

Model-Based Management of Lung Cancer Radiation Therapy [★]

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Abstract:

A truly personalized cancer therapy demands the availability of models, of which tumor dynamics model is imperative. This paper presents a feasibility study of using a tumor growth model for lung cancer treatment planning. Recent developments in radiation therapy are outlined in this work, including target tumor based delivery of limited but highly precise treatment doses during stereotactic body radiation therapy (SBRT). Based on our prior work, we propose a methodology for quality improvement in treatment management of lung cancer, including the lung tumor motion. The paper presents the tumor behavior in various therapy scenarios by simulating different time-dose schemes for drug administration. The results indicate that the model is adequate and can be further used into the feedback scheme for treatment updates.

Keywords: dynamic system modeling, tumor growth model, model-based treatment, lung cancer, radiation therapy, stereotactic body radiation therapy, decision support system

1. INTRODUCTION

Significant achievements have been obtained in improving the diagnosis, treatment planning and delivery for patients with lung cancer. However, survival rates remain poor and vary widely across Europe. With an estimated of 470,039 new cases in 2018 (11.1%), compared with 449,000 cases in 2015 (LuCE, 2015), lung cancer has increasing rates in Europe (WHO, 2018). Lung cancer in EU is the biggest cancer killer in cancer-related deaths, accounting for a number of 387,913 of deaths in 2018 (20%).

An investigation of World Health Organization (International Agency for Research on Cancer) (WHO, 2018) reports the statistical analysis of worldwide burden of lung cancer, our interest lying in Belgium, Hungary and Romania. The numbers related to lung cancer in Belgium

in 2018 were: 9,424 (12.18%) new cases of lung cancer in men (6,214) and women (3,210); with 7,037 lung cancer related deaths (25.43%). In the same year in Hungary, lung cancer incidence was 11,004 (15.6%) and the mortality 8,893 (26.9%). In 2018, lung cancer in Romania accounted for the following numbers: 11,340 (13.6%) new cases and 10,277 (20.2%) deaths. The results imply that lung cancer is ranked as number one cause of cancer deaths in all the three countries, being also the first in cancer incidence in Hungary and Romania and second in Belgium (WHO, 2018).

The main subtype of lung cancer is Non-Small Cell Lung Cancer (NSCLC), accounting for approximately 85% of all lung cancer sites (Zappa and Mousa, 2016). The histological subtypes of NSCLC (adenocarcinoma, squamous cell carcinoma, large cell carcinoma) are important for choosing the efficient angiogenesis inhibitors and therapies, as well as bio-markers (McLean et al., 2018). Angiogenesis is the physiological process of growing new blood vessels. Antiangiogenesis is critical for blocking the blood supply that supports the tumor and by default minimizing the growth of cancer cells.

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With the advancement of the changing landscape of lung cancer treatment, radiation therapy (RT) is the most used modality to address local-regional areas of tissue. RT is a well-known cancer treatment, with complex and varied toxic biological effects, wanted to be provoked in diseased cells, while simultaneously avoiding healthy cells. Stereotactic body radiation therapy (SBRT) is an advanced form of hypofractionated RT that consists of precise delivery of higher radiation doses on precised tumor location (Liauw et al., 2013). SBRT delivery in lung cancer is mostly performed using a linear accelerator. Clinical practice in lung cancer meets difficulties in motion management. Positioning variations of thoracic structures, including tumor, can occur on different time scale, in all three orthogonal directions, due to the cyclic breathing motion (Korreman, 2015). Variations in the breathing pattern are crucial for drawing trajectories of radiation in real time and for implementing a motion management strategy in SBRT. Programming the linear accelerator to move synchronously with the tumor target by introducing active feedback of tumor position updates the beam delivery.

The burden of lung cancer requires complex research, including describing it by means of mathematical formalism. Mathematical modeling enables an understanding of cancer mechanisms by providing quantitative predictions, describing relationships between biologic components and extrapolating validated facts (Altrock et al., 2015). Despite the available cancer models that provide useful insights into the possible underlying mechanisms of tumor progression, intra-tumor heterogeneity and treatment responses, modeling the tumor response to treatment is still missing.

The purpose of this study is to provide first-hand results towards broadening the improvements for cancer treatment management and follow up. We provide a mathematical framework of tumor dynamics and integrate it into the comprehensive mechanism for treatment planning in RT.

This paper is organized as follows. Section 1 introduces the clinical needs in radiation therapy and treatment planning for lung cancer. In Section 2, the current advances in radiation oncology delivery and the physics principles of therapeutic ratio used in SBRT are discussed. It also describes the potential approaches in order to facilitate accurate tumor targeting in lung cancer, proposing a strategy for setup correction of tumor position. Section 3 proposes a tumor growth model that incorporates tumor physiology and mechanisms. Section 4 presents the results obtained after simulation of different treatment schedules, followed by discussion, future directions and study limitations. The principal outcomes are outlined in the conclusions section.

2. STEREOTACTIC BODY RADIATION THERAPY

2.1 Background

Of the various lung cancer treatment protocols, SBRT represents the standard of care for peripherally located early stage NSCLC patients that are medically inoperable or refuse the surgical resection of the tumor. In practice, the clinical guidelines from national protocols and/or published literature are not enough in evaluation of the tumor and application of SBRT technique (Guckenberger et al., 2017).

SBRT is an unconventional external beam radiation therapy designed for very precise tumor localization and radiation delivery. SBRT implies the use of image guidance and specially designed coordinate-system to locate the tumor in the lungs in order to treat it with limited and highly precise treatment fields. In SBRT, the target area is mapped by physicians with four-dimensional imaging. The multiple non-coplanar beams are directed and intersect at the targeted tumor volume, called radiation "hot spot". The radiation plan takes into consideration also the movement of the target over time as a result of the patient breathing cycle. The optimal use of radiation therapy is tailored according to different relevant characteristics of both the patient and the tumor. In SBRT, hypofractionated doses are applied. The principle can be described as follows: high doses of irradiation are delivered in a single dose or a few treatment fractions, avoiding treating a volume outside of the tumor target (Roesch et al., 2014). Conventional fractionation schedules for non-small cell lung cancer consists of 3 to 5 fractions of 12 to 20 Gy, hence reducing the radiation induced toxicity and risks.

Strong emphasis has been placed on precise tumor localization at the time of radiation delivery to minimize healthy tissue damage. Clinical experience and a mathematical modeling of the dose effect pathway are key requirements of the procedure.

Therapeutic radiation is usually requiring rotating gantries with mounted linacs in order to overlap the external beams on the same area of the tumor, providing higher effects. Most commonly used is the CyberKnife system, a robotic arm manipulator (Shibamoto and Onishi, 2018). Investigations for local tumor control are made for using image-guided radiation therapy (IGRT), intensity-modulated RT (IMRT) or volumetric-modulated arc therapy (VMAT) (Diwanji et al., 2017).

Cross fertilization between engineering and medicine provides tools for personalized medicine, with the potential to quickly change the outcome of lung cancer treatment. During the last decades, SBRT has been widely applied in lung cancer with excellent results, but some issues regarding precise delivery remain controversial. One of the challenges is the implementation of real time target motion management caused by the cyclic breathing motion. An approach for respiration measurement is described in (Gu et al., 2012), using a radar sensor for experimental respiration measurements. Other approaches are described in (Diwanji et al., 2017; Korreman, 2015), but none are coupled to a predictive control strategy to maximize their outcome. Techniques and devices used to minimize the effects of respiratory motion refer to gating, tracking and immobilization (Ionescu et al., 2017b). These techniques consist of delivering the radiation in a single phase of the cyclic breathing, moving the beam delivery device with the tumor or limiting the respiration induced lung movement. Basic concepts of respiratory tumor motion exploit the tumor trajectory, defined as the spatial path described by the tumor while it is being monitored.

In our prior work, we have proposed a predictive control approach to update the robot arm responsible for locating the precise spot of radiation onto the tumor tissue while breathing. The movement of the tumor location as a result

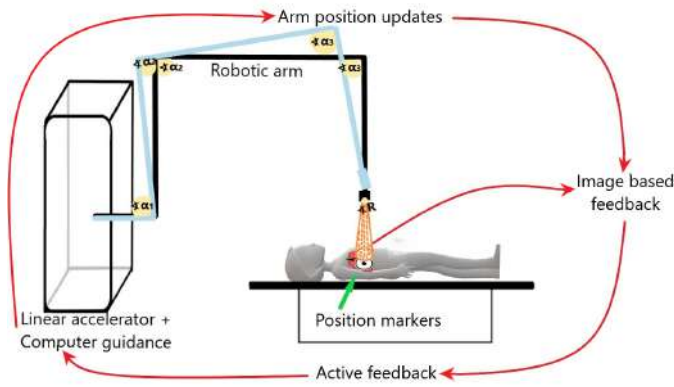


Fig. 1. Basic scheme of robotic radiotherapy system with model-based control strategy.

of the 3D variation in the lung tissue has been successfully compensated by using tumor dynamic model during tidal motion (Ionescu et al., 2017b). The study showed that the combination of predictive control and disturbance filtering (effects of breathing) increases the accuracy improvement with 15%.

This paper proposes another step forward towards achieving the fully personalised therapy management that could combine RT with antiangiogenesis drugs. It further provides a model of tumor dynamic response to drug therapies for scheduled treatment doses and time administrations, that could be integrated in the planning related decision-making process.

2.2 Proposed Context

The method proposed in this paper helps to further link the tumor dynamic response to treatment, expressed as a mathematical model, to the decision-making system of treatment planning. Specifically, the model provides insight into the dynamic response to medication, which in turn helps to decide which dose and intensity of radiation need to be next applied to the patient. Consequently, the robotic arm of radiation delivery will have the feedback and predictive control strategy as given in (Ionescu et al., 2017b) to apply the required dose and intensity to the tumor tissue only. Our protocol appears to be more practical and accurate than what the human eye can perceive or than individual camera can record. Ideally, all information could be integrated into a strategy for management of motion in SBRT treatment.

In order to reduce the position uncertainty of beam delivery, a mathematical correlation model between the tumor position during 3D movement and the robot position can be used. A schematic overview of the robotic angle adjustments for radiation delivery is given in Fig. 1. The result is a position error that may be further correlated with the toxicity measured during follow up visits of the patients. The final extent of the strategy is to develop a general prediction model for toxicity risk in a similar population, but with the possibility of individualization. Our focus is to take account of setup errors in real time delivery of radiation therapy and adapt the treatment management based on previous treatment response. The treatment strategy is thus changed from open-loop to closed-loop.

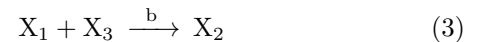
3. TUMOR GROWTH MODEL

The appropriate model structure and parameter identification of the mathematical models describing tumor dynamics within the respiratory tissue dynamics are crucial steps in providing improved healthcare for cancer patients. The aim of the current work is to verify the use of the model developed in Drexler et al. (2017, 2019) for simulating the effect of the treatment doses at different times. A realistic lung tumor growth model should involve the proliferation of the tumor, the necrosis of tumor cells and the effect of the treatment applied (drug - Bevacizumab or the therapeutic dose of ablative radiation). The original contribution proposed in this paper is to reproduce and predict the change of tumor volume by simulating different doses of treatment.

Cancer development is closely linked to the tumor micro-environment, as a result of temporal and spatial expansion that govern its dynamics (Altrock et al., 2015). This type of system can be described by differential equations, with one independent variable that is time (Ionescu et al., 2011; Ionescu, 2012). The work is based on previous validated research of (Drexler et al., 2017, 2019), where a third-order model is developed to include the most relevant physiological phenomena of cancer:

- proliferation of the tumor;
- necrosis of tumor cells;
- pharmacodynamics of the drug;
- pharmacokinetics of the drug.

These physiological relations are then transposed into a mathematical formulation. To describe the dynamics of the system cause-and-reactions, a compartmental model is developed based on an analogy with the chemical reactions of the network. Using *mass-action kinetics* and other schemes for *chemical reaction networks*, one may obtain a simplified model as given by:



These relations describe the essential physiological processes in a minimal formulation. For instance, (1) states that the tumor proliferates with the tumor growth rate a until potentially doubling its initial volume. This relation can be translated into $\dot{x}_1 = ax_1$. Necrosis of tumor cells is defined in (2), with a necrosis rate n independent of the treatment. The process is incorporated into both proliferating and dead tumor volumes by adding the terms $\dot{x}_1 = -nx_1$ and $\dot{x}_2 = nx_1$. We assume in (4) that there is an outflow of the drug treatment with a reaction rate coefficient c (defined as clearance). This generic assumption is used to form the term $\dot{x}_3 = -cx_3/(K_B + x_3)$. This equation represents a mixed-order model for describing the pharmacokinetics, adopting the Michaelis-Menten (M-M) kinetics with K_B as the Michaelis constant of the drug.

In order to define the pharmacodynamic of the treatment and to simulate its effects on proliferating and necrotic tumor volume (3), the terms $\dot{x}_1 = -bx_1x_3/(ED_{50} + x_3)$

and $\dot{x}_2 = bx_1x_3/(ED_{50} + x_3)$ are introduced. This means that the drug provokes the proliferation of tumor cells and necrosis takes place. This effect is considered in relation with the reaction rate coefficient b and Michaelis constant ED_{50} . The median effective dose (ED_{50}) generates the velocity term $x_1x_3/(ED_{50} + x_3)$, previously used. We introduce the constant b_k in $mg/(kg \cdot mm^3 \cdot day)$ in order to define those terms that had different dimensions: mm^3/day for velocity terms and $mg/(kg \cdot day)$ for drug level. The result is the term $\dot{x}_3 = -b_kx_1x_3/(ED_{50} + x_3)$.

The general construction of the chemical reaction equations is useful for the formulation of the lung tumor growth model. The differential equations that provides an insight into lung tumor proliferation or regression as a result of a treatment are:

$$\dot{x}_1 = (a - n)x_1 - b \frac{x_1x_3}{ED_{50} + x_3} \quad (5)$$

$$\dot{x}_2 = nx_1 + b \frac{x_1x_3}{ED_{50} + x_3} \quad (6)$$

$$\dot{x}_3 = -c \frac{x_3}{K_B + x_3} - b_k \frac{x_1x_3}{ED_{50} + x_3} + u \quad (7)$$

where x_1 is the time function of the proliferating tumor volume, measured in mm^3 , x_2 is the time function of the necrotic tumor volume, also in mm^3 , while x_3 is the time function of the drug level in time (mg/kg).

The input is represented by u that is the time function of the drug treatment in $mg/(kg \cdot day)$. The parameters of the model are defined by means of the equivalent chemical equations. These values are listed in (Drexler et al., 2017), after the parametric identification was carried out on mice experimental measurements. In this paper, the values of the tumor growth model parameters are re-scaled and extrapolated to define the dynamics and tumor volumes of human lung tumor. The output of the model is the total tumor volume in mm^3 , considered measurable, consisting of the sum of the proliferating and necrotic tumor volumes as:

$$y = x_1 + x_2. \quad (8)$$

The output dynamics is defined by

$$\dot{y} = ax_1, \quad (9)$$

as a function of tumor growth rate constant a and the present volume of proliferating tumor x_1 . The model has the potential to relate the effects of the treatment dose and administration according to variations in the tumor size. This mathematical modeling strategy can be defined as a predictor of tumor aggressiveness and treatment prognosis.

4. RESULTS AND DISCUSSION

This section presents the simulation analysis of the effects from various treatment strategies using the lung tumor growth model. Four therapies that can be encountered in clinical practice are examined.

Therapy 1. A single drug dose administration of 10 mg/kg at the beginning of the treatment.

Therapy 2. Periodic drug dose administration of 2 mg/kg at the beginning of the treatment and at each 3 days (Day 0, 3, 6, 9, 12). The drug administration is equidistant over the defined time period.

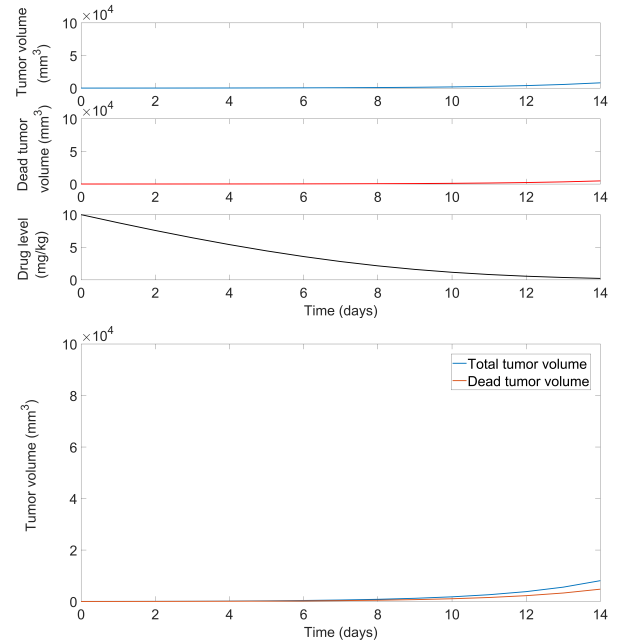


Fig. 2. **Simulation of Therapy 1.** Top: a dose input of 10 mg/kg administrated only in day 0 of the treatment. Bottom: tumor volumes over a period of 14 days.

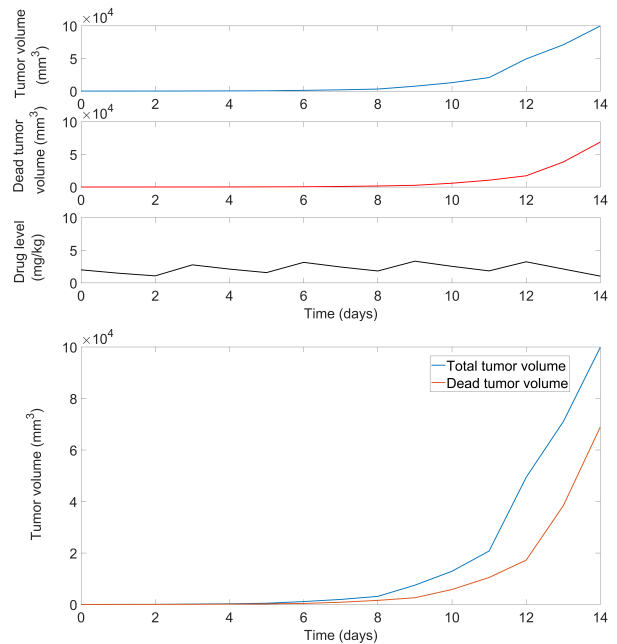


Fig. 3. **Simulation of Therapy 2.** Top: a dose input of 2 mg/kg administrated in each of the following days of the treatment: day 0, 3, 6, 9, 12. Bottom: tumor volumes over a period of 14 days.

The duration for Therapy 1 and 2 is 14 days. Using this approach we observed the tumor dynamic effects on a smaller time scale of fractionated doses of the drug. These two therapies are proposed in order to see the difference between a single, bigger dose of drug administrated one time and several equal smaller doses of drug administrated at several equal time distances.

The results obtained with Therapy 1 and Therapy 2 are presented in Figs. 2 and 3, respectively. We observe that

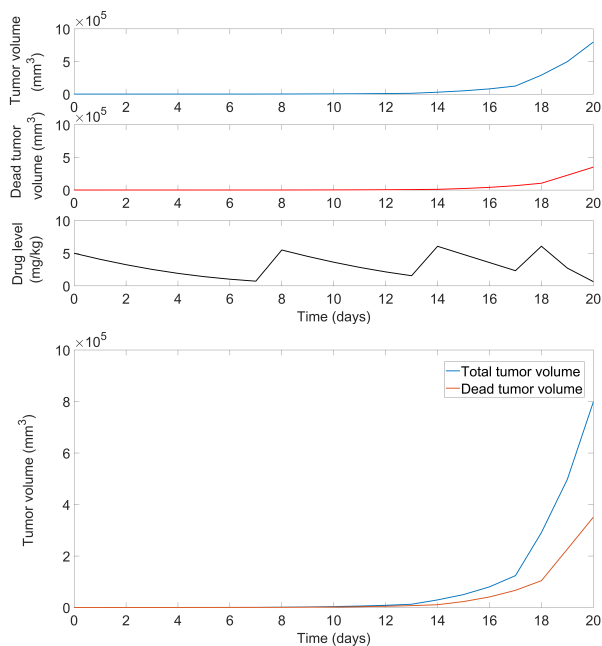


Fig. 4. **Simulation of Therapy 3.** Top: a dose input of 5 mg/kg administrated with an increased frequency, in the following days of the treatment: *day 0, 8, 14, 18*. Bottom: tumor volumes over a period of 20 days.

a complete, higher dose of drug provokes a slower growth of tumor volume compared with fractionated ratios of the same dose of the drug. The applied doses in the second therapy are less effective, as seen in the slow increasing values of total and dead tumor volumes.

Therapy 3. Drug dose administration of 5 mg/kg at the beginning of the treatment with an increased frequency over time, namely in Day 0, 8, 14, 18.

Therapy 4. Drug dose administration of 5 mg/kg at the beginning of the treatment with a decreased frequency, in the following days of the treatment: Day 0, 2, 6, 12.

Therapy 3 and 4 are simulated over a 20 days period of time. These therapies have been examined in order to analyze the changes in tumor volume related to the time administration of hypofractionated doses. Therapy 3 and Therapy 4 results are plotted in Figs. 4 and 5, respectively. Administrating the treatment doses more frequently at the beginning of the treatment for Therapy 3 results in overall smaller tumor volumes than in Therapy 4, where the doses frequency was increased only towards at the end of the treatment. In Therapy 4, the drug level goes to zero before the time period is finished, preventing overdosing.

We may conclude that administrating a high dose of drug in the first phase of the treatment (Therapy 1) or higher fractionated doses with increased frequency in time (Therapy 3) leads to a slower increase of tumor volume. In other words, this principle validates the clinical use of hypofractionated treatment doses applied in SBRT.

A generalization using fractional calculus to describe the compartmental models for pharmacokinetics in cancer treatment has been introduced in (Ionescu et al., 2016). Complex kinetics simulated with fractional models have

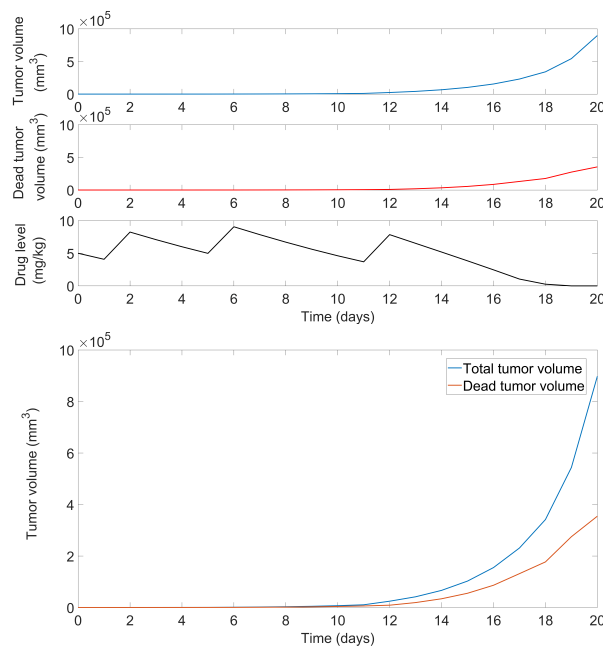


Fig. 5. **Simulation of Therapy 4.** Top: a dose input of 5 mg/kg administrated with a decreased frequency, in the following days of the treatment: *day 0, 2, 6, 12*. Bottom: tumor volumes over a period of 20 days.

been also recognized and appraised in (Ionescu et al., 2017a; Copot et al., 2017) for being natural solutions to models of biological tissues. The role of fractional calculus in tumor growth phenomena has been recently validated (Yildiz et al., 2018). As a further development of the model, one could assume fractional kinetics and anomalous diffusion in the tumor tissue, with applications in many fields (Zhou et al., 2015). As a next progressive step, the concomitant simulation of the system from Fig. 1 with the proposed tumor growth model will advance the engineering problem of lung cancer.

The major limitation of the study is the absence of validation of the simulated therapies and delivery adjustment of treatment on patient data. Evaluation of the combined use of different treatment patterns with control prediction of treatment delivery is desperately needed in clinical practice. In essence, this forms a closed-loop regulatory system where the controller decides the exact position for treatment delivery after active feedback. Fractional calculus is the solution for predicting the tumor behavior after the administration of therapy in different time-dose schemes.

5. CONCLUSIONS

A multidisciplinary approach of the radiation therapy planning of lung cancer treatment is proposed in this work. Including a physiologically-based, mathematical modeling of tumor dynamics is a key factor in ensuring a low-risk and accurate treatment for lung cancer patients. Optimal decision making process for the treatment dose and time-of-delivery is an essential contribution to clinical efficacy in cancer treatment management.

We have shown in this first-hand study that different scenarios of treatment delivery and dose configuration lead

to different response in tumor growth and provide insight into under- and over-dosing risk. Overall, such model could be integrated into the full SBRT treatment for further improvement of patient's life quality.

This research is conceptually outlining a roadmap for tackling the problem of SBRT treatment management by using our understanding of tumor physiology and radiation delivery. Although we still need to put it in practice, delivering radiation therapy in lung cancer has increasingly begun to resemble a predictive control strategy. Using the proposed simulation tools, it is feasible to simulate time-dependent effects during fractionated treatment and to compare different time-dose patterns in terms of their tumor control. The presented approach has the potential to support the clinicians in their clinical decisions.

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