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Lung Tumor Growth Modeling in Patients with NSCLC Undergoing Radiotherapy ⋆

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Abstract: This paper proposes two modeling approaches to predict lung tumor dynamics as an effect of radiotherapy. Real clinical information of non-small cell lung cancer (NSCLC) patients undergoing stereotactic body radiation therapy (SBRT) as the primary treatment method has been used for numerical simulations. The classical Gompertz model for tumor volume growth prediction was modified using a fractional parameter and combined with the linear-quadratic model to foresee the effect of SBRT on the targeted tumor. Another approach was implemented by following a pharmacokinetic-pharmacodynamic (PKPD) minimal compartmental model for single therapy with SBRT. Statistical analysis has been carried out to compare the two models. In terms of tumor growth prediction, obtained results indicated a decrease in the total tumor volume for both modeling approaches. A striking observation to emerge from the data comparison is the interesting perspective of fractional tools for further exploration in modeling tumor growth.

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Keywords: Mathematical modeling, lung cancer, stereotactic body radiation therapy, tumor dynamics, fractional calculus.

1. INTRODUCTION

Recent evidence suggests that in 2020 there were 2.2 million cases of lung cancer recorded worldwide, with 318.000 cases from the EU (Union for International Cancer Control, 2020). Belgium reported a considerable amount of cases (9.600) during last year (Europa Analytics, 2020). Non-small cell lung cancer represents the largest proportion of lung cancer which occurs at a rate of 85%. About 70% of the diagnosed patients have an advanced stage of NSCLC. The tumor cells in this stage grow rapidly and spread into the tissues surrounding the lungs and subsequently into other parts of the body.

The most commonly used conventional treatment methods to overcome NSCLC in different stages are: radiotherapy, chemotherapy, immunotherapy, and targeted therapy. The patients can undergo one therapy or a combination of two or more therapies applied consecutively (e.g., concurrent radio-chemotherapy, chemo-immunotherapy, etc.). The outcome of the combination of treatments can be predicted using mathematical modeling (Ionescu et al., 2020; Drexler et al., 2017). However, much uncertainty still exists regarding the relationship between different factors that influence the exact treatment plan, such as size and location of the tumor, degree of spread, patient response to treatment, and overall health. Radiotherapy (RT) is one of the most commonly used treatments for NSCLC patients. More specifically, SBRT is a comparatively novel radiation technique that improves the reduction of healthy cells' exposure to radiation. In SBRT, large doses per fraction of radiation are delivered to the target tissue precisely to maximize the tumor response (Lo et al., 2010). This choice of treatment promises high rates of local control of the tumor and provides an alternative to the non-surgical tumors (Joiner and van der Kogel, 2009; Verellen et al., 2007).

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In cancer research, there is a steady growth in the usage of computational modeling to optimize treatment planning (Altrock et al., 2015; Ghita et al., 2021). Optimization refers to the balance between the effect of the required amount of drug dosage to eliminate tumor cells and the minimization of the same effect on healthy cells. The tumor volume after treatment depends on the interaction between the therapies, patient response, and the effect of treatment on tumor cells. Modeling can serve as a research tool for moving towards individualized treatment methods through multiple parameter variations, notwithstanding the accuracy of current practice. (Ionescu et al., 2020).

The development of mathematical models of tumor growth leads to a very large class of possible methods to characterize the invasion and growth of tumors in living tissue. While there is a manifold of tumor growth models existing in literature, the major challenge is to translate clinical data describing the carcinogenic process by elucidation of different mechanisms. Modeling strategies usually address simple physiological principles in terms of ordinary differential equations (ODE). Two of the most simplistic tumor growth models are the exponential and linear exponential models (Sápi et al., 2015). However, they are unrealistic as the growth described by these models is not limited (i.e., bound by an upper limit). Three other models which describe the growth rate of tumor cells are Gompertz, Logistic, and Bertalnaffy (Murphy et al., 2016). In these models, the growth rate increases reaching a maximum value and finally achieving a state of equilibrium (Tabassum et al., 2019). ODE models allow fine-tuning of parameters and can be analytically solved, but lack in describing the full complexity of tumor evolution.

In this work, we propose two improved mathematical models of tumor growth that fit different SBRT treatment options for NSCLC patients. The study investigates the tumor dynamics using patient data representing planning target volume (PTV), treated using SBRT and three standard regimens depending on tumor location. Both models use improved approaches for model accuracy concerning clinical data, thus potentially helping decision-making treatment schedules in lung cancer. The first model is the Gompertzian model that was modified to introduce a fractional operator and effect of radiotherapy to describe the behavior of irradiated tumor volume. The second model is the pharmacokinetic-pharmacodynamic (PKPD) compartmental model from Ionescu et al. (2020), employed for investigating the effect of radiation therapy on tumor cells. Using data of NSCLC patients undergoing SBRT, we were able to simulate different approaches that describe tumor development with growth behavior. Given the variety of dosing schemes available, comparisons using computer simulations are convenient for quantifying the association between tumor volumetric changes and SBRT.

The remainder of this paper is structured as follows. In section 2, we describe the mathematical methodology by introducing the fractional Gompertz and PKPD models considered in this study, while discussing the adopted improvement tools. Patient data and the clinical protocol are also mentioned. Section 3 analyzes the simulation and comparative results, while section 4 discusses the differences between the obtained results and their physical meaning. Finally, section 5 draws the main conclusions.

2. MODELS AND METHODS

2.1 Gompertz Model with Fractional Operator

One of the most common models to describe the dose-response of radiotherapy and cell survival under radiation is the Linear Quadratic model (Altrock et al., 2015). Having the same dose per fraction in a multidose schedule, we assume equal radio-biological effect for each successive fraction, expressed as (Joiner and van der Kogel, 2009):

$$E_r = \alpha D + \beta d D \tag{1}$$

where E_r is the level of radiotherapy effect, $D = m \cdot d$ is the total dose in Gy, m is the number of fractions, d is the dose per fraction in Gy, α and β are radio-sensitivity parameters in Gy^{-1} and Gy^{-2} respectively. In the model, the ratio of the radio-parameters was considered to be 10 Gy, NSCLC exhibiting usually low fractionation sensitivity (high α/β) (van Leeuwen et al., 2018).

Gompertz fractional model is governed by gompertzian growth pattern where the tumor growth has a sigmoid shape with an inflection point, after which the growth slows down in time and converges to a plateau. In this model, the tumor volume growth is limited by a lack of cell nutrients. The equation describing the Gompertzian model is as follows (Hong and Zhang, 2019):

$$\dot{x_1} = a^f x_1(t) - b x_1(t) ln x_1(t) \tag{2}$$

where x_1 is the proliferation tumor volume in mm^3, a is the rate of growth of tumor volume in 1/day and b is the coefficient of tumor growth deceleration constant ($1/\mathrm{mm}^3 \cdot$day). The equation (2) was previously modified to include the fractional operator f that can be varied between 0 and 1.

The changing necrotic tumor volume is given by:

$$\dot{x_2} = n x_1(t) - w x_2(t) + E_{t_r} x_1 \tag{3}$$

where n is the necrotic rate of the tumor cells in 1/day, w is the washout rate of the necrotic tumor cells in 1/day. Including the effect of radiotherapy on the tumor cells, we obtain:

$$\dot{x_1} = a^f x_1(t) - b x_1(t) ln x_1(t) - n x_1 - (E_{t_r} x_1 + u_r) \tag{4}$$

while adding E_{t_r} the effect of radiotherapy on the tumor cells. The input that contains the fractionated ratios according to the treatment scheme is u_r in Gy/day. The overall output of the model y, giving the total tumor volume in mm^3, is:

$$y = x_1 + x_2 \tag{5}$$

2.2 PKPD Compartmental Model with Interaction Term

The PKPD model formulation considers the relevant characteristics for the tumor growth model under RT: tumor cell proliferation, necrotic volume and radiotherapy, including the interaction of tumor cells with RT. Instead of the Linear Quadratic model, the Incomplete Repair (IR) model has been used as it is more robust for the entire range of tumor cells radiosensitivity (Ionescu et al., 2020):

$$\begin{aligned} \dot{x_1} &= (a - n) x_1 - E_{t_r} x_1 \\ \dot{x_2} &= n x_1 + E_{t_r} x_1 \end{aligned} \tag{6}$$

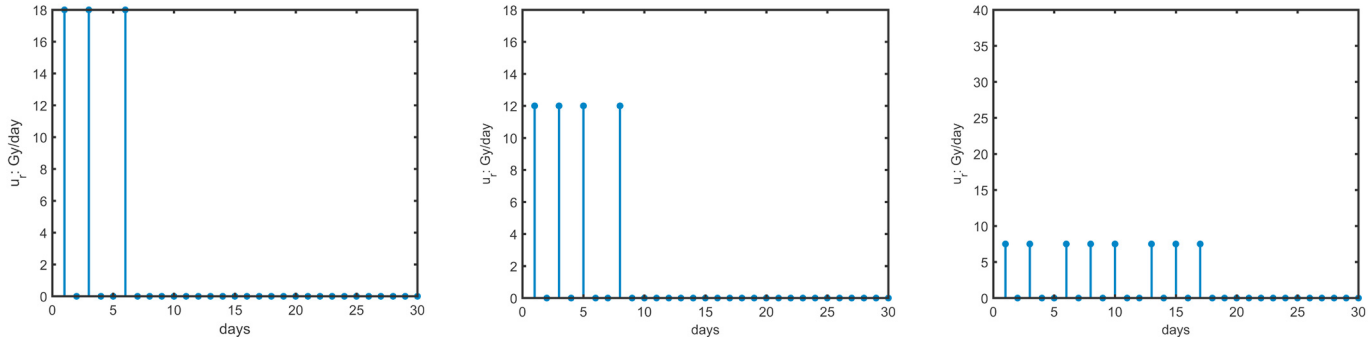

Fig. 1. Distribution of radiotherapy profiles for Patient 1 (left), Patient 2 (middle) and Patient 3 (right) with total dose representation of 54 Gy (single doses of 18 Gy), 48 Gy (single doses of 12 Gy) and 60 Gy (single doses of 7.5 Gy).

Interactions that occur when the functional effect of tumor cells come in contact with radiation therapy have been addressed in Ionescu et al. (2020). This approach enables the identification of event dynamics further introduced for both presented models:

$$\dot{x_3} = -c_r x_3 + u_r \tag{7}$$

$$\dot{x}e_3 = -c_r x e_3 + E_{t_r} x_3 \tag{8}$$

where c_r is the clearance of the radiation effect in 1/day, xe_3 is the effect of radiotherapy concentration and x_3 is the radiotherapy level in mg/(ml·day). The effect upon interactions of tumor cells with radiotherapy applied has been further described as:

$$E_{tumor/RT} = \frac{I^\gamma}{1 + I^\gamma} \tag{9}$$

where γ is the patient response and I the interaction term:

$$I_{t_r} = n_{nt} + n_{nr} + \sigma \cdot n_{nt} \cdot n_{nr} \tag{10}$$

where $n_{nt} = x_1/E_{50t}$ and $n_{nr} = xe_3/E_{50r}$ in $(1/\text{day}^3)$ are the normalized concentrations terms with respect to tumor cells and radiotherapy concentration, E_{50t} and E_{50r} in mg/ml are the associated half effect terms for tumor cells and RT, and σ is the synergy term.

2.3 Clinical Data and Protocol

Before commencing the study, ethical clearance was obtained from the Medical Ethics Committee, GZA Hospital Antwerp, Belgium (clinical study protocol RIMIRT no. CTOR20105GZA). All the applicable regulatory requirements were fulfilled. All involved patients provided written consent after receiving an explanation of the study. Data collection was done for patients with NSCLC and lung metastases eligible for SBRT according to the oncology center guidelines.

Three different treatment schedules used in the standard care path for SBRT were considered for modeling. No cancer-specific concomitant medications were administrated for these patients. The fractionated SBRT protocol and specific RT delivery days for the three patients are presented in Figure 1, according to the clinical protocol performed. The administrated radiation profiles are presented for patient 1 (initial tumor volume: 4.9 cm^3), patient 2 (initial tumor volume: 23.6 cm^3) and patient 3 (initial tumor volume: 63.1 cm^3). The tumor volume was assessed during CT-based simulations used for establishing the SBRT treatment, usually 7 to 14 days before starting the treatment delivery. The planning target volume (PTV) was considered for numerical simulations. PTV is preferably used in treatment planning to select appropriate beam sizes and beam arrangements for ensuring the delivery of the prescribed dose to the targeted internal tumor volume. MATLAB R2020B was used to carry out the simulations and statistical analysis.

3. RESULTS

In this paper, the simulations were carried for a period of time that included the clinical SBRT protocol and an extension until 30 days where no doses were given in the remaining days.

In the figures 2, 3, and 4, the blue stems indicate the total tumor volume and the red stems the necrotic tumor volume for the three patients. In these plots, the identical parameters in both models are kept constant for comparison and visualization purposes, while two parameters are varied for each set of figures. The mathematical models presented were used to predict the patient-specific responses to treatment expressed by tumor volume. The models were parameterized with patient data collected at diagnosis and literature-specific values. For both models, the value for growth rate a was kept constant at 0.56, leading to an increased final tumor as the higher rate of proliferation consists of a higher number of active tumor cells. For the validation of the proposed work, future simulations will include more clinical data, as well as values before and after the patient has undergone SBRT treatment.

3.1 Simulation results for the PKPD model

Figure 2 shows the representation of simulation results for the PKPD model. It can be observed that the end total tumor volume decreases for all patients. The decrease in the single fractionated doses from patients 1 to 3 corresponds to the increasing total tumor volume, though to a large extent, it also depends on the initial tumor volume. All parameters in the model were similar to the literature (Ionescu et al., 2020; Hong and Zhang, 2019; Talkington and Durrett, 2015). For all three cases, the total tumor volume and necrotic tumor volume decrease over the period of 30 days. In the case of the PKPD model, increasing the necrotic rate led to a decrease in the total

tumor volume. The active tumor cells were eliminated at a rapid rate due to the high n value, and this resulted in the decrease of overall tumor volume. A lower value of γ parameter indicated a more sensitive response to treatment and led to increasing end tumor volume, being a monotherapy. Therefore, γ was taken as 0.1, as at higher values of γ, very low values of total tumor volume were obtained. The synergy term σ was taken as a default value of 4. This behavior could be influenced by the use of a single therapy, instead of combined therapies, thus low to none synergy. However, the resulting total tumor volume is lower compared to a more realistic patient response.

3.2 Simulation results for the fractional Gompertz model

Figures 3 and 4 present the results obtained from the preliminary analysis of the fractional Gompertz model. The common parameters found in the two models such as necrotic rate (n=0.1), growth rate (a=0.56), and patient response (γ=0.1) were maintained at the same value as that in the PKPD model. The additional fractional component (f), washout rate (w), and the Gompertzian parameter (b) were varied from their original values used in the literature (Hong and Zhang, 2019). Two different values were envisioned for the f parameter (0.25 and 0.5), which may potentially capture a better description of tumor growth experienced in clinical practice. Closer inspection of the figure 4 shows a higher decrease in the tumor volume results presented for f=0.5, comparable with the results obtained for the PKPD model. It is apparent from these representations that the fractional-order parameter is capable of capturing the natural behavior of respiratory tissue (Ionescu and Kelly, 2017). As clinical guidelines predict, radiation-induced effects can influence the tumor volume to an extent of 3 months, after which the smallest tumor volume can be seen. Even better results in terms of smaller tumor volume after 30 days can be observed for figures 2 and 4 compared to 3. Such a trend may indicate that smaller f values may successfully describe the realistic tumor dynamics for more than one month.

In the Gompertzian model, the fractional component f was added to improve its performance. Two sets of simulations were obtained for two different values of f=0.25 and f=0.5. The results showed that for the lower value of f (Figure 3), increased (but more realistic) end tumor volume is obtained compared to a higher value of f (Figure 4), closer to the clinical results (Vu et al., 2020). For both values of f, the tumor volume increases accordingly to the initial tumor volume. However, the initial tumor volume and the protocol play a significant role in determining the end tumor volume. Comparison with more patient data and statistical analysis is part of future work.

Another influencing parameter in the Gompertzian model is b, with lower values resulting in higher tumor end volume. The limiting factor b is related to nutrients, or rather lack of nutrients around the tumor cells. With the growth of tumor cells, the nutrients gradually decrease which limits the growth of active tumor cells after one point. A higher value of b corresponds to a higher growth limitation, which decreases the total tumor volume. With radiation therapy, many of the active tumor cells are destroyed, leaving the surviving tumor cells with more access to nutrients. This explains the increase in tumor end volume with a corresponding decrease in b value.

The decrease in washout rate w led to an increase in the tumor end volume. The washout rate defines the rate at which the necrotic tumor volume is cleared away from the tumor site. RT at the tumor site affects the tumor cells, together with the surrounding healthy cells, even if the exposure is reduced with SBRT. The washout mechanism can be affected by high-energy radiation. The rate of washout is reduced resulting in a much slower removal of dead tumor cells. The necrotic rate n behavior is different compared to the PKPD model as increasing the necrotic rate increased the total tumor volume. This behavior can be explained due to the presence of washout rate w used to control the rate of outflow of dead tumor cells. If the necrotic rate increases, then the dead tumor volume increases as a part of the total tumor volume. As the washout rate is quite low, these dead cells are washed away at a much lower rate, indicating that they are present at the tumor site for a much longer time.

3.3 Statistical analysis

Results were analyzed using a one-way analysis of variance (ANOVA). The tests were performed to compare the performance of the presented models, by determining whether there are statistically significant differences between the means of the 3 groups. A statistically significant difference (p-value ≤ 0.05) was apparent for each patient grouping the three model cases, even if tumor volume decreases with treatment applied.

The tumor volume reported using CT images on the treatment simulation day was used as the baseline for comparison. Taking into consideration the results obtained from computer simulations, the tumor volume changes were further examined. The percentage change in tumor volume (TV), on comparing the values on the simulation day (TV_{day0}) with the obtained values for 30 days period including treatment (TV_{day30}), was calculated using the following formula: $TV_{change}(\%) = \frac{TV_{day30} - TV_{day0}}{TV_{day0}}$. Using the PKPD model for simulations, the results showed a tumor volume decrease between 97-99%. By contrast, the fractional Gompertz model with fractional operator f=0.25 provides a varied decrease in TV depending on each patient: 29% (P1-smallest initial TV and second highest total RT dose), 78% (P2-smallest total RT dose) and 91% (P3-highest initial TV and total RT dose).

4. DISCUSSION

A high-quality SBRT strategy involves comprehensive techniques to create a multi-professional development, implementation, and practice of the SBRT (Guckenberger et al., 2017). Building a multidisciplinary approach may foster the transition of research to clinical practice by consolidating the collaboration of researchers and professionals, both medical and engineers (Lievens et al., 2019).

Currently, treatment scheduling in NSCLC patients remains open field research. The practical working of mathematical equations may result in the prediction of treatment outcomes carefully using fractionation experiments, comparable to real practice. The larger radiation fractions used

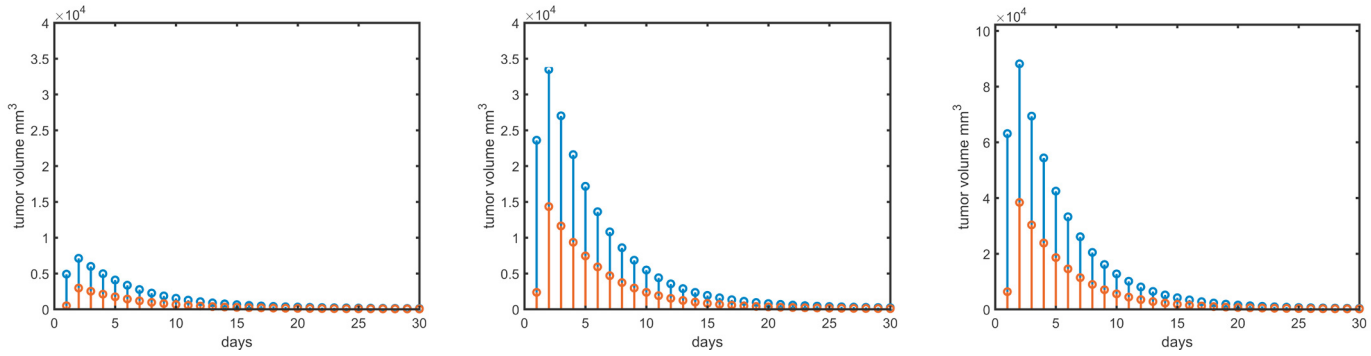

Fig. 2. Numerical predictions for tumor growth using PKPD model in Patient 1 (left), Patient 2 (middle) and Patient 3 (right); blue stems represent the total tumor volume, while red stems indicate the necrotic tumor volume.

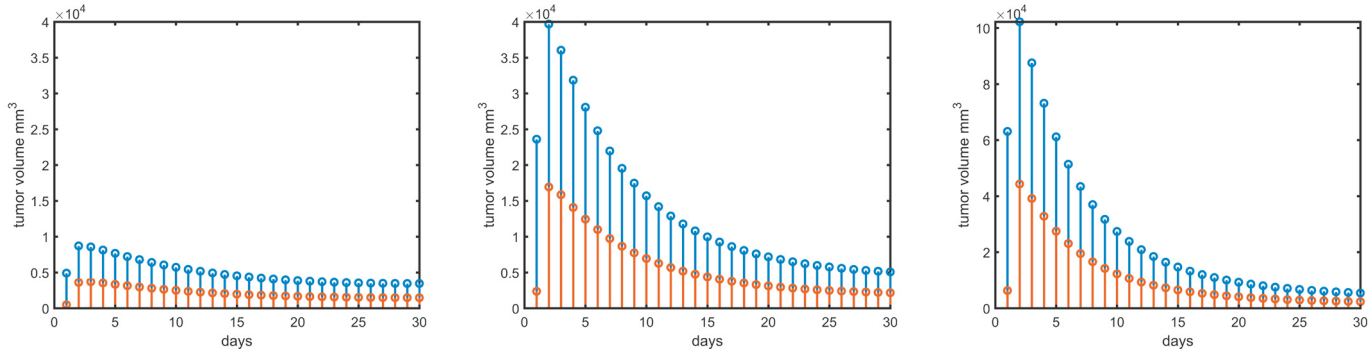

Fig. 3. Numerical predictions for tumor growth using fractional Gompertz model (with f=0.25) in Patient 1 (left), Patient 2 (middle) and Patient 3 (right); blue stems represent the total tumor volume, while red stems indicate the necrotic tumor volume.

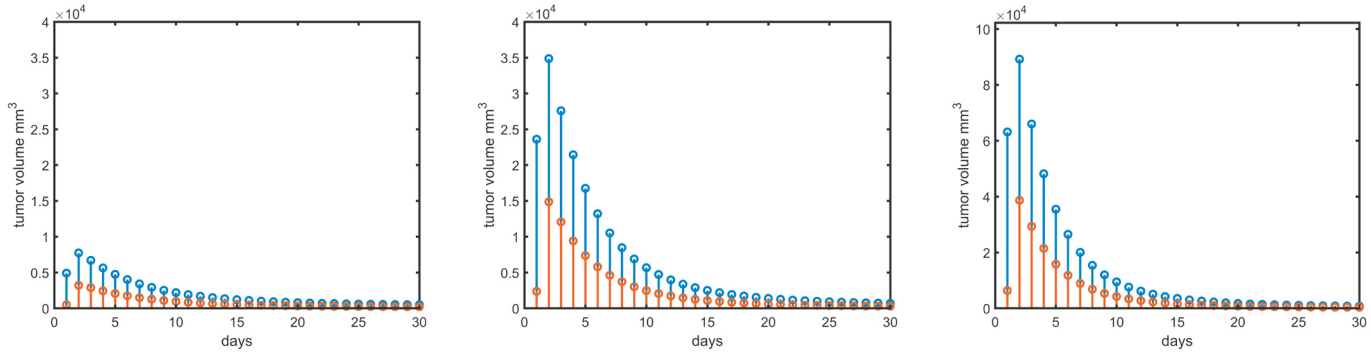

Fig. 4. Numerical predictions for tumor growth using fractional Gompertz model (with f=0.5) in Patient 1 (left), Patient 2 (middle) and Patient 3 (right); blue stems represent the total tumor volume, while red stems indicate the necrotic tumor volume.

in SBRT produce a reduction in the possibility of tumor proliferation and repopulation, as well as an increase of tumor control probability (TCP) (Verellen et al., 2007). The models comprise patient and disease-specific characteristics capable to qualitatively reproduce tumor growth response to radiation therapy. Heterogeneous study designs make it impossible to summarize a general conclusion for changes in tumor volumes with respect to treatment outcome (Käsmann et al., 2018).

The mathematical models considered for this work require further fine-tuning of parameters that best reflect all physiological and biological conditions of the patient. These findings will be further tested after assessment of the tumor volume in the same patients, three months after treatment. This will allow us to compare these encouraging results in tumor dynamics with real data, by extending the simulation time to 90 days. Unfortunately, the clinical protocols usually require that a CT scan have to be performed 3-6 months after the delivery of the last dose of radiotherapy, limiting the radiation exposure for the patients compared with monthly CT scans.

The models are not capable of reflecting the tumor increase during treatment due to inflammation. Both a decrease and an increase in inter-fractional tumor volumes have been previously reported in different studies (Vu et al., 2020). Rapid tumor volume decrease is expected during SBRT or immediately after, due to the tumor's sensitivity to radiation. But an increase in tumor volume can be

a reflection of inflammation that occurred at the site of administration.

Another study limitation is the finite number of patients. We need a larger cohort of patients to validate the proposed models for the same treatment strategies. Our primary purpose was to investigate the changes in parameters according to tumor volume and dose fractionation. Further research is needed to optimize the modeling approaches for reflecting the tumor decrease according to clinical data acquired during a follow-up visit for an increased number of patients. Even so, extended research will consider a much larger period of time to update the model parameters and validate the predictive values to real clinical data for most-used clinical strategies in SBRT.

5. CONCLUSION

In this paper, we derived clinical-based solutions for two different tumor growth models. The choice of the model can lead to similar prediction outcomes but vary significantly with the change in parameters. We have investigated a novel fractional Gompertz model and a PKPD model scaled up for NSCLC patients treated with conventional SBRT schemes. According to the simulation results for the particular clinical data used, the models were able to characterize the tumor dynamics in a 30 days simulation. Therefore, the lung tumor volume observed following SBRT administration is decreasing for all simulations. With tumor volume values too close to 0 after one month for part of the simulations, the fractional Gompertz model permits changes in tumor volume to more realistic values due to the inclusion of the fractional parameter.

The extension of this study will include modeling concurrent therapies, increasing simulation time, and analysis of more patients treated with the same SBRT scheme or total dose of radiation.total dose of radiation. Therefore, the synergy between treatments can be further validated and explored using both models and their performance can be evaluated. Of particular clinical interest is the assessment of the effect of radiation on neighboring healthy cells and tissue. Furthermore, prediction of radiation-induced toxicity can be achieved to identify optimum radiation administration schedules. The extent and impact of this research should be dispersed over an enlarged period of time to quantify and validate the approach.

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