1-t)X_{i+1})}{tX_i+(1-t)X_{i+1}} \right)^2 d\alpha \right)
\]

There are two cases, first where \(k_2 = 0\), then we simplify above term as

\[
\frac{\partial}{\partial t} \left( \int_0^{tX_i+(1-t)X_{i+1}} \alpha^{k_1+1} d\alpha \right) = k_1 + 1 \frac{\partial}{\partial t} \left( \frac{z_i(t)}{tX_i+(1-t)X_{i+1}} \right) = k_1 + 1 \frac{z_i'(t)(tX_i + (1-t)X_{i+1}) + z_i(t)(X_{i+1} - X_i)}{(tX_i + (1-t)X_{i+1})^2}
\]

For critical points we have \(z_i'(t) = 0\), therefore \(z_i(t)\) is concave for all critical points of \(z_i(t), 0 \leq t \leq 1\). The second case is when \(k_2 \geq 1\). Let’s define \(u = \frac{z_i(t)}{tX_i+(1-t)X_{i+1}}\) and \(v = z_i(t) - \alpha(tX_i + (1-t)X_{i+1})\), then we can simplify above term as

\[
k_2 \left[ \int_0^u \alpha^{k_1+1}v^{k_2-1}da \right] \left[ \int_0^u \alpha^{k_1+1}v^{k_2}da \right] - \left[ \int_0^u \alpha^{k_1+1}v^{k_2-1}da \right]^2
\]

Note that \(v' = z_i'(t) + \alpha(X_{i+1} - X_i)\), and at critical points of \(z_i(t)\), we have \(z_i'(t) = 0\), therefore we have \(v' = \alpha(X_{i+1} - X_i) \geq 0\) at critical points of \(z_i(t)\). Hence to show the positivity of above term, it suffices to show that

\[
\int_0^u \alpha^{k_1+2}v^{k_2-1}da \int_0^u \alpha^{k_1}v^{k_2}da \geq \left( \int_0^u \alpha^{k_1+1}v^{k_2}da \right)^2
\]

Let’s assume \(v = a - ba\), then we can use the integration by part and simplify some terms of above inequality as follows:

\[
\int_0^u \alpha^{k_1+2}(a - ba)^{k_2-1}da = \frac{1}{k_2b} \left( -u^{k_1+2}(a - ba)^{k_2} + (k_1 + 2) \int_0^u \alpha^{k_1+1}(a - ba)^{k_2}da \right)
\]

and

\[
\int_0^u \alpha^{k_1+1}(a - ba)^{k_2-1}da = \frac{1}{k_2b} \left( -u^{k_1+1}(a - ba)^{k_2} + (k_1 + 1) \int_0^u \alpha^{k_1}(a - ba)^{k_2}da \right).
\]

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and inequality (6.27) can be expanded to

\[-u^{k_1+2}(a - bu)^{k_2} \int_0^u \alpha^{k_1}(a - b\alpha)^{k_2} d\alpha + \frac{k_1 + 2}{k_2 b} \int_0^u \alpha^{k_1+1}(a - b\alpha)^{k_2} d\alpha \int_0^u \alpha^{k_1}(a - b\alpha)^{k_2} d\alpha \geq
\]

\[-u^{k_1+1}(a - bu)^{k_2} \int_0^u \alpha^{k_1+1}(a - b\alpha)^{k_2} d\alpha + \frac{k_1 + 1}{k_2 b} \int_0^u \alpha^{k_1}(a - b\alpha)^{k_2} d\alpha \int_0^u \alpha^{k_1+1}(a - b\alpha)^{k_2} d\alpha
\]

which is equal to

\[\left[ \int_0^u \alpha^{k_1+1}(a - b\alpha)^{k_2} d\alpha \right] \left[ \int_0^u \alpha^{k_1}(a - b\alpha)^{k_2} d\alpha + u^{k_1+1}(a - bu)^{k_2} \right] \geq \left( u^{k_1+2}(a - bu)^{k_2} \right) \int_0^u \alpha^{k_1}(a - b\alpha)^{k_2} d\alpha
\]

Note that \( u = \frac{a}{b} \) and since \( k_2 \geq 1 \), above inequality simplifies to

\[\left[ \int_0^u \alpha^{k_1+1}(a - b\alpha)^{k_2} d\alpha \right] \left[ \int_0^u \alpha^{k_1}(a - b\alpha)^{k_2} d\alpha \right] \geq 0
\]

and since \( 0 \leq \alpha \leq u = \frac{a}{b} \), above inequality always hold.
6.5 Figures
(a) The model (2.3) modified based on (3.16)  
(b) The model (2.5) modified based on (3.16)  
(c) The model (2.6) modified based on (3.16)  

Figure 1: The most constricting normal tissues in optimality: (a) shows that the limiting normal tissue is the Larynx normal tissue for \( N_{\text{max}} \leq 35 \). When \( N_{\text{max}} > 35 \), optimal solution happens at a degenerate corner with all constraints to be active. (b) shows that the limiting normal tissue switches from the Mandible normal tissue to the oral cavity as the number of fractions is varied from 1 to 105. (c) shows that when \( N_{\text{max}} \leq 67 \), the most limiting constraint is Mandible and for \( N_{\text{max}} \in [68, 105] \) the most constrictive normal tissues are both Mandible and Skin. The values of \( \alpha \) and \( \beta \) are set to be 0.1708 and 0.0537, respectively (values obtained by assuming \( T_k = 21 \) days).
Figure 2: This plot shows the sensitivity of tumor BED with respect to tumor growth rate $\gamma$. For treatments lasting more than 29 days, shorter treatments result in higher BED on fast growing tumors. The values of $\alpha$ and $\beta$ are set to be 0.1708 and 0.0537, respectively (values obtained by assuming $T_k = 21$ days).
Figure 3: This plot shows the sensitivity of tumor BED with respect to tumor kick off time $T_k$. This plot suggests that the effect of kick off time on tumor BED is almost negligible for short treatments and becomes more significant as treatment duration increases. Longer treatments result in higher BED on tumor when $N_{max} \leq 105$. The values of $\alpha$ and $\beta$ are set to be 0.1708 and 0.0537, respectively (values obtained by assuming $T_k = 21$ days).
Figure 4: This plot shows the sensitivity of tumor BED with respect to the number of daily radiation fractions, $n$. By increasing the number of daily fractions from 1 to 3, tumor BED can be increased by more than 20%. The values of $\alpha$ and $\beta$ are set to be 0.1708 and 0.0537, respectively (values obtained by assuming $T_k = 21$ days).
### 6.6 Tables

#### Table 1: Head and neck tumor parameters used for finding optimal schedule

| Parameters   | Without tumor proliferation | With tumor proliferation | unit |
|--------------|-----------------------------|--------------------------|------|
| $T_k = 0$    | $T_k = 21$                  | $T_k = 28$               |      |
| $\mu_\alpha$| 0.2611                      | 0.2089                   | 0.2909| $1/Gy$ |
| $\mu_\beta$ | 0.0463                      | 0.0281                   | 0.0138| $1/Gy^2$ |
| $\sigma_\alpha$| 0.3345                    | 0.2341                   | 0.3132| $1/Gy$ |
| $\sigma_\beta$| 0.0849                     | 0.0490                   | 0.0346| $1/Gy^2$ |

Table 2: Normal tissue parameters

| Parameters   | Spinal Cord | Brain Stem | Skin | Unit |
|--------------|-------------|------------|------|------|
| $\mu_{(\beta/\alpha)}$| 0.48        | 0.39       | 0.12 | $1/Gy$ |
| $\sigma_{(\beta/\alpha)}$| 0.09        | 0.05       | 0.01 | $1/Gy$ |
| $([\beta/\alpha - l, \beta/\alpha + l])$| (0.30,0.67) | (0.30,0.48) | (0.09,0.14) | $1/Gy$ |
| $\mu_8$      | 58.52%      | 74.92%     | 25.29%|      |
| $\sigma_8$   |             |            |      |      |
| $(a, b)$     | (53.71%,63.33%) | (68.94%,80.91%) | (23.83%,26.75%) |      |
| $BED_{max}$  | 63.98       | 83.10      | 18.78|      |

Table 3: Optimal solution of model (6.20) and (3.16)

| Without tumor proliferation | With tumor proliferation |
|-----------------------------|--------------------------|
| $X^*$ | $Y^*$ | $\frac{Y^*}{X^*}$ | $z^*$ | $X^*$ | $Y^*$ | $W^*$ | $N_{optimal}$ | $z^*$ |
| $T_k = 0$ days | 70.01 | 139.98 | 35.02 | 24.76 | 70.00 | 140.00 | 0.0467 | 35 | 19.97 |
| $T_k = 21$ days | 70.01 | 139.98 | 35.02 | 18.56 | 70.00 | 139.99 | 0.0000 | 38 | 19.39 |
| $T_k = 28$ days | 70.01 | 139.98 | 35.02 | 18.56 | 70.01 | 139.98 | 0.0000 | 44 | 22.04 |

Table 4: Optimal solution of model (6.21) and (3.16)

| Without tumor proliferation | With tumor proliferation |
|-----------------------------|--------------------------|
| $X^*$ | $Y^*$ | $\frac{Y^*}{X^*}$ | $z^*$ | $X^*$ | $Y^*$ | $W^*$ | $N_{optimal}$ | $z^*$ |
| $T_k = 0$ days | 72.50 | 49.67 | 105.83 | 21.23 | 72.37 | 49.88 | 0.1410 | 105 | 17.09 |
| $T_k = 21$ days | 72.50 | 49.67 | 105.83 | 16.54 | 72.37 | 49.88 | 0.0780 | 105 | 14.96 |
| $T_k = 28$ days | 72.50 | 49.67 | 105.83 | 21.78 | 72.37 | 49.88 | 0.0570 | 105 | 18.77 |
| Without tumor proliferation | With tumor proliferation |
|-----------------------------|--------------------------|
| $X^*$ | $Y^*$ | $\frac{z^*}{z}$ | $\frac{z^*}{z}$ |
| $T_k = 0$ days | 68.00 | 68.61 | 67.40 | 20.93 |
| $T_k = 21$ days | 68.00 | 68.61 | 67.40 | 16.13 |
| $T_k = 28$ days | 68.00 | 68.61 | 67.40 | 20.73 |

Table 5: Optimal solution of model (6.22) and (3.16)

| Without tumor proliferation | With tumor proliferation |
|-----------------------------|--------------------------|
| $X^*$ | $Y^*$ | $\frac{z^*}{z}$ | $X^*$ | $Y^*$ | $W^*$ | $N_{optimal}$ | $z^*$ |
| $T_k = 0$ days | 68.83 | 130.01 | 36.44 | 35.96 | 68.83 | 130.01 | 0.0490 | 37 |
| $T_k = 21$ days | 70.52 | 123.32 | 40.33 | 25.03 | 68.83 | 130.01 | 0.0000 | 37 - 47 |
| $T_k = 28$ days | 70.52 | 123.32 | 40.33 | 29.58 | 68.83 | 130.01 | 0.0000 | 37 - 62 |

Table 6: Optimal solution of model (3.10) and (3.17); $p_z = p_i = 50\%$

| Without tumor proliferation | With tumor proliferation |
|-----------------------------|--------------------------|
| $X^*$ | $Y^*$ | $\frac{z^*}{z}$ | $X^*$ | $Y^*$ | $W^*$ | $N_{optimal}$ | $z^*$ |
| $T_k = 0$ days | 71.05 | 103.66 | 48.7 | 29.45 | 68.51 | 111.76 | 0.0540 | 42 |
| $T_k = 21$ days | 71.05 | 103.66 | 48.7 | 20.63 | 68.40 | 112.11 | 0.0000 | 42 - 47 |
| $T_k = 28$ days | 71.05 | 103.66 | 48.7 | 24.44 | 68.51 | 111.76 | 0.0000 | 42 - 62 |

Table 7: Optimal solution of model (3.10) and (3.17); $p_z = p_i = 60\%$

| Without tumor proliferation | With tumor proliferation |
|-----------------------------|--------------------------|
| $X^*$ | $Y^*$ | $\frac{z^*}{z}$ | $X^*$ | $Y^*$ | $W^*$ | $N_{optimal}$ | $z^*$ |
| $T_k = 0$ days | 68.11 | 97.48 | 47.59 | 23.42 | 68.11 | 97.48 | 0.0660 | 48 |
| $T_k = 21$ days | 71.46 | 88.24 | 57.87 | 16.45 | 68.11 | 97.48 | 0.0030 | 48 |
| $T_k = 28$ days | 71.46 | 88.24 | 57.87 | 19.39 | 68.11 | 97.48 | 0.0000 | 48 - 62 |

Table 8: Optimal solution of model (3.10) and (3.17); $p_z = p_i = 70\%$

| Without tumor proliferation | With tumor proliferation |
|-----------------------------|--------------------------|
| $X^*$ | $Y^*$ | $\frac{z^*}{z}$ | $X^*$ | $Y^*$ | $W^*$ | $N_{optimal}$ | $z^*$ |
| $T_k = 0$ days | 67.83 | 84.43 | 54.49 | 17.53 | 67.83 | 84.43 | 0.0730 | 55 |
| $T_k = 21$ days | 71.82 | 74.96 | 68.81 | 12.23 | 67.83 | 84.43 | 0.0100 | 55 |
| $T_k = 28$ days | 71.82 | 74.96 | 68.81 | 14.15 | 67.83 | 84.43 | 0.0000 | 55 - 62 |

Table 9: Optimal solution of model (3.10) and (3.17); $p_z = p_i = 80\%$

| Without tumor proliferation | With tumor proliferation |
|-----------------------------|--------------------------|
| $X^*$ | $Y^*$ | $\frac{z^*}{z}$ | $X^*$ | $Y^*$ | $W^*$ | $N_{optimal}$ | $z^*$ |
| $T_k = 0$ days | 70.01 | 139.99 | 35.01 | 24.76 | 70.01 | 139.99 | 0.0480 | 36 |
| $T_k = 21$ days | 70.01 | 139.99 | 35.01 | 18.56 | 70.01 | 139.99 | 0.0000 | 36 - 47 |
| $T_k = 28$ days | 70.01 | 139.99 | 35.01 | 22.30 | 70.01 | 139.99 | 0.0000 | 36 - 62 |

Table 10: Optimal solution of model (6.23) and (3.16); $p_z = p_i = 50\%$
| Without tumor proliferation | With tumor proliferation |
|-----------------------------|-------------------------|
| $X^*$ $Y^*$ $\frac{X^*}{Y^*}$ $z^*$ | $X^*$ $Y^*$ $W^*$ $N_{optimal}$ $z^*$ |
| $T_k = 0$ days | 69.72 120.38 40.38 23.78 | 69.72 120.38 0.0527 41 19.26 |
| $T_k = 21$ days | 69.72 120.38 40.38 17.95 | 69.72 120.38 0.0000 41 – 47 18.37 |
| $T_k = 28$ days | 69.72 120.38 40.38 21.94 | 69.72 120.38 0.0000 41 – 62 21.20 |

Table 11: Optimal solution of model (6.23) and (3.16); $p_z = p_i = 60\%$

| Without tumor proliferation | With tumor proliferation |
|-----------------------------|-------------------------|
| $X^*$ $Y^*$ $\frac{X^*}{Y^*}$ $z^*$ | $X^*$ $Y^*$ $W^*$ $N_{optimal}$ $z^*$ |
| $T_k = 0$ days | 69.33 104.05 46.20 22.92 | 69.33 104.05 0.0647 47 18.56 |
| $T_k = 21$ days | 69.33 104.05 46.20 17.41 | 69.33 104.05 0.0017 47 17.43 |
| $T_k = 28$ days | 69.33 104.05 46.20 21.61 | 69.33 104.05 0.0000 47 – 62 20.42 |

Table 12: Optimal solution of model (6.23) and (3.16); $p_z = p_i = 70\%$

| Without tumor proliferation | With tumor proliferation |
|-----------------------------|-------------------------|
| $X^*$ $Y^*$ $\frac{X^*}{Y^*}$ $z^*$ | $X^*$ $Y^*$ $W^*$ $N_{optimal}$ $z^*$ |
| $T_k = 0$ days | 68.93 90.29 52.62 22.17 | 68.93 90.29 0.0707 53 17.95 |
| $T_k = 21$ days | 68.93 90.29 52.62 16.94 | 68.93 90.29 0.0077 53 16.61 |
| $T_k = 28$ days | 68.93 90.29 52.62 21.30 | 68.93 90.29 0.0000 53 – 62 19.74 |

Table 13: Optimal solution of model (6.23) and (3.16); $p_z = p_i = 80\%$
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