Optimizing chemoradiotherapy to target multi-site metastatic disease and tumor growth

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Abstract

The majority of cancer-related fatalities are due to metastatic disease [17]. In chemoradiotherapy, chemotherapeutic agents are administered along with radiation to increase damage to the primary tumor and control systemic disease such as metastasis. This work introduces a mathematical model to obtain optimal drug and radiation protocols in a chemoradiotherapy scheduling problem with the objective of minimizing metastatic cancer cell populations at multiple potential sites while maintaining a minimum level of damage to the primary tumor site. We derive closed-form expressions for an optimal chemotherapy fractionation regimen. A dynamic programming framework is used to determine the optimal radiotherapy fractionation regimen. Results show that chemotherapeutic agents do not change the optimal radiation fractionation regimens, and vice-versa. Interestingly, we observe that regardless of radio-sensitivity parameters, hypo-fractionated schedules are optimal solutions for the radiotherapy fractionation problem. Furthermore, it is optimal to immediately start radiotherapy. However, for chemotherapy, we find that the structure of the optimal schedule depends on model parameters such as chemotherapy-induced cell-kill at primary and metastatic sites, as well as the ability of primary tumor cells to initiate successful metastasis at different body sites. We quantify the trade-off between the new and traditional objectives of minimizing the metastatic population size and maximizing the tumor control probability, respectively, for a cervical cancer case. The trade-off information indicates the potential for significant reduction in the metastatic population with minimal loss in primary tumor control.

Keywords: Chemoradiotherapy, Multi-site Metastasis, Dynamic Programming, Optimal Fractionation.

1 Introduction

Metastasis occurs when cancer cells spread from the location of a primary tumor to anatomically distant locations. The process of cancer metastasis consists of the following steps: tumor cells detach from the primary tumor site, invade a blood or lymphatic vessel, transit in the bloodstream, and extravasate from the blood vessels to distant sites where they proliferate to form new colonies. It is thought that cancer cells evolve a special set of traits that improve their ability to carry out this process [9]. Single or multi-site metastasis is a common occurrence in cancer patients. For instance, bone metastasis occurs in up to 70% of patients with advanced prostate or breast cancer [35], or 20% of patients with carcinoma of the uterine cervix develop single (32%) or multi-site (68%) metastasis at distant locations such as lymph nodes, lung, bone, or abdomen [8]. The development
of metastases significantly lessens the chances of successful therapy and represents a major cause of mortality in cancer patients. For instance, only 20% of patients with breast cancer [35] and less than 1% of patients with carcinoma of the uterine cervix [3] are still alive five years after the discovery of metastasis.

Many researchers have used mathematical modeling and various optimization techniques to find clinically relevant optimal radiation delivery schedules. The mathematical building block for the majority of radiotherapy response modeling is the linear-quadratic (LQ) model [19]. This model states that following exposure to $d$ Gy of radiation, the surviving fraction of tumor cells is given by $e^{-\alpha d - \beta d^2}$, where $\alpha$ and $\beta$ are cell-specific parameters. In a conventional radiotherapy fractionation problem, the goal is to maximize the biological effect of radiation on the tumor while inflicting the least amount of healthy-tissue damage, which are evaluated using tumor control probability (TCP) and normal-tissue complication probability (NTCP), respectively [44]. Some important questions concern the best total treatment size, the best way to divide the total dose into fractional doses, and the optimal inter-fraction interval times. An important result emerging from recent work is that for low values of tumor $[\alpha/\beta]$, a hypo-fractionated schedule, where large fraction sizes are delivered over a small number of treatment days, is optimal. However for large values of $[\alpha/\beta]$, a hyper-fractionated schedule, where small fraction sizes are delivered over a large number of treatment days, is optimal [29, 4, 2, 5].

For many inoperable tumors, radiotherapy alone is not enough to successfully control the primary tumor. For these tumors, chemoradiotherapy is the standard of care, in which one or several chemotherapeutic agents are administered along with radiation. There are at least two basic mechanisms by which the combination of the two modalities may result in a therapeutic gain. First, chemotherapy may be effective against (occult) systemic disease, such as metastasis. This mechanism is called spatial cooperation. Second, the two modalities act independently (so-called additivity) or dependently (so-called radio-sensitization) to enhance tumor cell-kill at the primary site [40]. Recently, Salari et al. [37] studied changes in optimal radiation fractionation regimens that result from adding chemotherapeutic agents to radiotherapy when maximizing TCP. More specifically, they incorporated additivity and radio-sensitization mechanisms into the radiation fractionation decision to identify corresponding changes in optimal radiation fractionation schemes. Their results suggest that chemotherapeutic agents with only an additive effect do not impact optimal radiation fractionation schemes; however, radio-sensitizers may change the optimal fractionation schemes and in particular may give rise to optimal nonstationary schemes.

In our very recent work [3], we introduced a novel biologically driven objective function that takes into account metastatic risk instead of maximizing TCP. We observed that when designing optimal radiotherapy treatments with the goal of minimizing metastatic production, hypo-fractionation is preferable for many parameter choices, and standard fractionation is only preferable when the $[\alpha/\beta]$ value of the tumor is sufficiently large and the long-term metastasis risk (several years after therapy) is considered.

Our prior results [3] demonstrated a proof of concept that radiation scheduling decisions have the potential to significantly impact metastatic risk. However, that work left out several important features in the modeling of advanced carcinomas. First, we only considered single-site metastatic disease. However, it is well known that some tumors, e.g., lung cancers, metastasize quickly to multiple sites, whereas others, such as breast and prostate carcinomas, often take years to develop metastatic colonies and then only in a relatively limited number of sites [22]. Importantly, metastatic colonies at different anatomical sites may respond differently to anti-cancer drugs or have drastically different growth kinetics. Another shortcoming of the previous work [3] was that
the mathematical model ignored the growth of tumors at metastatic sites. In particular, [3] only looked at metastatic risk, which was measured by the total number of successful metastatic cells produced, and thus treated all successful metastatic cells equally, regardless of what point in time they initiated metastatic lesions. However, a more accurate model of the clinical situation allows for the metastatic cells to reproduce in their new location [9]. Incorporating this important phenomenon now means that metastatic sites that are initiated earlier are much more dangerous than metastatic lesions initiated late in the course of the disease. Finally, our prior work [3] focused solely on radiotherapy. However, when studying the evolution of metastatic disease under treatment, the role of chemotherapy is clearly paramount, given its systemic nature. This has been born out in clinical trials where it has been observed that concurrent chemoradiotherapy reduces the risk of distant metastasis compared to radiotherapy alone (e.g., see [43, 27]). In the current work, we address these shortcomings by developing a mathematical model that allows for multi-site metastatic disease with possible growth at each location, and include systemic chemotherapy as a possible treatment.

In this work, we consider the problem of finding optimal radiotherapy dosing and a chemotherapy regimen that minimizes the total expected number of metastatic tumor cells at multiple body sites while keeping normal-tissue damage below clinically acceptable levels. To study the trade-off between the conventional objective, maximizing TCP, and our novel approach of minimizing the metastatic population, we consider an additional constraint requiring the tumor damage associated with the optimal regimen to exceed a user-specified percentage of that of conventional regimens. To the best of our knowledge, the present study is the first to address optimal chemoradiotherapy fractionation in the context of targeting multi-site metastatic disease and primary tumor control. We examine the mathematical properties of the optimal fractionation scheme in the context of cervical tumors.

The remainder of this paper is organized as follows. In Section 2, we discuss a model for multi-site metastasis production and how it can be used to develop a function that reflects metastatic production at different body locations. In Section 3, we formulate an optimization model for the chemoradiotherapy fractionation problem, derive some mathematical results regarding the properties of optimal regimens, and develop a dynamic programming solution approach. In Section 4, we present numerical results in the situation of cervical cancer. Finally, we summarize and conclude the paper in Section 5.

2 Mathematical model of treatment and metastasis development

Consider a treatment regimen in which a radiation dose of $d_i$ and a drug concentration of $c_i$ are administered at treatment fraction $i = 1, \ldots, N$. Our objective is to minimize total metastatic cell population produced by the primary tumor at $n$ different sites within a patient’s body at time $T$, where the time horizon $T$ consists of treatment days and a potentially long period of no treatment, at the end of which total metastatic population is evaluated. We consider a sufficiently large $N$ to include all three possible chemoradiotherapy regimens, which are neoadjuvant, concurrent, or adjuvant, depending on whether, in the optimal solution, the chemotherapeutic agents are administered before, during, or after the course of radiotherapy, respectively.

We start by assuming that the total population of primary tumor cells at time $t$ is large enough and that we can approximate it by a deterministic function $X_t$. To formulate the total population of primary tumor cells at time $t$, we adopt the common approach used in most studies, i.e., survival curves of irradiated cell lines follow a linear-quadratic fit on a logarithmic scale (see [19] for a
discussion of the linear-quadratic model), and survival curves of cell lines that are exposed to
to chemotherapeutic agents have an exponential form in terms of the drug’s concentration \[39\]. Taking
both models into account, we can compute the number of tumor cells at time \(t \in [0, T]\) by (2.1):

\[
X_t = \begin{cases} 
X_0 e^{-\sum_{i=1}^{t} (\alpha d_i + \beta d_i^2 + \theta c_i) + \frac{\ln 2}{\tau_d} (t - T_k)^+}, & t \leq N \\
X_0 e^{-\sum_{i=1}^{N} (\alpha d_i + \beta d_i^2 + \theta c_i) + \frac{\ln 2}{\tau_d} (t - T_k)^+}, & t > N
\end{cases}
\]

(2.1)

where \(X_0\) is the initial tumor population, \(\alpha\) and \(\beta\) are tumor radio-sensitivity parameters, \(\theta\) is
the tissue-specific parameter associated with chemotherapy additive effect, \(T_k\) is the tumor kick-off
time, and \(\tau_d\) shows the tumor doubling time in units of days (see [33] and [11] for sources).

The choice of tumor growth function is strongly driven by the size of cancer being modeled. Exponential
growth is a good model for small-size tumors. However, limitations of the availability
of nutrients, oxygen, and space imply that exponential growth is not appropriate for the long-
term growth of solid tumors, so we must consider alternative formulations such as Gompertz or
logistic models. The current view of tumor-growth kinetics during therapy is based on the general
assumption that tumor cells grow exponentially due to the small population [19]. Here, we also
assume that the tumor is small enough and that it grows exponentially with a time lag during
the course of the treatment. In particular, we are interested in the long-term metastatic risk associated
with a chemoradiotherapy regimen evaluated at any time point between the conclusion of therapy
and the local recurrence, i.e., \(T < \min\{t > 0|X_t = X_0\}\). During this time period, the primary
tumor has not yet reached a clinically detectable size again and thus is sufficiently small in order
to use the exponential function in (2.1) to fit the growth of the tumor cell population.

The notion of biologically equivalent dose (BED), originally motivated by the LQ model, is used
in clinical practice to quantify the biological damage caused by a radiation fractionation scheme in
a given structure. More specifically, the BED for a fractionation regimen with \(n\) treatment fractions
in which radiation dose \(d_i\) is administered in fraction \(i (i = 1, \ldots, n)\) is given by

\[
BED = \sum_{i=1}^{n} d_i \left(1 + \frac{d_i}{[\alpha/\beta]}\right)
\]

(2.2)

where \([\alpha/\beta]\) is a structure-specific radio-sensitivity parameter. Several clinical studies have asso-
ciated different BED values, independent of the number of fractions and the radiation dose per
fraction \(d_i\) \((i = 1, \ldots, n)\), to TCP and NTCP values calculated, based on clinical data [13].

Metastasis is the process by which the primary tumor cells detach from the tumor, invade
the circulatory or lymph system, and colonize other parts of the body. To model the metastatic
formation and growth process, we assume that a fraction of the primary tumor cells are capable of
producing successful metastatic cells and that these cells do so at rate \(\nu\). This fraction is dictated
by the fractal dimension of the blood vessels infiltrating the tumor, which we denote by \(\xi \in [0, 1]\),
(see [23]). For example, if we assume that the tumor is roughly spherical and all cells on the
surface are capable of metastasis, then we would take \(\xi = 2/3\); however, if we assume only the cells
along the boundary of a one-dimensional blood vessel are capable of metastasis, then we would set
\(\xi = 1/3\) (see [21] for a more detailed discussion and estimation of this parameter). To summarize,
we assume that metastatic cells are produced according to a non-homogeneous Poisson process with
intensity function at time \(t\) given by \(\nu X_t^\xi\). Furthermore, we assume that each successful metastatic
cell, independent of other metastatic cells, initiates a metastatic colony at site \(i (i = 1, \ldots, n)\) with
probability \(p_i\) \((\sum_{i=1}^{n} p_i = 1)\) and that the probability of secondary metastasis, which is the formation
of new metastasis originating in other metastatic colonies, is negligible. Therefore, thinning our
original Poisson process tells us that metastasis formation at site \( i \) follows a non-homogeneous Poisson process with rate \( b_i(t) = p_i \nu X_t^i \).

We model the growth of each metastatic lesion using a non-homogeneous branching process with a rate dependent on time \( t \) and the metastasis site. More specifically, the birth and death rates at site \( i \) \((i = 1, \ldots, n)\) are denoted by \( u_i(t) \) and \( v_i(t) \), respectively. This is similar to the modeling approach taken in [18], which used multi-type branching processes to study metastasis and then applied the work to study pancreatic cancer data, thus fitting the model to metastasis data from patients. We consider the growth rate of metastatic cells \( \mu_i(t) = u_i(t) - v_i(t) \) in the absence of chemotherapeutic agents as a positive value that is constant with respect to time \( \mu_i(t) = \mu_i \).

During chemotherapy, we assume that the growth rate of metastatic cells decreases linearly as a function of the magnitude of the last dose of chemotherapy drug administrated [30]. Written mathematically we have

\[
\mu_i(t) = \begin{cases} 
\mu_i - \omega_i c_{\lfloor t \rfloor}, & t \leq N \\
\mu_i, & t \in (N, T]
\end{cases}, \quad i = 1, \ldots, n
\]  

(2.3)

where \( \omega_i \) is a positive constant, depending on heterogeneity in drug concentrations among different sites and sensitivity of tumor cells to the chemotherapy at \( i \)th site.

If we have a total evaluation horizon of time \( T \), then the expected number of total metastatic cells at site \( i \) is given by the convolution (see [12])

\[
R_i(T) = \int_0^T b_i(t) \exp \left( \int_t^{T-t} \mu_i(\eta + t)d\eta \right) dt.
\]

Our goal is to determine an optimal chemo- and radiotherapy fractionation scheme that minimizes the total expected number of metastatic tumor cells at time \( T \) at \( n \) body sites, i.e.,

\[
R(T) = \sum_{i=1}^n R_i(T) = \nu \sum_{i=1}^n p_i \int_0^T X_t^i \exp \left( \int_t^{T-t} \mu_i(\eta + t)d\eta \right) dt.
\]  

(2.4)

Notice that in order to minimize \( R(T) \), it is sufficient to optimize \( R(T)/\nu \), and there is no need to know parameter \( \nu \), which is difficult to estimate.

### 3 Optimization model and solution approach

Our goal is to determine the optimal radiation dose vector \( \vec{d}^* = \{d_1^*, \ldots, d_N^*\} \) and optimal chemotherapy drug concentration vector \( \vec{c}^* = \{c_1^*, \ldots, c_N^*\} \) that minimize the total expected number of metastatic cancer cells at time \( T \) at \( n \) different anatomical sites. We do not consider the metastatic dissemination prior to the start of the treatment course. One reason for this is that it is difficult to estimate the total life history of a tumor prior to diagnosis. In addition our model is primarily intended for locally advanced cancer cases, whereas metastasis formation typically occurs in later stages of the disease once the tumor has reached a significantly large size [20].

We start by computing

\[
\int_0^{T-t} \mu_i(\eta + t)d\eta = \int_t^T \mu_i(s)ds = \begin{cases} 
\mu_i(T - t) - \omega_i \left( c_{\lfloor t \rfloor}(\lfloor t \rfloor - t) + \sum_{j=\lfloor t \rfloor}^N c_j \right), & t < N + 1 \\
\mu_i(T - t), & t \in [N + 1, T]
\end{cases}
\]
with notation \( c_0 = 0 \) and \( \sum_{j=[t]}^N c_j = 0 \) for \( t > N \). For computational ease, we assume an equal metastasis production for \( t \in [\lfloor t \rfloor, \lceil t \rceil) \), which is evaluated at time \([t]\). Specifically we replace \( X_t \) with \( X_t^- \) and \( \mu_i(T-t)-\omega_i\left( c_{[t]}([t]-t)+\sum_{j=[t]}^N c_j \right) \) with \( \mu_i(T-t)-\omega_i\sum_{j=[t]}^N c_j \) for \( 0 \leq t < N+1 \), where \( X_t^- \) is the number of cells immediately before the delivery of doses \( d_t \) and \( c_t \) (note that \( X_0^- = X_0 \)). In addition, we use a similar approximation approach as that taken in [3], which uses a summation rather than an integral during therapy. To summarize, we make the following approximation:

\[
R(T)/\nu \approx \sum_{i=1}^n p_i \left( \sum_{t=0}^{N+1} (X_t^-)^t \exp \left( \mu_i(T-t) - \omega_i \sum_{j=t}^T c_j \right) + \int_{N+1}^T X_t e^{\mu_i(T-t)} dt \right) \quad (3.5)
\]

Substituting \( X_t \) from (2.1) into (3.5) yields

\[
R(T)/\nu \approx f(\vec{d}, \vec{c}) + g \left( \sum_{t=1}^N d_t, \sum_{t=1}^N d_t^2, \sum_{t=1}^N c_t \right)
\]

where

\[
f(\vec{d}, \vec{c}) = X_0^\xi \sum_{i=1}^n p_i e^{\mu_i T} \sum_{t=0}^{N+1} e^{-\xi \left( \sum_{j=1}^{t-1} (\alpha d_j + \beta d_j^2 + \theta c_j) - \frac{\ln 2}{\tau_d} (t-T_k) \right)} - \mu_i t - \omega_i \sum_{j=t}^T c_j \quad (3.6)
\]

and

\[
g \left( \sum_{t=1}^N d_t, \sum_{t=1}^N d_t^2, \sum_{t=1}^N c_t \right) = X_0^\xi e^{-\xi \left( \sum_{i=1}^n (\alpha d_i + \beta d_i^2 + \theta c_i) + \frac{\ln 2}{\tau_d} T_k \right)} \sum_{i=1}^n p_i e^{\mu_i T} e^{-\left( \mu_i - \xi \frac{\ln 2}{\tau_d} \right)(N+1)} - e^{-\left( \mu_i - \xi \frac{\ln 2}{\tau_d} \right)T_k} \mu_i - \xi \frac{\ln 2}{\tau_d} \quad (3.7)
\]

Note that in (3.6), the summation inside the exponential for \( t = 0, 1 \) is zero, i.e.,

\[
\sum_{j=1}^{t-1} (\alpha d_j + \beta d_j^2 + \theta c_j) = 0
\]

for \( t = 0, 1 \), and we assume \( T_k < N \), which is typically the case for all disease sites. We now consider the fractionation problem in terms of decision variables of radiation dose \( d_t \) and drug concentration \( c_t \) at fraction \( i = 1, \ldots, N \), which lead to a minimal metastasis population size while maintaining acceptable levels of normal tissues damage.

\[
\text{minimize} \quad f(\vec{d}, \vec{c}) + g \left( \sum_{t=1}^N d_t, \sum_{t=1}^N d_t^2, \sum_{t=1}^N c_t \right) \quad (3.8)
\]

s.t.

\[
\sum_{t=1}^N \gamma_j d_t \left( 1 + \frac{\gamma_j d_t}{[\alpha/\beta]_j} \right) \leq \text{BED}_j, \quad j = 1, \ldots, M \quad (3.9)
\]

\[
\sum_{t=1}^N d_t \left( 1 + \frac{d_t}{[\alpha/\beta]} \right) \geq f_{\text{BED}_{\text{std}}} \quad (3.10)
\]

\[
\sum_{t=1}^N c_t \leq C_{\max} \quad (3.11)
\]
The objective function evaluates the cumulative metastasis production divided by \( \nu \) at time \( T \) at \( n \) different body organs over all treatment fractions. Constraints (3.9) and (3.11) are toxicity constraints associated with radiotherapy and chemotherapy, respectively. More specifically, we use the BED model in (2.2) to constrain the radiation side effects in the surrounding healthy structures around the tumor \[19\]. In doing so, we assume that there are \( M \) healthy tissues in the vicinity of the tumor, and a dose \( d \) results in a homogeneous dose \( \gamma_jd \) in the \( j \)th normal tissue, where \( \gamma_j \) is the sparing factor. Parameter \([\alpha/\beta]_j \) represents the BED parameter, and \( \text{BED}_j \) specifies the maximum BED allowed in the \( j \)th healthy tissue. We limit the maximum cumulative chemotherapy dose by \( C_{\text{max}} \), which is the total amount of a drug that can be delivered to a patient over the period of treatment, measured in milligrams/meter squared \[28\]. Inequalities (3.12) and (3.13) limit the maximum allowable daily radiation dose and chemotherapy drug concentration, respectively, where \( d_{\text{max}} \) and \( c_{\text{max}} \) show the maximum tolerable dose, measured in Gy and milligrams/meter squared, respectively, that can be delivered in a single day \[28\].

Finally, constraint (3.10) guarantees that tumor BED imposed by the optimal schedule is greater than or equal to \( f \times 100 \) percent of the tumor BED realized by the standard schedule. Note that TCP is an increasing function of tumor BED for a homogeneous radiation dose, and thus TCP and tumor BED maximization are equivalent. The parameter \( 0 \leq f \leq 1 \) is an input to our model and characterizes the trade-off between maximizing TCP and minimizing metastatic cells population (see, e.g., \[10\] for a review of optimization methods to characterize the trade-off between the two objectives). If we assume that the primary cause of cancer-related death in a specific tumor (e.g., pancreatic or cervical cancer) is metastatic dissemination, then we choose a low value of \( f \), e.g., 70%. However, if the primary tumor may cause patient death (e.g., lung cancer), then a high value of \( f \) will be taken, e.g., 98%.

Formulation (3.8)–(3.13) is a nonconvex quadratically constrained program. Such problems are computationally difficult to solve in general. In the rest of this section, we first derive some mathematical results regarding the structure of the optimal solution of (3.8)–(3.13) and then develop a dynamic programming algorithm to solve the problem.

We start by discussing an important property of the optimal chemotherapy dose vector.

\[ d_t \leq d_{\text{max}}, \quad t = 1, \ldots, N \quad (3.12) \]

\[ c_t \leq c_{\text{max}}, \quad t = 1, \ldots, N \quad (3.13) \]

\[ \sum_{t=1}^{N} c_t^* = C_{\text{max}}. \]

Next, we use the new form of function \( f(d, \bar{c}) \) stated in (3.14) and show an interesting property of the radiation and chemotherapy ordering.
Lemma 2. Let the optimal dose and drug vector of problem (3.8)–(3.13) be \( \vec{d}^* = \{d_1^*, \ldots, d_N^*\} \) and \( \vec{c}^* = \{c_1^*, \ldots, c_N^*\} \), respectively; then, in optimality, we have

\[
d_1^* \geq d_2^* \geq \cdots \geq d_N^*
\]

and

\[
\begin{align*}
&c_1^* \geq c_2^* \geq \cdots \geq c_N^*, \quad \text{if } \theta \xi \geq \max_{i=1,\ldots,\omega_i} c_{1,i}^* - \gamma_{1,i}^* \\
&c_1^* \leq c_2^* \leq \cdots \leq c_N^*, \quad \text{if } \theta \xi < \min_{i=1,\ldots,\omega_i} c_{1,i}^*.
\end{align*}
\]

The proof is in Appendix B. In Lemma 2, we specify the general structure of the optimal chemoradiotherapy regimen. In the following result, we find the optimal chemotherapy drug vector for two special cases.

Theorem 1. Let the optimal drug vector of problem (3.8)–(3.13) be \( \vec{c}^* = \{c_1^*, \ldots, c_N^*\} \); then, \( \vec{c}^* \) takes one of the following two forms, if we have \( \theta \xi \geq \max_{i=1,\ldots,\omega_i} c_{1,i}^* \) or \( \theta \xi < \min_{i=1,\ldots,\omega_i} c_{1,i}^* \):

1. \( \theta \xi \geq \max_{i=1,\ldots,\omega_i} c_{1,i}^* \): Optimal schedule is given by \( c_i^* = c_{\max} \) for \( i = 1, \ldots, k \), \( c_{k+1}^* = C_{\max} - \gamma_{k+1}^* \), and \( c_j^* = 0 \) for \( i = k + 2, \ldots, N \), where \( k = \left\lfloor C_{\max}/c_{\max} \right\rfloor \).

2. \( \theta \xi < \min_{i=1,\ldots,\omega_i} c_{1,i}^* \): Optimal schedule is given by \( c_i^* = c_{\max} \) for \( i = N - k + 1, \ldots, N \), \( c_{N-k}^* = C_{\max} - \gamma_{N-k}^* \), and \( c_j^* = 0 \) for \( i = 1, \ldots, N - k - 1 \), where \( k = \left\lfloor C_{\max}/c_{\max} \right\rfloor \).

The proof is in Appendix C. The following three important observations are made for optimal treatment regimes associated with chemoradiotherapy based on the results of Lemma 2 and Theorem 1. Note that in the following, we use the fact that in the traditional optimal fractionation problem where one is interested in minimizing local tumor population (or maximizing TCP) at the end of treatment, the ordering of \( d_i^* \) and \( c_i^* \) does not affect the TCP (see [37] and [2]).

Remark 1. The non-increasing order of the optimal radiation dose vector obtained in Lemma 3 suggests that it is always optimal to immediately start the radiotherapy treatment. Furthermore, it is optimal to immediately initiate chemotherapy if \( \theta \xi \geq \max_{i=1,\ldots,\omega_i} c_{1,i}^* \), or to postpone chemotherapy until the end of the treatment if \( \theta \xi < \min_{i=1,\ldots,\omega_i} c_{1,i}^* \), suggesting a concurrent and adjuvant chemoradiotherapy regimen, respectively. Hence, Lemma 2 tells us that it is never optimal to use neoadjuvant chemoradiotherapy regimes, which is consistent with clinical observations [16] (see conclusion for more discussion).

Remark 2. The resulting radiotherapy fractionation schedules for minimizing total metastatic cancer cells suggest a non-increasing radiation fractionated structure, which is due to the structure of the model. Metastatic cells initiated at distant locations are not killed by radiotherapy doses. Thus, in order to minimize the metastatic cell population using radiation, it is necessary to quickly reduce the primary tumor cell population since this is the source of metastatic lesions. Also, note that given the growth of metastatic lesions, we are particularly concerned with metastatic lesions created early in the course of therapy.

Remark 3. The resulting chemotherapy fractionation schedules for minimizing total metastatic cancer cells suggest a hypo-fractionated structure concentrated at the beginning or the end of the schedule. This is due to the fact that if the combined effect (\( \theta \xi \)) of chemotherapy-induced cell-kill (\( \theta \)) and the fraction of cells capable of metastasis in the primary tumor (\( \xi \)) is larger than the chemotherapy-induced metastatic cell-kill at all distant locations (\( \max_{i=1,\ldots,\omega_i} \{c_{1,i}^*\} \)), then we consider the primary tumor cell population as dangerous, due to the inability of chemotherapy to control...
the metastatic cell populations. Hence, it is preferable to target the primary tumor and reduce its size as quickly as possible. However, if the effect of the chemotherapeutic agents on all distant metastatic sites \( \min_{i=1,...,n} \{ \omega_i \} \) is larger than the product of chemotherapy-induced cell-kill \( (\theta) \) and the fraction of cells that are capable of metastasis in the primary tumor \( (\xi) \), then we consider that the chemotherapeutic agents are more effective in controlling metastatic disease than the primary tumor control. Hence, we prefer to administer chemotherapy at the end of treatment when we can target the accumulated metastatic cells.

Finally, we establish a result that describes the closed-form solution of the optimal radiotherapy schedule for a special case where \( \beta = 0 \) and \( [\alpha/\beta]_j \rightarrow \infty \) \((j = 1, \ldots, M)\), which implies the use of linear log-survival, rather than LQ, and physical dose, rather than BED, to describe tumor cell-kill and normal-tissue toxicity, respectively. This case is motivated by the fact that tissue response to small radiation doses is dominated by the linear term \([36][1]\), which is applicable to our model when \( d_{\max} \) is sufficiently small (around 2 Gy \([31]\)).

**Proposition 1.** If we assume that radiation-induced tumor cell-kill has a linear form, i.e., \( \beta = 0 \) and radiation-induced toxicity in normal tissue \( j \) \((j = 1, \ldots, M)\) is evaluated using the physical dose, i.e., \([\alpha/\beta]_j \rightarrow \infty \), then the optimal radiotherapy schedule is given by \( d^*_i = d_{\max} \) for \( i = 1, \ldots, k \), \( d^*_{k+1} = D_{\max} - k d_{\max} \) and \( d^*_i = 0 \) for \( i = k + 2, \ldots, N \), where \( k = [D_{\max}/d_{\max}] \) and \( D_{\max} = \min_{j=1,...,M} \{ \text{BED}_j/\gamma_j \} \).

In order to explain this result, we first note that the inequality \( \sum_{t=1}^{N} d_t \leq \min_{j=1,...,M} \{ \text{BED}_j/\gamma_j \} \) defines the set of feasible regions associated with the radiation-induced toxicity constraints in normal tissues, and thus we can remove the remaining \( M - 1 \) redundant inequalities from the constraint set. Then, an almost identical argument as used in proof of Theorem 3 for the case of \( \theta \xi \geq \max_{i=1,...,n} \omega_i \) can be implemented to derive the optimal dose vector.

If it is possible to apply Theorem 1, then we immediately know the optimal chemotherapy concentrations. It then remains to find the optimal radiation doses, which can be determined using dynamic programming, similar to our work in \([3]\). The states of the system required to decide the dose \( d_t \) are \( U_t \) and \( V_t \), which \( U_t \) and \( V_t \) are the cumulative dose and cumulative dose squared delivered to the tumor immediately after time \( t \), respectively. We can update states of the system by

\[
U_t = U_{t-1} + d_t, \\
V_t = V_{t-1} + d_t^2.
\]

Using the functions introduced in \([3.7] \) and \([3.14] \), the forward recursion of our dynamic programming algorithm can be written as

\[
J_t(U_t, V_t) = \begin{cases} 
\min_{d_t \geq 0} & J_t-1(U_{t-1}, V_{t-1}) + L(d_t, U_{t-1}, V_{t-1}), & 1 \leq t \leq N \\
\min_{d_t \geq 0} & J_t-1(U_{t-1}, V_{t-1}) + g(U_{t-1} + d_t, V_{t-1} + d_t^2, C_{\max}), & t = N + 1
\end{cases}
\]

where

\[
L(d_t, U_{t-1}, V_{t-1}) = X_0^\xi \sum_{i=1}^n p_i e^{-\xi(\alpha(U_{t-1} + d_t) + \beta(V_{t-1} + d_t^2) + (\theta - \omega_i/\xi) \sum_{i=1}^t c_i - \frac{\ln 2}{\theta}(t - T_h)\xi^2 + \mu_i(T - t) - \omega_i C_{\max})}
\]

with initial conditions \( (U_0, V_0) = (0, 0) \) and \( J_0(0,0) = X_0^\xi \sum_{i=1}^n p_i e^{\mu_i T - \omega_i C_{\max}} \). We set the function \( J_N(U_N, V_N) \) to be \( \infty \) if

\[
\alpha U_N + \beta V_N < f \text{BED}_{\text{std}}
\]
and \( J_t(U_t, V_t) \), \( t = 1, \ldots, N \) to be \( \infty \), if any of the following constraints is violated:

\[
\gamma_j U_t + \frac{\gamma_j^2 V_t}{(\alpha/\beta)_j} > \text{BED}_j, \quad j = 1, \ldots, M.
\]

If it is not possible to apply Theorem 1, then we can still implement a dynamic programming method with an additional state of system, \( S_t \), the cumulative drug concentration delivered to the patient immediately after time \( t \). The states of the system required to decide the radiation dose \( d_t \) and drug concentration \( c_t \) are \( U_t, V_t \), and \( S_t \) (note that in this case, we have \( S_t = S_{t-1} + c_t \)). Now we can write the revised forward recursion equation as

\[
J_t(U_t, V_t, S_t) = \begin{cases} \min_{d_t,c_t \geq 0} & J_{t-1}(U_{t-1}, V_{t-1}, S_{t-1}) + L(d_t, c_t, U_{t-1}, V_{t-1}, S_{t-1}), & 1 \leq t \leq N \\ \min_{d_t,c_t \geq 0} & J_{t-1}(U_{t-1}, V_{t-1}, S_{t-1}) + g(U_{t-1} + d_t, V_{t-1} + d_t^2, C_{\text{max}}), & t = N + 1 \end{cases}
\]

where

\[
L(d_t, c_t, U_{t-1}, V_{t-1}, S_{t-1}) = X_0^n \sum_{i=1}^n p_i e^{-\xi(\alpha(U_{t-1}+d_t)+\beta(V_{t-1}+d_t^2)+\theta-\omega_i/\xi)(S_{t-1}+c_t)-\ln 2(t-T_k)^+} + \mu(T-t-\omega_i C_{\text{max}})
\]

with similar initial conditions as introduced before. The TCP feasibility constraint control inequalities now are defined as \( J_N(U_N, V_N, S_N) \) to be \( \infty \) if

\[
\alpha U_N + \beta V_N < f \text{BED}_{\text{std}}
\]

and the similar inequalities for radiotherapy toxicity constraints with an additional control for chemotherapy cumulative dose, i.e. \( J_t(U_t, V_t, S_t) \), \( t = 1, \ldots, N \), to be \( \infty \) if

\[
S_t > C_{\text{max}}.
\]

In both cases, since there are two or three state variables, we can solve our optimization problem by discretizing the states and using the dynamic programming algorithm.

### 4 Numerical results

In this section, we apply our methods in the optimization of a chemoradiotherapy regimen for locally advanced cervical tumors. We consider the toxicity effects of radiotherapy in three different normal tissues: bladder, small intestine, and rectum \[34\], using the BED model introduced in \[2.2\]. A standard fractionated treatment for cervical cancer is to deliver 45 Gy to the tumor over five weeks (25 working days). The maximum tolerated doses for each normal tissue are computed based on the standard fractionation scheme (1.8 Gy × 25).

Treatment days comprise a course of external beam radiotherapy and chemotherapy administration, followed by a short rest period lasting \( N_r \) days, and low-dose-rate brachytherapy with a dose rate of \( R \) Gy per day delivered within \( N_b \) days, respectively. The treatment sequence is motivated by combined-modality treatment protocols for cervical cancer used in clinical practice that often involve adjuvant brachytherapy. Equation \[2.1\] is adjusted in the presence of brachytherapy as \[4.15\] (see \[33\] for the adjusted formulation in the presence of brachytherapy):

\[
X_t = \begin{cases} X_0 e^{-\sum_{i=1}^n (\alpha d_i + \beta d_i^2 + \theta c_i) + \eta \frac{\mu}{2} (t-T_k)^+}, & t \leq N + N_r \\ X_0 e^{-\sum_{i=1}^n (\alpha d_i + \beta d_i^2 + \theta c_i) - \epsilon_y R(t-N-N_r)(\alpha+2\beta R/\sigma)+\eta \frac{\mu}{2} (t-T_k)^+}, & N + N_r < t \leq N + N_r + N_b \\ X_0 e^{-\sum_{i=1}^n (\alpha d_i + \beta d_i^2 + \theta c_i) - \epsilon_y R N_t(\alpha+2\beta R/\sigma)+\eta \frac{\mu}{2} (t-T_k)^+}, & t > N + N_r + N_b \end{cases}
\]

10
where \( \sigma \) is the monoexponential repair rate of sublethal damage \[23\] and \( g \) represents the effects of the dose gradients around the brachytherapy sources (see \[23\] and \[11\]). We assume low-dose brachytherapy is performed in two days within one week after the completion of pelvic external radiotherapy \[23\]. Note that this assumption does not affect the optimal solution, and our result still applies to different brachytherapy schedules.

The standard radiosensitizer agent used in locally advanced cervical tumors is Cisplatin, given at low daily doses, and the standard chemotherapy agent is Fluorouracil (5-FU), given at high daily doses, \[25\] \[43\]. We assume Cisplatin delivered at low doses augments the effects of radiotherapy by sensitizing tumor cells to radiation \[7\] \[11\], which can be modeled as an increase in the linear term of the LQ model without any significant change in the quadratic term \[14\]. Hence, the LQ parameter \( \alpha \) in \[1.15\] is substituted with \( \alpha + \kappa c_{cis} \), where \( c_{cis} \) shows the average daily dose of Cisplatin. Cisplatin is usually administered intravenously at a dose of 40 mg per square meter of body-surface area per week (mg/m\(^2\)) \[25\], therefore we set \( c_{cis} = 8 \) mg/m\(^2\). Note that Cisplatin is given at low doses; hence, its resulting independent cell-kill is negligible. The agent 5-FU administrated at high doses is considered to have an inherent cytotoxic activity and acts as a systemic therapeutic agent \[35\]. The standard chemotherapy protocol for delivering 5-FU concurrently with radiotherapy consists of administrating a dose of 1,000 mg/m\(^2\) per day for 8 days \[32\]. Hence, we set the maximum daily dose of 5-FU to be \( c_{max} = 1,000 \) mg/m\(^2\) and the total dose to be \( C_{max} = 8,000 \) mg/m\(^2\).

We set \( N \) to be 25 days (five weeks, considering weekends as breaks) since 5-FU is given concurrently with radiotherapy. We employ the calibration method discussed in \[23\] to estimate the value of \( \kappa \) and \( \theta \) associated with the radiosensitizer (Cisplatin) and chemotherapeutic agent (5-FU), respectively, from clinical trial studies. In particular, to estimate the \( \kappa \) and \( \theta \) values, we compare the progression-free survival rates reported in \[25\] (radiotherapy vs radiotherapy+Cisplatin) and \[32\] (radiotherapy vs radiotherapy+Cisplatin+5-FU), respectively, among patients treated with radiotherapy alone and those who were treated with chemoradiotherapy, which are denoted by TCP\(_r\) and TCP\(_{cr}\), respectively. This yields the following estimation for parameter \( \kappa \) and \( \theta \) (see \[23\] for more details):

\[
\kappa = - \frac{\ln(\ln(TCP_{cr})/\ln(TCP_r))}{c_{cis} \times \sum_{i=1}^{N} d_i}, \quad \theta = - \frac{\ln(\ln(TCP_{cr})/\ln(TCP_r)) + \kappa c_{cis} \sum_{i=1}^{N} d_i}{\sum_{i=1}^{N} c_i}.
\]

Note that in the above equations we use different values of \( c_{cis} \), TCP\(_r\), and TCP\(_{cr}\), as reported in \[25\] and \[32\], to estimate \( \kappa \) and \( \theta \), respectively. All of the tumor and normal tissue parameters are summarized in Table \[1\]. Note that to fully explore how the structure of the optimal solution relates to the optimal conventional fractionation regimes in different scenarios, we consider a wide range of values for the parameter \( \alpha/\beta \). There is a significant amount of debate as to whether or not the linear quadratic model applies to large doses \[26\] \[6\]. In view of this, we set \( d_{max} \) to be 5 Gy.

Distribution of the most common sites of cervical cancer metastases is outlined in Table \[2\] (see \[8\]). Metastases often grow at the same rate as the primary tumor \[15\]; hence, it is natural to assume \( \mu_1 = \cdots = \mu_9 = \ln 2 \). Although distant metastases may appear any time after treatment, approximately 88% of multi-organ metastases in cervical cancer occur within three years of the conclusion of treatment \[8\]. Hence, we set parameter \( T \) to three years. Parameter \( \omega_i \) represents the reduction in metastatic cell growth rate at site \( i \) in relation to the chemotherapy dose administrated and has a unit of mg/m\(^2\) per day. There is a lack of reliable clinical data on the rate of chemotherapy-induced cell-kill in metastatic lesions. Therefore, to estimate \( \omega_i \), we compare it to the drug’s cell-kill effect in the primary tumor. More specifically, a chemotherapy dose of \( c_t \) mg/m\(^2\) on day \( t \) reduces the primary-tumor cell population by a factor of \( e^{-\theta c_t} \), in which \( \theta \) has a m\(^2\)/mg unit (see equation
Table 1: Tumor and normal tissues parameters

| Structure       | Parameters | Values                          | Source |
|-----------------|------------|---------------------------------|--------|
| Cervical Tumor  | \(\alpha\) | 0.43 Gy\(^{-1}\)               | [41]   |
|                 | \([\alpha/\beta]\) | \{3,12,20\} Gy               |        |
|                 | \(\kappa\) | \(3.21 \times 10^{-3}\) m\(^2\)/(mg \times\) Gy | [25]   |
|                 | \(\theta\) | \(2.373 \times 10^{-4}\) m\(^2\)/mg  | [32]   |
|                 | \(R\)     | 20 Gy/day                       | [33]   |
|                 | \(e_g\)   | 1.16                           | [33]   |
|                 | \(\sigma\) | 12 day\(^{-1}\)                | [33]   |
|                 | \(\tau_d\) | 4.5 days                       | [42]   |
|                 | \(T_k\)   | 21 days                        | [33]   |
|                 | \(X_0\)   | \(10^9\) cells                 | [33]   |
| Bladder         | \([\alpha/\beta]\) | 2.00                           | [41]   |
|                 | \(\gamma\) | 60.48\%                       | [34]   |
| Small Intestine | \([\alpha/\beta]\) | 8.00                           | [24]   |
|                 | \(\gamma\) | 34.24\%                       | [34]   |
| Rectum          | \([\alpha/\beta]\) | 5.00                           | [41]   |
|                 | \(\gamma\) | 46.37\%                       | [34]   |

\(\alpha\) and \(\beta\) are the parameters of the cell kill rate function in the RTOG model, and \([\alpha/\beta]\) is the \(\alpha/\beta\) ratio. \(\kappa\) is the cell kill rate constant in the RTOG model. \(\theta\) is the cell kill rate constant in the RTOG model. \(R\) is the radiation dose rate. \(e_g\) is the radiation dose equivalent. \(\sigma\) is the radiation dose rate. \(\tau_d\) is the time to kill 1 cell. \(T_k\) is the time to kill the whole population. \(X_0\) is the initial cell population.

Table 2: Metastasis site probabilities based on data presented in [8]

| Parameters | Nodes | Lung | Bone | Abdomen |
|------------|-------|------|------|---------|
| \(p_i\)   | 33.3\% | 40.30\% | 18.11\% | 8.29\% |

Figure 1 shows the optimal chemotherapy fractionation schedule when assuming equal
Figure 1: (a) Schematic of optimal regimens for chemotherapy when assuming same \( \omega_i \) for all distant metastasis sites. Green and blue regions illustrate whether it is optimal to immediately initiate the chemotherapy or to postpone it until the end of the planning horizon, respectively. (b) Optimal chemotherapy fractionation schedule associated with each region displayed in Figure 1(a) for planning horizon of five weeks (25 days).

chemotherapy effects at distant metastatic sites \((\zeta_1 = \cdots = \zeta_n)\) for a wide range of values of parameters \(\zeta_i\) and \(\xi\). In particular, when we assume equal \(\zeta_i\) for all distant metastasis sites or the goal is to minimize metastatic tumor cells at a single metastatic site, then conditions stated in Theorem 1 are always satisfied, and the optimal regimen is delivering \(c_{\text{max}}\) mg/m\(^2\) at consecutive treatment sessions concentrated at either the beginning or the end of the planning horizon.

Figure 2 plots the optimal radiotherapy fractionation schedule for three different values of \([\alpha/\beta] = \{3, 12, 20\}\) and \(f = \{70\%, 98\%\}\). We observe that when we are evaluating metastatic cell population, independent of the relationship between \([\alpha/\beta]\) and \(\min\{[\alpha/\beta]/\gamma_{ij}\}\}_{j=1,...,M}\), the resulting fractionation schedules for minimizing expected metastatic cell population is a hypo-fractionated structure with large initial doses that taper off quickly. However, when \([\alpha/\beta]\) is sufficiently large and we choose a value for \(f\) close to 1, then in order to satisfy inequality (3.10), the optimal schedule tends to be a semi-hypo-fractionation schedule with large initial doses that taper off slowly.

We perform an extensive sensitivity analysis of the radiotherapy optimal solution with respect to model parameters \((T, \xi, N, T_k)\). We observe that the radiotherapy optimal schedule is robust to perturbations in these parameters and only depends on \([\alpha/\beta]\), \(\{[\alpha/\beta]/\gamma_{ij}\}_{i=1,...,M}\) and \(f\).

To study the structure of the optimal schedules when conditions stated in Theorem 1 are not satisfied, we use our dynamic programming approach with a 3D state space to solve our optimization problem for a wide range of values of \(\xi\) and \(p_i\). We observe that the optimal radiotherapy schedule is determined independently of \(\xi\), \(\theta\), \(p_i\), and \(\omega_i\) and follows the same pattern as displayed in Figure 2.

Figure 3 illustrates optimal chemotherapy regimens for different values of \(p_i\) and \(\xi\) when reducing \(\zeta\) of the lung to one-third for fixed values of \([\alpha/\beta] = 12\) and \(f = 70\%\). By reducing the value of \(\omega\) in the lung, we ensure that a hypo-fractionated chemotherapy regimen concentrated at the beginning of therapy minimizes the metastasis population in the lung, whereas a hypo-fractionated
Figure 2: Optimal radiotherapy fractionation schedule for different values of $[\alpha/\beta]$. Black bars in plots (a) and (b) indicate that when $[\alpha/\beta] \leq \min_j \{ [\alpha/\beta]_j / \gamma_j \}$, a hypo-fractionated schedule minimizes both tumor cell population and expected metastatic cell population. For larger values of $[\alpha/\beta]$, i.e., $[\alpha/\beta] > \min_j \{ [\alpha/\beta]_j / \gamma_j \}$, where an equal-dosage routine (hyper-fractionated schedule) minimizes the number of tumor cells at the conclusion of therapy, a hypo-fractionated schedules is still the best solution to minimizing the metastatic cell population. By increasing the parameter $f$ for tumors with large values of $[\alpha/\beta]$, in order to satisfy the BED constraint stated in (3.10), we observe that the resulting fractionation schedules is a semi-hypo-fractionated structure with large initial doses that taper off slowly.
Figure 3: Optimal chemotherapy regimen when conditions stated in Theorem 1 do not hold. For these examples, we assume that $\omega_{\text{nodes}} = \omega_{\text{bone}} = \omega_{\text{abdomen}} = \theta$, $\omega_{\text{lung}} = 0.3 \times \theta$, $[\alpha/\beta] = 12$ and $f = 70\%$. (a) Optimal chemotherapy regimen for different values of $p_{\text{lung}}$. (b) Optimal chemotherapy regimen for different values of $\xi$. The arrow position represents the time of dose during the Monday-to-Friday treatment window. The size of the arrow correlates with the size of the 5-FU dose, given that the maximum daily dose cannot exceed 1,000 m$^2$/mg, $c_{\text{max}} = 1,000$ m$^2$/mg.

chemotherapy regimen concentrated at the end of the planning horizon minimizes the metastasis population at three other distant metastatic sites, i.e., nodes, bone, and abdomen. Figure 3 (a) shows that if the probability of metastasis occurrence in the lung is small (large), then the optimal chemotherapy regimen is dominated by the schedule that minimizes expected metastatic population at the other three sites (lung), i.e., a hypo-fractionated chemotherapy regimen concentrated at the end (beginning) of the planning horizon. For moderate values of $p_{\text{lung}}$, e.g., $p_{\text{lung}} = 0.35$, approximately half of the total chemotherapy doses is administrated at the beginning of the therapy, and the rest is delivered toward the end of the planning horizon. Figure 3 (b) illustrates how parameter $\xi$ changes the optimal solution in the case where conditions stated in Theorem 1 do not hold, e.g., $\xi \in (0.3, 1)$. In particular, we observe that for high (low) values of $\xi$, the overall structure of an optimal solution is dominated by the schedule that minimizes the expected metastatic population in the lung (nodes, bones and abdomen).

We consider the relative effectiveness of an optimized schedule versus a standard schedule (delivering 45 Gy of radiotherapy with 1.8 Gy fractions per day in five weeks and 8,000 m$^2$/mg of 5-FU with 1,000 m$^2$/mg per day delivered on Tuesdays, Wednesday, Thursday, and Fridays of the first and fourth weeks). In particular, we approximate the metastatic population at $n$ sites under the optimized schedule when setting $f = x\%$ in (3.10) by $R_{\text{opt}}^x$ and the metastatic population under a standard uniform fractionation by $R_{\text{std}}$. Then we denote the BED delivered to the primary tumor under optimized and standard schedules by $\text{BED}_{\text{opt}}^x$ and $\text{BED}_{\text{std}}$, respectively. The ratios $(R_{\text{std}} - R_{\text{opt}}^x)/R_{\text{std}}$ and $(\text{BED}_{\text{std}} - \text{BED}_{\text{opt}}^x)/\text{BED}_{\text{std}}$ will give us a measure of the predicted relative reduction in metastasis population and tumor BED, respectively, associated with using the optimized schedule with $f = x\%$ instead of the standard schedule. The results illustrated in Figure 4 show that the choice of $f < 100\%$ can lead to a significant reduction in metastasis population for all values of $[\alpha/\beta]$ and $\xi$. Note that for $[\alpha/\beta] \geq (\min_i [\alpha/\beta]_i / \gamma_i = 3.3)$, the standard
regimen is indeed the optimal schedule for the conventional fractionation problem that maximizes TCP \cite{1,2}, whereas a hypo-fractionated radiotherapy schedule minimizes the metastatic population size. Hence, Figure 4 illustrates the trade-off between the two conflicting objectives: (i) minimizing metastatic population size and (ii) maximizing tumor TCP for different \(\frac{\alpha}{\beta}\) and \(\xi\) values. One can observe a diminishing return in the reduction of the metastatic population. In particular, the fractionation solution obtained by setting \(1 - f = 4\%\) seems to yield an interesting trade-off between the two objectives beyond which allowing for larger tumor BED reductions, i.e., using smaller \(f = x\%\), does not lead to any significant gain in metastatic-population reduction (with the exception of very small values of \(\xi\)). Last, for the tumor \(\frac{\alpha}{\beta} < 3.3\), the two objectives (i) and (ii) are not of a conflicting nature since a hypo-fractionated regimen is desired by both objectives.

5 Conclusion

In previous work that considers optimal fractionation of chemotherapy and radiotherapy, the goal has been to maximize the probability of controlling the primary tumor, i.e., local control. From the observation that the majority of cancer fatalities are due to metastatic disease \cite{17}, we consider an alternative objective: design fractionation schedules of chemotherapy and radiotherapy that minimize the metastatic population over a sufficiently long window of time. The current work is a significant extension of our previous work \cite{3}, which incorporates multi-site metastatic disease, cell growth at the metastatic site, and additive and spatial cooperation mechanisms of chemoradiotherapy. We modeled the metastasis population as a multi-type non-homogeneous branching process, where each successful metastatic cell is able to colonize a new tumor at one of the several potential distant sites with a known probability. We were able to derive closed-form solutions to optimal chemotherapy regimens under easily verified conditions and proved an interesting structure of op-
timal radiotherapy schedules. We numerically solved this optimization problem using a dynamic programming approach.

The resulting optimal schedules had an interesting structure that is quite different from that observed in the traditional optimal fractionation problem where, the goal is to minimize the local tumor population at the conclusion of therapy. In the traditional optimal fractionation problem, it was shown that if the tumor $[\alpha/\beta]$ ratio is smaller (bigger) than the effective $[\alpha/\beta]$ ratio of all organs-at-risk (OAR), then a hypo-fractionated (hyper-fractionated) schedule is optimal [29]. In the current work, we proved that optimal radiation dose vector suggests a non-increasing structure and furthermore that it is optimal to immediately start radiotherapy treatment. In this paper, we numerically observed that, independent of the relationship between tumor $[\alpha/\beta]$ ratios and all OARs, the fractionation schedule that minimizes the metastatic population is a hypo-fractionated structure with large initial doses that taper off quickly. This result is partially consistent with our previous work, where the benefit of hypo-fractionation was observed for low values of the tumor $[\alpha/\beta]$ ratio and high values of the tumor $[\alpha/\beta]$ ratio, if the length of time for which we evaluated metastatic risk is short [3]. In the current work, we observed that if we consider metastases as actively growing tumor cell colonies and model them as a non-homogeneous branching process, then regardless of evaluation period and magnitude of tumor $[\alpha/\beta]$ ratio, our results show that a hypo-fractionated schedule is nearly always optimal.

Our sensitivity analysis reveals that chemotherapeutic agents do not change the optimal radiation fractionation regimens, and vice-versa. We proved that it is always optimal to deliver the maximum drug concentration allowed during the course of therapy, $C_{\text{max}}$. When the value $\theta \xi$, where $\theta$ is the chemotherapy-induced cell-kill at the primary site and $\xi$ is the fractal dimension of the primary tumor cells capable of metastasizing, is larger than the chemotherapy-induced cell-kill at all distant sites ($\max_{i=1,...,n} \{\omega_i\}$), the optimal chemotherapy fractionation regimen suggests delivering $C_{\text{max}}$ in consecutive days starting from the first day of the planning horizon and administering the maximum tolerable daily dose at each fraction (concurrent regimen). However, under condition $\theta \xi < \min_{i=1,...,n} \{\omega_i\}$, it is optimal to postpone delivering chemotherapy until the end of treatment (adjuvant regimen). We observed that when these two conditions are not satisfied, the optimal regimen is delivering a portion of the total chemotherapeutic agents at the beginning of the planning horizon and administrating the remaining amount at the end of the therapy. This portion is a function of $\theta$, $\xi$, the probability that a successful metastatic cell colonizes at a specific distant site and $\omega_i$ for each site. This can be compared to the chemoradiotherapy regimens obtained by Salari et al. [37] for TCP maximization in which chemotherapeutic agents with only an additive tumor cell-kill are administered at the maximum dose allowed without influencing the optimal radiation fractionation scheme.

Interestingly, previous clinical trials (e.g., for a review see [16]) show the benefit of chemoradiotherapy on overall and progression-free survival, and local and distant control in patients with cervical cancer. In particular, in clinical trials, it was observed that there is a significant reduction in the rate of distant metastases in patients diagnosed with cervical cancer treated with both platinum and non-platinum chemotherapy. This reduction was achieved with a short course of chemotherapy combined with local treatment. However, there is presently no evidence that neoadjuvant chemoradiotherapy reduces the incidence of distant metastases, which is consistent with our result discussed in Remark 1 of Section 3 [16].

Our goal here is not to recommend alternative clinical practice but to assist clinicians with hypothesis generation to design novel chemoradiotherapy fractionation schemes that can be tested in clinical trials. Our results provide a motivation for using hypo-fractionated schedules ordered in a
non-increasing structure and delivering maximum daily chemotherapeutic agents at the beginning or towards the end of therapy in pursuit of the reduction of the metastatic population. Our numerical results suggest that using optimal schedules instead of standard regimens has the potential of reducing the metastatic population by more than 40%, and even for some cases where the tumor $[\alpha/\beta]$ ratio is small, we can improve the tumor BED as well.

This paper motivates an initial idea at developing a new framework for designing more efficient chemoradiotherapy treatment regimens. Our framework can be elaborated in several directions as follows. In our model, it is assumed that the chemotherapeutic drugs administered at previous treatment fractions do not carry over to the current fraction. However, this may not be necessarily a valid assumption. Therefore, an important extension of this work will be to incorporate the effects of previously administered drugs to subsequent fractions. A possible solution to this could be modeling the effective dose at each fraction as a weighted moving average of the current and previously administrated doses.

This work considers the problem of finding radiation and chemotherapy schedules that optimally minimize the total metastatic populations. While the parameter values for the present work are focused on cervical cancer, our work is applicable to a wider range of cancers that are treated via radiotherapy and chemotherapy. In particular, we are very eager to further investigate additional cancers where we can implement our model in order to find the optimal chemoradiotherapy regimen and see how these optimal fractionation schedules vary in different cancer cases.

Last, our model is based on the assumption that the total population of the primary tumor can be accurately approximated with a deterministic function. However, the nature of tumor response to chemotherapeutic agents and ionizing radiation is stochastic and varies across different patients. Therefore, a potentially interesting extension of this work could be modeling the primary tumor site as a stochastic process as well.

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Appendices

A  Proof of Lemma 1

Proof. We use contradiction to prove our result. Let the optimal dose vector be \( \vec{c} = \{c'_1, \ldots, c'_N\} \) such that \( \sum_{i=1}^N c'_i < C_{\text{max}} \). Then, we can always construct a feasible solution \( \vec{d}' \) based on \( \vec{c} \) that contradicts the optimality of \( \vec{c} \). For example first we set \( c'_i = \vec{d}'_i = \vec{c}_i \) for all \( i \) and then for an arbitrary integer \( i, 1 \leq i \leq N, \) such that \( c'_i < c_{\text{max}} \) (note that this integer must exist since we have \( C_{\text{max}} < Nc_{\text{max}} \)), we set \( c''_i = \min\{c_{\text{max}}, c'_i + C_{\text{max}} - \sum_{t=1}^N c'_t\} \) and observe that

\[
g \left( \sum_{t=1}^N d'_t, \sum_{t=1}^N d''_t, \sum_{t=1}^N c''_t \right) \leq g \left( \sum_{t=1}^N d'_t, \sum_{t=1}^N d'_t, \sum_{t=1}^N c'_t \right) \quad \text{and} \quad f(\vec{d}, \vec{d}') \leq f(\vec{d}, \vec{c}')
\]

since \( \alpha, \beta, \) and \( \theta \) are always positive values.

B  Proof of Lemma 2

Proof. We use contradiction to prove our result. Assume that there exists an optimal dose vector \( \vec{d}^* = \{d'_1, \ldots, d'_N\} \) such that for some \( j > i \), we have \( d'_j > d'_i \). Now we construct a new feasible solution \( \vec{d}' = \{d'_1, \ldots, d'_N\} \), where \( d'_i = d'_j, d'_j = d'_i \) and \( d'_k = d'_k \) for \( k \neq i, j \) with the identical drug vector \( \vec{c} \). Note that the feasibility constraints and the value of function \( g \) in (3.8) are order independent, i.e., if we change the order of the dose vector, then the resulting dose vector is still feasible with the same value for function \( g \); hence, \( \vec{d}' \) is a feasible solution to (3.8)–(3.13) where

\[
g \left( \sum_{t=1}^N d'_t, \sum_{t=1}^N (d'_t)^2, \sum_{t=1}^N c_t \right) = g \left( \sum_{t=1}^N d'_t, \sum_{t=1}^N (d'_t)^2, \sum_{t=1}^N c_t \right).
\]

Thus to prove the result it is sufficient to show that \( f(\vec{d}', \vec{c}) \leq f(\vec{d}^*, \vec{c}) \), i.e.

\[
\sum_{i=1}^{N+1} e^{-\epsilon \left( \sum_{j=i}^{t} (\alpha d'_j + \beta (d'_j)^2 + (\theta - \omega_i / \xi) c_j) - \frac{\omega_i}{d_t} (T - T_k)^+ \right)} - \mu, t - \omega_i C_{\text{max}} \leq \sum_{i=1}^{N+1} e^{-\epsilon \left( \sum_{j=i}^{t} (\alpha d'_j + \beta (d'_j)^2 + (\theta - \omega_i / \xi) c_j) - \frac{\omega_i}{d_t} (T - T_k)^+ \right)} - \mu, t - \omega_i C_{\text{max}}
\]

for all \( i = 1, \ldots, n \). The above inequality is implied by

\[
\alpha \sum_{j=1}^{t-1} d'_j + \beta \sum_{j=1}^{t-1} (d'_j)^2 \geq \alpha \sum_{j=1}^{t-1} d'_j + \beta \sum_{j=1}^{t-1} (d''_j)^2 \quad \text{for all} \quad t = 1, \ldots, N + 1 \text{ and } i = 1, \ldots, n
\]

We can use the same approach to prove the same result for \( e^\vec{x} \) (see proof of Theorem 1 for more details).

C  Proof of Theorem 1

Proof. We first prove our results when \( \theta \xi \geq \max_{i=1, \ldots, n} \omega_i \). This condition implies that \( \theta - \omega_i / \xi \geq 0 \) for all \( i = 1, \ldots, n \). First, we use contradiction to show that, in optimality, we must have \( c'_j = \cdots = c'_k = c_{\text{max}} \) for \( k = \left\lfloor C_{\text{max}} / c_{\text{max}} \right\rfloor \). Assume that there exists an optimal dose vector \( \vec{c}^* = \{c'_1, \ldots, c'_i, \ldots, c'_j, \ldots, c'_N\} \) such that for some \( j > i \), we have \( c'_i < c_{\text{max}} \) and \( c'_j > 0 \). Now we construct a new feasible solution \( \vec{d} = \{c'_1, \ldots, c'_N\} \), where \( c'_j = \min\{c_{\text{max}}, c'_i + c'_j\} \), \( c'_j = c'_j - (c'_i - c'_j) \)
and \( c'_k = c'_k \) for all \( k \neq i, j \) with the identical dose vector \( \vec{d} \). First, note that the drug vector \( \vec{c} \) is a feasible solution, since \( \sum_{t=1}^{N} c'_t = \sum_{t=1}^{N} c^*_t \) and \( c'_t \leq c_{\text{max}} \) for \( t = 1, \ldots, N \). Second, the value of function \( g \) in (3.8) has the same value for both \( \vec{c}^* \) and \( \vec{c} \), since \( \sum_{t=1}^{N} c'_t = \sum_{t=1}^{N} c^*_t \), i.e.,

\[
g \left( \sum_{t=1}^{N} d_t, \sum_{t=1}^{N} d^*_t, \sum_{t=1}^{N} c'_t \right) = g \left( \sum_{t=1}^{N} d_t, \sum_{t=1}^{N} d^*_t, \sum_{t=1}^{N} c^*_t \right).
\]

Thus, to prove that \( \vec{c} \) results in a smaller objective function, it is sufficient to show that \( f(\vec{d}, \vec{c}) \leq f(\vec{d}, \vec{c}^*) \), i.e.,

\[
\sum_{t=0}^{N+1} e^{-\xi \left( \sum_{j=1}^{t-1} \left( ad_j + \beta d^2_j + (\theta - \omega_i / \xi) c'_j \right) - \frac{\ln 2}{\tau_d} (t - T_k)^+ \right) - \mu_i t - \omega_i C_{\text{max}}} \leq \sum_{t=0}^{N+1} e^{-\xi \left( \sum_{j=1}^{t-1} \left( ad_j + \beta d^2_j + (\theta - \omega_i / \xi) c^*_j \right) - \frac{\ln 2}{\tau_d} (t - T_k)^+ \right) - \mu_i t - \omega_i C_{\text{max}}}
\]

for all \( i = 1, \ldots, n \). The above inequality can be shown if and only if we show the following inequality for \( \forall t = 0, \ldots, N + 1 \)

\[
\sum_{t=1}^{t-1} \left( ad_k + \beta d^2_k + (\theta - \omega_i / \xi) c'_k \right) \geq \sum_{t=1}^{t-1} \left( ad_k + \beta d^2_k + (\theta - \omega_i / \xi) c^*_k \right), \quad \forall i = 1, \ldots, n
\]

Since both schedules have an identical radiation dose vector, we need to show that

\[
(\theta - \omega_i / \xi) \sum_{k=1}^{t-1} c'_k \geq (\theta - \omega_i / \xi) \sum_{k=1}^{t-1} c^*_k \quad \forall t = 1, \ldots, N + 1 \text{ and } \forall i = 1, \ldots, n.
\]

We assume that \( \theta - \omega_i / \xi \geq 0 \) for all \( i = 1, \ldots, n \); therefore, the above inequality is implied by

\[
\sum_{k=1}^{t-1} c'_k \geq \sum_{k=1}^{t-1} c^*_k \quad \forall t = 1, \ldots, N + 1.
\]

Note that \( c'_i = \min\{c_{\text{max}}, c^*_i + c^*_j\} \), \( c'_j = c^*_j - (c'_i - c^*_i) \) and \( c'_k = c^*_k \) for \( j > i \) and \( \forall k \neq i, j \); therefore, we have \( c'_i > c^*_i \), which implies that \( \sum_{l=1}^{t-1} c'_l > \sum_{l=1}^{t-1} c^*_l \) for all \( \forall l \geq j \) and \( \forall l < i \).

Next, note that as a result of Lemma 1, we know that \( \sum_{t=1}^{N} c^*_t = C_{\text{max}} \). Hence, we can repeat the above procedure to improve the optimal solution until we get \( c^*_1 = \cdots = c^*_k = c_{\text{max}} \) for \( k = \lfloor C_{\text{max}}/c_{\text{max}} \rfloor \), where no more improvement can be achieved. At this step, we have two scenarios: first, \( \lfloor C_{\text{max}}/c_{\text{max}} \rfloor \in \mathbb{N} \), where we must have \( c^*_{k+1} = \cdots = c^*_N = 0 \), which proves our result; second, \( \lfloor C_{\text{max}}/c_{\text{max}} \rfloor \neq C_{\text{max}}/c_{\text{max}} \), where \( \sum_{t=k+1}^{N} c_t = C_{\text{max}} - kc_{\text{max}} < c_{\text{max}} \). In this case, by using the same contradiction as before, we can show that if we choose \( c_{k+1} < C_{\text{max}} - k c_{\text{max}} \), then we can always construct a feasible solution with a smaller objective function.

We can use a similar approach when \( \omega_i < \min_{i=1, \ldots, n} \omega_i \). In this case, we have \( \theta - \omega_i / \xi < 0 \), \( \forall i = 1, \ldots, n \). Therefore, for any schedule with \( c^*_i < c_{\text{max}} \) and \( c^*_j > 0 \) for \( i > j \), we can construct a new feasible solution \( \vec{c} = \{c'_1, \ldots, c'_N\} \), where \( c'_i = \min\{c_{\text{max}}, c^*_i + c^*_j\} > c^*_i, c'_j = c^*_j - (c'_i - c^*_i) < c^*_j \).
and $c'_k = c^*_k$ for $\forall k \neq i, j$ with a smaller objective function. Similar to the previous case, here we require that

$$\sum_{k=1}^{t-1} (\alpha d_k + \beta d_k^2 + (\theta - \omega_i / \xi) c'_k) \geq \sum_{k=1}^{t-1} (\alpha d_k + \beta d_k^2 + (\theta - \omega_i / \xi) c^*_k), \ \forall i = 1, \ldots, n$$

since $\theta - \omega_i / \xi < 0 \ \forall i$, which equivalently shows that

$$\sum_{k=1}^{t-1} c'_k \leq \sum_{k=1}^{t-1} c^*_k \text{ for all } t = 1, \ldots, N + 1.$$

This inequality is implied by $\sum_{t=1}^{l} c'_t < \sum_{t=1}^{l} c^*_t$ for $\forall l : j \leq l < i$ and $\sum_{t=1}^{l} c'_t = \sum_{t=1}^{l} c^*_t$ for $\forall l \geq i$ and $\forall l < j$. The rest is similar to the situation where $\theta \xi > \max_{i=1, \ldots, n} \omega_i$. \qed