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Numerical Simulation and Optimization of Radiotherapy Cancer Treatments Using the Caputo Fractional Derivative

Faraloya, M. F. [1], Shafie, S. [*1], Siam, F. M.[1], Mahmud, R. [2], and Ajadi, S. O.[3]

[1]*Department of Mathematical Sciences, Faculty of Science, Universiti Teknologi Malaysia, Malaysia*
[2]*Imaging Department, Faculty of Medicine and Health Sciences, Universiti Putra Malaysia, Malaysia*
[3]*Department of Mathematics, Faculty of Science, Obafemi Awolowo University, Nigeria*

E-mail: sharidan@utm.my
[*]*Corresponding author*

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Abstract

This paper presents an improved numerical simulation and optimization of radiotherapy cancer treatments. The model used was obtained by integrating the Caputo fractional derivative and the linear-quadratic with the repopulation model into the previous radiotherapy cancer treatment model. Taking advantage of the existing model factors and parameters, especially the clinical data of six cancer patients treated with radiotherapy, the resulting model equations were simulated in MATLAB. The Caputo fractional derivatives were evaluated by using the fractional differential equation code (FDE12.m). The biologically effective dose formula was used to obtain six regression equations that were used for determining the appropriate fractional-order for each radiation protocol. Thereafter, the simulations were done in four cases. First, the fractionated doses of six patients were varied from 1.0 Gy to 6.0 Gy. Secondly, the fractionated doses were also varied from 1.0 Gy and 6.0 Gy but with 20 fractions. Thirdly, the doses of the six patients were unaltered but the number of fractions was varied from 25 to 35 fractions. Finally, a single regression equation was used to simulate the six patients' cancer treatment. The simulations had minimal errors and it was concluded that the simulated results are better predictions of the different radiation protocols.

Keywords: Radiotherapy; caputo fractional derivative; radiation protocols; optimal cancer treatment.

1 Introduction

Cancer is an acknowledged global disease and has attracted commensurate global attention from researchers in different disciplines. Therefore, cancer treatment is of paramount importance to many world leaders with various contributions from researchers. Unfortunately, despite these contributions, the disease still has a high mortality rate especially amongst women and the elderly, and in North America, it is ranked as the second major cause of death after heart disease [8]. The cancer treatment procedure is either aimed at being a curative or a palliative measure. However, irrespective of the treatment's aim, the cancer patient is always optimistic of being completely cured. The medical practitioner, on the other hand, is not only interested in the treatment but also the outcomes and effects of such treatments on the patient. As a result, it is important to have a foreknowledge of the outcomes of different cancer treatment procedures.

There are several clinical procedures for treating various cancer types including surgery, immunotherapy, radiotherapy, and chemotherapy [8]. At times, one or more procedures can be combined for a patient. In this article, the focus is on radiotherapy. Radiotherapy is the most cost-effective treatment procedure because it accounts for only about five percent of the total cost of treatment and it can also be used for curative or palliative purposes [6]. For a successful radiotherapy treatment process, it is imperative to monitor the progress of treatment by knowing the effects of radiation on both the tumor and the patient. Furthermore, a foreknowledge of treatment outcomes for different radiation protocols will assist the medical team to choose an optimal radiation schedule. But apart from clinical records, mainly based on the results of clinical trials and the use of animal models, is it possible to know the outcome of a radiation schedule or predict an approximate result of a radiation protocol? To answer this important question, the use of mathematical models has proven to be very significant. Generally, a mathematical model represents a real-life process and from this model, the process can be analyzed and future outcomes predicted.

There have been many proposed mathematical models aimed at describing the radiotherapy cancer treatment process. Some of these models approached the cancer treatment process from the molecular or cellular point of view while some treated the tumor as a system or body that grows uniformly. In this article, we focus on the latter type of models. The most prominent of these latter types of models is the cancer treatment model proposed by Belostotski and Freedman [8]. The cancer treatment model was based on the Lotka-Volterra competitive model and it represented the process by assuming that the cancer region was made up of two competing species. The two competing species are the cancer cells and normal cells. The proliferation of the cells was represented with proliferating coefficients and this proliferation followed a logistic equation pattern with a carrying capacity bounding the populations of the cells. Although cancer and normal cells proliferate, the proliferation of the cancer cells is uncontrollable and is much more aggressive resulting in the formation of a tumor which can lead to the death of the patient if not treated. Since cancer and the normal cells are in continuous competition for resources, the cells populations will decrease due to this competition. In the cancer treatment model, Belostotski and Freedman [8] represented this feature with competition coefficients. Furthermore, the administration of radiation greatly reduces the population of the cancer cells. The cancer cells population decay due to radiation was represented by a harvesting control mechanism in the model.

However, the bottleneck of the model proposed by Belostotski and Freedman [8] was the assumption that only the targeted rapidly proliferating cancer cells were affected by the radiation doses while the slowly proliferating normal cells were spared. This assumption goes against clinical evidence because the radiation also affects the untargeted normal cells [26]. Therefore, the cancer treatment model was improved by Freedman and Belostotski [21] with the inclusion of a perturbation constant to account for the normal cells population decay. Also, the improved cancer

treatment model presented by Freedman and Belostotski [21] was analyzed numerically by Liu and Yang [25]. But the analysis was not done with clinical data, giving room for more work.

In continuation, Dokuyucu, et al. [16] modified the cancer treatment model with the integration of the Caputo-Fabrizio fractional derivative into it. The fractional derivative model presented by Dokuyucu, et al. [16] had the same structure as that presented by Freedman and Belostotski [21]. The only distinction was that the ordinary derivative was replaced with the Caputo-Fabrizio fractional derivative. Dokuyucu, et al. [16] established the existence of unique solutions for their model using the fixed point theory. Furthermore, Awadalla, et al.[4] integrated the Hadamard fractional derivative into the cancer treatment model. Similarly, Awadalla, et al. [4] established the existence of unique solutions for the model. The integration of fractional derivatives into the cancer treatment model included the memory feature, which is part of all biological processes, into the model. Although this integration improved the cancer treatment model, the establishment of unique solutions is a mathematical exercise that might not be meaningful to a typical medical practitioner. Therefore, it became necessary to give the cancer treatment model a clinical relevance.

As a result of this necessity, the cancer treatment model was used to simulate cancer treatment processes of cancer patients treated with fractionated radiotherapy by Farayola, et al. [19]. This was done by integrating the Caputo fractional derivative into the cancer treatment model and the cells population decay due to radiotherapy was accounted for with the linear-quadratic model. This work was later extended by the same authors with the inclusion of the repopulation of cancer cells into the linear-quadratic model [18]. In the extended work, the biologically effective dose (BED) was used to simulate 96 different radiation protocols from the clinical data of six cancer patients treated with radiotherapy. These 96 radiation protocols were used to obtain a linear regression equation for obtaining the value of the Caputo fractional derivative from the value of the fractionated dose. Although Farayola, et al. [18] simulated the cancer treatment process of six cancer patients and compared the results with the clinical data, some critical questions still need clarification. These questions include, how can the cancer treatment model be used to predict results for different radiation protocols such as with different doses, with a different number of fractions, and when the number of fractions is reduced to avoid repopulation of cancer cells? Furthermore, can the radiotherapy cancer treatment be optimized, and which radiation protocol produces optimal treatment, or which radiation protocols will produce complete treatment?

In this article, these questions were addressed, and various radiotherapy cancer treatments were simulated with different radiation protocols. The clinical data of six cancer patients treated with radiotherapy were used and the values of the Caputo fractional derivative were obtained with regression equations. The simulations were done in four parts, the first part includes simulations with 500 different doses between 1.0 Gy and 6.0 Gy with the same number of fractions. Furthermore, the accuracy of these simulations was investigated by comparing the six clinical final tumor volumes with their corresponding simulated final tumor volumes. The second part comprises 500 different doses between 1.0 Gy and 6.0 Gy with the same number of fractions that excluded the repopulation of the cancer cells, and the third part involves 11 different fractions with the same dose. The fourth part involves the simulation of the patients' treatment with a single regression equation. From these simulations, the different radiation protocols were analyzed. These analyses were done from a mathematical point of view with the population of eliminated cancer cells representing cancer treatment and the population of eliminated normal cells representing normal cells damage. Also, the optimal cancer treatment solutions and the complete cancer treatment solutions were obtained.

This article is organized into sections. In Section 2, the methods used for the simulations which include definitions of the Caputo fractional derivative, the mathematical model, the numerical

and radiation parameters, the population variables, and the model factors are presented. Furthermore, the regression equations for evaluating the values of the Caputo fractional derivatives are presented. Also, the numerical simulations of the radiotherapy cancer treatment process of six patients are carried out in four parts with various radiation protocols. In Section 3, the results of the simulations and the optimal and complete treatment solutions are presented. In Section 4, the results and interpretation of findings are explained and discussed. Lastly, the article is concluded with a summary of the potential implications of this research and suggestions for further research.

2 Method

This section presents definitions and numerical simulations of the radiotherapy cancer treatments.

2.1 Caputo Fractional Derivative

Definition 1. The Caputo fractional derivative [11] was given by equation (1)

$$ {}_0^C D_t^{\mu}(f(t)) = \frac{1}{\Gamma(1-\mu)} \int_0^t \left(\frac{1}{(t-x)^{\mu}} \right) \frac{d}{dx} f(x) dx, \qquad 0 < \mu < 1, \tag{1} $$

where $f(t) \epsilon H^{/}(0,b)$, $H^{/}$ is a Sobolev space.

There are various definitions of fractional derivatives presented by different authors [12]. However, amongst these definitions, the most popular ones are the Reimann-Liouville fractional derivative and the Caputo fractional derivative. But the Reimann-Liouville fractional derivative of a constant is not zero while the Caputo fractional derivative of a constant is zero. Therefore, the Caputo fractional derivative is more useful for modeling physical processes than the Reimann-Liouville fractional derivative. Furthermore, the Caputo fractional derivative has non-kernel versions which are the Caputo-Fabrizio fractional derivative [11] and the Atangana Baleanu Caputo fractional derivative [3]. But, at present, the standard MATLAB codes for solving these non-kernel versions have not been formulated. The Caputo fractional derivative has a comparative advantage because the standard MATLAB codes FDE12.m and FLMM2.m can be used for solving the fractional derivatives. The FDE12.m code was jointly written by Diethelm [13], Diethelm, et al.[14], Diethelm and Freed [15], Garrappa [22], and Hairer, et al. [23]. The FLMM2.m code was written by Garrappa [22]. Therefore, the Caputo fractional derivative was used in this article with the FDE12.m chosen to solve the fractional derivatives in the fractional differential equations. The FDE12.m code is easier to use because it does not require obtaining the Jacobian matrix which is always required when using the FLMM2.m code.

2.2 The Mathematical Model

The radiotherapy cancer treatment model formulated and presented by Farayola, et al. [18] was given by equations (2) and (3). The equations (2) and (3) were formulated by improving the previous cancer treatment model proposed by Belostotski and Freedman [8] which was later extended by Freedman and Belostotski [21].

$$
\begin{aligned}
{}_0^C D_T^{\mu}(u_1(t)) &= \alpha_1 \left(1 - \frac{u_1}{K_1}\right) u_1 - \beta_1 u_2 u_1 - \\
\varepsilon \left[\alpha s(t) + 2\beta s(t) \left(\int_0^t \left[exp(-\lambda(t-\tau))\right] s(\tau) d\tau\right)\right] u_1, \qquad (2)
\end{aligned}
$$

$$
\begin{aligned}
{}_0^C D_T^{\mu}(u_2(t)) &= \alpha_2 \left(1 - \frac{u_2}{K_2}\right) u_2 - \beta_2 u_1 u_2 - \\
\left[\alpha s(t) + 2\beta s(t) \left(\int_0^t \left[exp(-\lambda(t-\tau))\right] s(\tau) d\tau\right) - \frac{ln2}{T_p} \frac{(T_d - T_K)}{T_d}\right] u_2, \qquad (3)
\end{aligned}
$$

where,
u_1, u_2 are the populations of normal and cancer cells respectively,
α_1, α_2 are the respective proliferation coefficients of the cells,
K_1, K_2 are the carrying capacities of the normal and cancer cells respectively,
β_1, β_2 are the respective competition coefficients of the cells,
ε is the perturbation constant,
${}_0^C D_T^{\mu}$ is the Caputo fractional derivative with fractional-order μ,
α is the yield rate for lethal lesions,
β is the yield rate for sublethal lesions,
T_d is the total time of treatment (number of days),
T_K is the "kick-off" time for the repopulation of the cancer cells,
T_p is the effective doubling time of the cancer cells,
$s(t)$ is the time-varying fractionated dose rate,
λ is the repair time constant defined as $\frac{ln(2)}{T_{\frac{1}{2}}}$,
T is the total time for radiotherapy,
t is the time for each fractionated dose, and
$T_{\frac{1}{2}}$ is the half time for repair.

The model equations (2) and (3) represented the radiotherapy treatment process. The equations included the competing species and the time of treatments represented by model variables, the proliferation and the competition of cells represented by model factors, the change in the populations of the cells over the treatment time interval represented by the Caputo fractional derivative, the memory feature of the biological process represented by the fractional-order of the derivative, the effect of radiation on the normal cells represented by perturbation constant, and the cells population decay due to radiation doses represented by the linear-quadratic with the repopulation model. The model factors and variables included in equations (2) and (3) are time-dependent, therefore assigning accurate values for them might be difficult. However, to simulate the radiotherapy cancer treatment process, numerical values were assigned to represent these factors and variables. These numerical values were obtained from previous publications and reported clinical data. The model variables and factors with their corresponding numerical values were presented in the next sections.

2.3 Competing Species u_1, u_2

In a cancer region, the two competing species are cancer and normal cells. The populations of cancer and normal cells are proportional to the volumes occupied by the tumor and normal cells

respectively. For the cancer cells, 1 cm^3 of the tumor contains approximately 1 billion cancer cells [9]. Therefore, a patient with a tumor volume of 15 cm^3 will have the cancer cells initial population to be 15×10^9. As for normal cells, obtaining the initial population might pose a challenge therefore the initial population was assigned the same value as that of the cancer cells. This is a valid mathematical assumption because the important value used for analysis is the difference between the initial and final population of the normal cells and not the actual value of the initial population. For simulations, the initial cells populations were scaled to 1. Therefore, the initial cell population of 15×10^9 cells will have a scaled value of 0.15 signifying a volume of 15 cm^3. The initial populations used for the simulations were obtained from the initial tumor volumes of six cancer patients treated with radiotherapy [7].

Although cancer and normal cells proliferate, the cancer cells proliferate more rapidly. The proliferating coefficients α_1, α_2 of the cells can be obtained from the growth fractions. The equation relating the proliferating coefficient and the growth fraction was given by equation (4). The growth fraction for the cancer cells is approximately 0.49 and for the normal cells, it is approximately 1.4×10^{-3}[8]. Therefore, the proliferating coefficients for cancer and normal cells were assigned the numerical values of 0.3396 and 9.7041×10^{-4} respectively.

$$\alpha_i = GFln2 \qquad i = 1, 2, \tag{4}$$

where,
α_i is the proliferating coefficient
GF is the growth fraction for the cells.

During the proliferation of cells, the populations of cells approach maximum values which are the carrying capacities. Since the populations were scaled to 1 and the proliferation followed a logistic equation, the carrying capacities K_1, K_2 of the normal and cancer cells were assigned the value of 1. Furthermore, after the radiotherapy treatment, the populations of the cells decrease. The population of the eliminated cancer cells signifies cancer treatment while it can be assumed that the population of the eliminated normal cells will indicate the extent of normal cells damage associated with the radiotherapy cancer treatment process. Finally, the simulation of the treatment process with the scaled initial populations produces scaled final populations of cells. The scaled final populations will give the final tumor volumes and the volume occupied by the normal cells respectively. For instance, a scaled final population of 0.03 will give a final volume of 3 cm^3 with a population of 3×10^9 cells.

In continuation, the normal and cancer cells are in continuous competition for space and survival. Generally, the normal cells need oxygen for survival while the cancer cells need sugar or glucose for survival. Therefore, the competition process was represented by competition coefficients β_1, β_2 . The values for the competition coefficients are not certain, but numerical values can be assigned with the use of inequalities (5) and (6) presented by Belostotski and Freedman [8], Freedman and Belostotski [21], and Liu and Yang [25]. As a result, the values of $\beta_2 = 0.2385$ and $\beta_1 = 0.0433$ were assigned for the competition coefficients of cancer and normal cells respectively.

$$\frac{\alpha_1}{\beta_1} < K_2, \tag{5}$$

$$\frac{\alpha_2}{\beta_2} > K_1. \tag{6}$$

Finally, the independent variable for the process is the time of treatment. The six patients were treated with fractionated schedules. External radiotherapy is like having a regular x-ray, the treat-

ment is a painless one and it takes only some minutes. Each session (fractionated dose schedule) can last for 15 to 30 minutes because of the time it takes to set and put the patient in the right position [2]. Therefore, in the numerical simulations, the time for each fraction t was assigned the value of 15 minutes while the entire treatment time T was the cumulated time for the fractions, and it was obtained by multiplying the number of fractions by 15 minutes . It is noteworthy to state that the entire treatment time T in the model is the summation of the fractionated times t and not the number of minutes in the total treatment days.

2.4 Radiotherapy Process and its Parameters

The radiotherapy process decreases the populations of the cancer cells as well as that of the normal cells. The perturbation constant was used to represent the effect of radiation on the normal cells. The value of 0.0008 (0.08%) was used for the perturbation constant because it was assumed to be less than 0.1% [21]. During radiotherapy, the destruction of the cancer cells to the radiation dose always follows a linear-quadratic path. The one-track linear path is the lethal lesion where the radiation dose is proportional to the population of eliminated cancer cells and is caused by double-stranded DNA breaks. This was represented by the yield rate of the lethal lesion α. The quadratic path is the sub-lethal lesion characterized by single-stranded DNA breaks. The yield rate of the sub-lethal lesions was represented by β . However, the linear-quadratic model is a single equation with two variables α and β . Therefore, to assign values to α and β, the radiosensitivity dose $\left(\frac{\alpha}{\beta}\right)$ was used. The radiosensitivity dose is the dose at which the linear and the quadratic part of the linear-quadratic model are equal. The radiosensitivity dose for early responding tissues and cells is generally 10 Gy. The six cancer patients considered were treated for uterine cervical cancer of the Squamous Cell Carcinoma (SCC) which is an early responding type. Since the cancer cells are proliferating rapidly then it is also early responding. Therefore, the radiosensitivity value of 10 Gy was assigned for the normal and cancer cells. So, the values of 0.3 and 0.03 were used for α and β respectively. Furthermore, the time in between fractionated doses causes the cancer cells to repair. The repair time constant λ can be obtained from the half time for repair $T_{\frac{1}{2}}$. The repair time for early responding tissues is approximately 30 minutes [10].

Finally, after about 4 weeks of treatment, the cancer cells will start repopulating [20]. The rate of repopulation $\frac{ln(2)}{T_{\frac{1}{2}}}$ is approximately 0.6 Gy/day [20]. The "kick-off" time for the repopulation to begin is approximately 28 days [20] and the number of days for treatment was obtained from the number fractions. Clinically, the fractionated doses are administered five times in a week, therefore 25 fractions will cover 5 weeks making a total of 35 days for T_d . The numerical values for the model factors and parameters were summarized in Table 1, while Table 2 gives a summary of the reported clinical data [7] of the six cancer patients.

Table 1: Numerical values for model factors and parameters

Numerical Parameters	Numerical Values
α_1	9.7041×10^{-4}
α_2	0.3396
β_1	0.0433
β_2	0.2385
K_1	1
K_2	1
ε	0.0008
$\alpha\ (Gy^{-1})$	0.3
$\beta\ (Gy^{-2})$	0.03
t (mins)	15
$T_{\frac{1}{2}}$ (mins)	15
T_K (days)	28
Rate of repopulation	0.6

Table 2: Reported clinical data of six cancer patients treated with fractionated radiotherapy

Patient	Initial Vol. cm^3	Final Vol. cm^3	Fractionated Dose (Gy)	Number of Fractions	Total Dose (Gy)	Initial Pop.
1	24.1	3.59	2	25	50	0.241
2	17.4	8.61	2	25	50	0.174
3	28.4	5.67	1.8	25	45	0.284
4	18.8	4.36	1.8	28	50.4	0.188
5	30.6	5.74	1.8	28	50.4	0.306
6	12.6	6.11	1.8	25	45	0.126

2.5 Memory Factor of Radiotherapy and the Fractional-Order μ

The biological process of radiotherapy is characterized by two important features. The two features are the interval of the process and the memory. The interval part of the process can be included in the time variables, but the memory part is more subtle. The characteristics of most biological systems are that they exhibit memory effects, for instance, the delay caused by the incubation time of vectors to become infectious [1].The non-local property of fractional derivative makes it suitable for measuring the memory effect of real-life processes, unlike ordinary derivatives that are local and instantaneous. Since the radiotherapy process is a biological process, the fractional derivative model is more suitable. It has also been established that biological models formulated with fractional order differential equations presented more realistic results than those of integer order differential equations [5].

This memory effect was given a physical interpretation by Du, et al. [17]. In [17] used Scott-Blair's model to show that the fractional-order is an index of memory for the process. The fractional-order of zero indicates that nothing was memorized while the fractional order of 1 indicates that nothing was forgotten. Many physical processes fall between these two extremes, for instance, viscoelasticity materials operate between elasticity (which obeys Hooke's law where nothing was memorized) and viscosity (which obeys Newton's viscosity law where nothing was forgotten). Therefore, a viscoelastic process should be modeled with a fractional derivative with an order between 0 and 1. Du, et al.[17] used the fractional derivative model to fit the three-point bending test data of a viscoelastic creep of SiAYON ceramics at 12000C and 240 MPa. By using a fractional

order of 0.44, the model fitted SiAYON ceramics specimen perfectively for a time interval of 400 minutes. In addition to viscoelastic processes, the authors showed that the fractional derivative models are most suitable for modeling biological kinetics and processes because they are associated with memory. This was shown by fitting the protein absorption kinetics of fibronectin over 1150 seconds using a model with fractional order of 0.435. The results showed a good fit of the model with test data. Also, the fractional derivative model was applied to cognitive dynamics in psychology by fitting the memorizing data implemented by Hermann Ebbinghaus, which was reported in the year 1885, with a fractional order of 0.71 and the model fitted well with the test data. Based on these results, it can be concluded that fractional derivative models are suitable for describing memory-based processes in different fields. Radiotherapy cancer treatment, like many real-life processes, is memory-based, therefore fractional derivative models are more appropriate.

However, the choice of fractional-order for the model cannot be done randomly. For instance, all the three processes modeled by Du, et al.[17] had distinct fractional values, the use of a different fractional value would have given inaccurate results. Therefore, it can be concluded that each process must be modeled by a specific fractional order. The fractional-order is the most sensitive model factor in the model equations (2) and (3) [18] [19], therefore different radiation protocols (different fractionated doses and number of fractions) will have specific fractional orders. As a result, we obtained a regression equation for each patient from which the approximate fractional-order was obtained for each radiation protocol by using the value of the dose.

This was done with the biologically effective dose (BED) formula given by equation (7) [24]. The BED is the dose that gives the same biological effect as a radiation protocol.

$$BED = nd\left[1+\frac{d}{\left(\frac{\alpha}{\beta}\right)}\right], \tag{7}$$

where,
BED is the biologically effective dose (Gy),
n is the number of fractions,
d is the fractionated dose $s(t)$, and
$\left(\frac{\alpha}{\beta}\right)$ is the radiosensitivity dose which was 10 Gy.

The BED was used to produce different radiation protocols that gave the same effect as those given by the clinical radiation protocol of the six patients. For instance, the radiation protocol of 2.0 Gy with 25 fractions will have the same effect as 3.0 Gy with 16 fractions. The different fractionated doses, with their corresponding number of fractions, obtained with the BED ranged from 1.7 Gy to 3.0 Gy. After obtaining these radiation protocols, they were used in the model equations (2) and (3) as radiation parameters for simulations. During the different simulations, the different fractional orders of the Caputo fractional derivative μ which gave the same final tumor volumes as those in Table 2 were obtained. Subsequently, the regression equations connecting the fractional-order μ with the value of the radiation dose were obtained for each patient. Also obtained were the R^2 which indicated the accuracy of the regression equation based on the percentage of the captured data. The number of fractions was not included as a separate variable in the regression equations because it was already implied in the BED formula. The results of the radiation protocols obtained with the BED as well as their corresponding regression equations were presented in Tables 3-5.

Table 3: Radiation protocols and regression equations obtained with BED

Patient 1 BED = 60 Gy			Patient 2 BED = 60 Gy		
d	n	μ	d	n	μ
1.7	31	0.155	1.7	31	0.12816
1.8	29	0.15998	1.8	29	0.14903
1.9	27	0.1803	1.9	27	0.16834
2.0	25	0.1993	2.0	25	0.1863
2.1	24	0.2171	2.1	24	0.2029
2.2	23	0.2339	2.2	23	0.21846
2.3	22	0.2497	2.3	22	0.233
2.4	21	0.2646	2.4	21	0.2467
2.5	20	0.2789	2.5	20	0.2597
2.6	19	0.2925	2.6	19	0.27196
2.7	18	0.3054	2.7	18	0.2836
2.8	17	0.3178	2.8	17	0.2948
2.9	16	0.3297	2.9	16	0.3055
3.0	16	0.3408	3.0	16	0.315
$\mu = 0.1492d - 0.0989$ $R^2 = 0.9938$			$\mu = 0.1418d - 0.1001$ $R^2 = 0.988$		

Table 4: Radiation protocols and regression equations obtained with BED

Patient 3 BED = 53.1 Gy			Patient 4 BED = 59.472 Gy		
d	n	μ	d	n	μ
1.7	27	0.13776	1.7	30	0.13084
1.8	25	0.1588	1.8	28	0.1532
1.9	24	0.1783	1.9	27	0.17389
2.0	23	0.1965	2.0	25	0.1932
2.1	21	0.21379	2.1	24	0.2112
2.2	20	0.2301	2.2	23	0.2281
2.3	19	0.245	2.3	21	0.2442
2.4	18	0.25935	2.4	20	0.25924
2.5	17	0.27301	2.5	19	0.2735
2.6	17	0.2857	2.6	18	0.2871
2.7	16	0.2981	2.7	18	0.2997
2.8	15	0.31	2.8	17	0.3121
2.9	15	0.3207	2.9	16	0.3239
3.0	14	0.3317	3.0	16	0.3348
$\mu = 0.1473d - 0.1005$ $R^2 = 0.9897$			$\mu = 0.1549d - 0.1194$ $R^2 = 0.9893$		

Table 5: Radiation protocols and regression equations obtained with BED

Patient 5 BED = 59.472 Gy			Patient 6 BED = 53.1 Gy		
d	n	μ	d	n	μ
1.7	30	0.13537	1.7	27	0.1289
1.8	28	0.1566	1.8	25	0.1508
1.9	27	0.17626	1.9	24	0.17101
2.0	25	0.19467	2.0	23	0.1898
2.1	24	0.21181	2.1	21	0.2075
2.2	23	0.2279	2.2	20	0.224
2.3	21	0.2433	2.3	19	0.2395
2.4	20	0.2577	2.4	18	0.2541
2.5	19	0.2713	2.5	17	0.268
2.6	18	0.2842	2.6	17	0.2808
2.7	18	0.2962	2.7	16	0.2933
2.8	17	0.308	2.8	15	0.3053
2.9	16	0.3192	2.9	15	0.3162
3.0	16	0.3295	3.0	14	0.3272
$\mu = 0.1476d - 0.1031$ $R^2 = 0.9893$			$\mu = 0.1504d - 0.1137$ $R^2 = 0.9887$		

2.6 Numerical Simulation of Radiotherapy Treatments

A total of six patients were treated with specific radiation protocols as specified in Table 2. However, different radiation protocols were simulated for each of the patients. This was done in MATLAB by solving equations (2) and (3) with numerical values shown in Table 1. The Caputo fractional derivative was solved using the fractional differential equation code (FDE12.m). The radiation protocols were divided into four cases explained in the subsections below.

2.6.1 Case 1: Radiation protocols with the same number of fractions but varying doses

For each of the patients, the number of fractions was not changed but the doses were varied from 1.0 Gy to 6.0 Gy with an interval of 0.01 Gy. In the MATLAB code for each patient, the fractional-order of the Caputo fractional derivative in the FDE12.m code was assigned values using the regression equations. Therefore, during simulations, as the doses were changing their corresponding fractional orders were assigned. As a result, there were 500 solutions for each patient. The solutions were scaled final populations of the normal and cancer cells. From these scaled final populations, the final tumor volumes and the volumes occupied by the normal cells can be obtained as explained in Section 2.3. Furthermore, the percentage of cancer treatment and normal cells damage for each patient were calculated. The percentage of cancer treatment was obtained from the populations of the eliminated cancer cells while the populations of eliminated normal cells were used for the percentage of normal cells damage. The errors of the solutions were obtained by comparing the clinical data with their equivalent simulated radiation protocols. Thereafter, the optimal solutions, signifying the best treatment with the least normal cell damage were obtained.

2.6.2 Case 2: Radiation protocols with varying doses but without repopulation

The repopulation of cancer cells begins after 28 days, an equivalent of 20 fractions. Therefore, the number of fractions for each patient was made to be 20 fractions making the values of T to be 300, and the doses were varied from 1.0 Gy to 6.0 Gy with an interval of 0.01 Gy. Since there was no repopulation of cancer cells, the value of the rate of repopulation $\frac{ln2}{T_p}$ was made 0 in the MATLAB code for all the simulations. Similarly, the regression equations were used for assigning values to the Caputo fractional derivatives for each patient. Also, each patient's simulation had 500 solutions and the final populations of the cells, the percentages of cancer treatments and normal cells damage, and the optimal solutions were obtained.

2.6.3 Case 3: Radiation protocols with the same doses but different number of fractions

In this case, the doses for the patients were unchanged, therefore the values in Table 2 were used for the simulations with 11 different numbers of fractions. Since the doses were not varied, then the same Caputo fractional derivative values were used for each patient's 11 different fractions. The values of the Caputo fractional derivative used in simulating the six cancer treatments that were obtained in our previous work [18] were used. The number of fractions ranged from 25 to 35 and the corresponding T ranged from 375 to 525 with 15 minutes intervals. Also, the appropriate number of days for treatment T_d of each fraction was included in the MATLAB code. The final populations of cells and the percentage of cancer treatments and normal cells damage were obtained.

2.6.4 Case 4: Radiation protocols of the six patients with the same regression equation

In our previous work [18], we formulated a single regression equation from 96 protocols obtained from the six patient's radiation protocols. This single regression equation was used to assign values for the fractional orders for the six patient's simulations. Similarly, the final populations of cells were obtained and compared with the clinical data to investigate the errors.

3 Results

This section presents the results of the simulations according to the four cases.

3.1 Case 1: Radiation Protocols with the Same Number of Fractions but Varying Doses

The solutions of Case 1 were shown in Fig 1 to 6. The figures showed the final populations of the normal and cancer cells with varying doses ranging from 1.0 Gy to 6.0 Gy and interval 0.01 Gy.

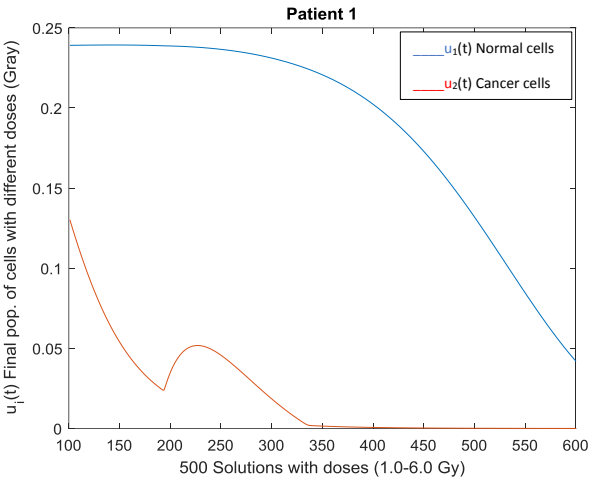

Fig 1: Final pop. of the normal and cancer cells for 1.0-6.0 Gy for Patient 1 (25 fractions)

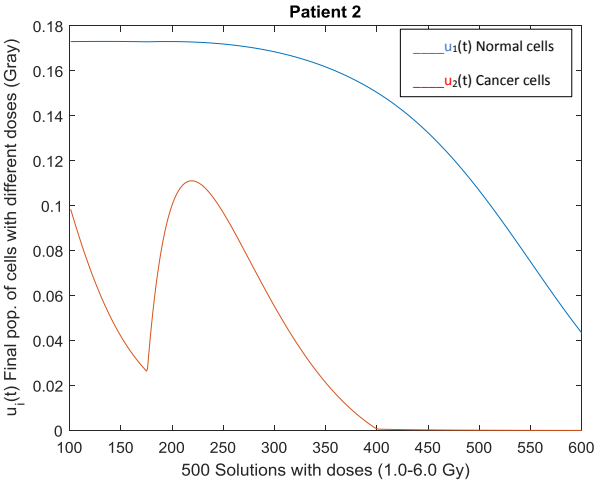

Fig 2: Final pop. of the normal and cancer cells for 1.0-6.0 Gy for Patient 2 (25 fractions)

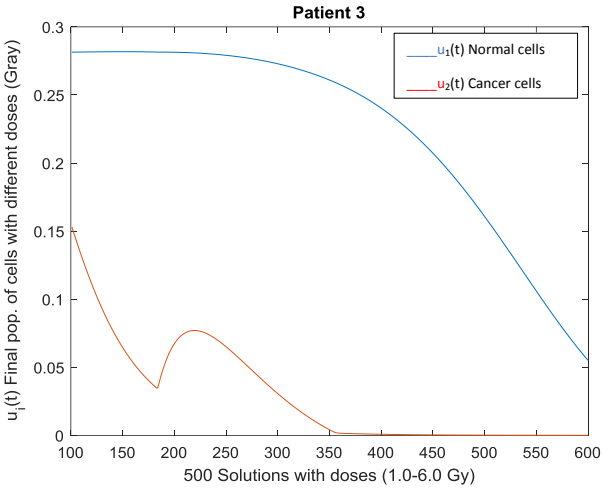

Fig 3: Final pop. of the normal and cancer cells for 1.0-6.0 Gy for Patient 3 (25 fractions)

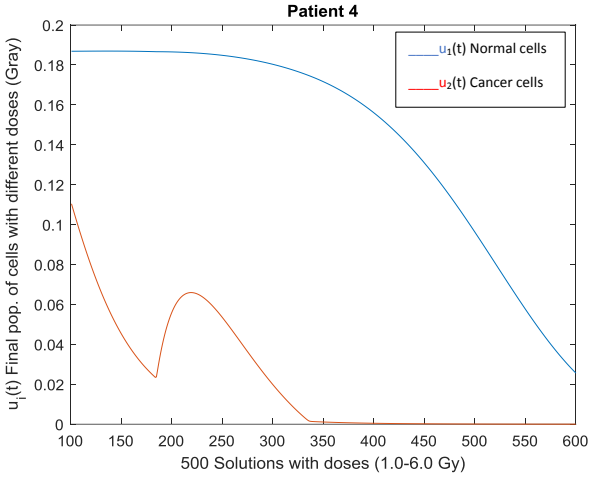

Fig 4: Final pop. of the normal and cancer cells for 1.0-6.0 Gy for Patient 4 (28 fractions)

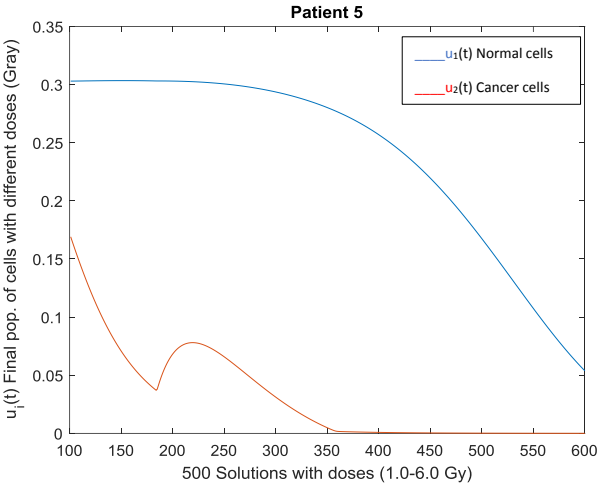

Fig 5: Final pop. of the normal and cancer cells for 1.0-6.0 Gy for Patient 5 (28 fractions)

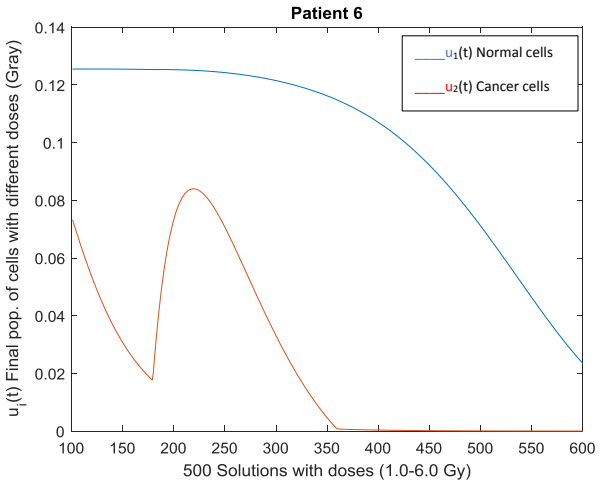

Fig 6: Final pop. of the normal and cancer cells for 1.0-6.0 Gy for Patient 6 (25 fractions)

The accuracy of these simulations was investigated by comparing the reported clinical data of the six patients with their corresponding simulated final tumor volumes in Fig 1-6. The corresponding simulations are those with the same radiation protocol (number of fractions and simulated dose) as the clinical data. In Table 6, the simulated results of the patients' corresponding radiation protocol were converted to tumor volumes and compared with the reported clinical values in Table 2, then the errors between the simulated and clinical final tumor volumes were obtained. The scaled final populations of cells were part of the 500 solutions obtained for each patient presented in Fig 1-6.

An important observation from Fig 1-6 is that when the values of the fractionated doses are between 1.8 Gy and 2.4 Gy, the final populations of the cancer cells increased in all the figures. This anomaly can be attributed to the high sensitivity of the fractional order of the Caputo fractional

derivative [18]. Since the simulated final populations of cells in the figures are obtained with regression equations, a slight deviation in the fractional-order will affect the result. For instance, the simulation of Patient 1 cancer treatment with a fractional order of 0.1993 gives a final cancer cells population of 0.0358 signifying a simulated final tumor volume of 3.58 cm^3. However, the regression equation for Patient 1 gives a fractional-order 0.1995 which gives a final cancer cells population of 0.0349. Therefore, the difference between the regression equation values and the exact values of the fractional orders is responsible for the slight anomaly in the figures within the range of 1.8 Gy and 2.4 Gy. Similar behavior is observed in the Case 2 simulations shown in Fig 7-12. This anomaly did not affect the normal cells populations.

Table 6: Results of radiation protocols of the six patients with the six regression equations

Patient	Scaled final pop. of Normal cells	Scaled final pop. of Cancer cells	Simulated final tumor vol.cm^3	Error cm^3
1	0.2387	0.0349	3.49	0.10
2	0.1730	0.1003	10.03	1.42
3	0.2815	0.0368	3.68	1.99
4	0.1867	0.0253	2.53	1.83
5	0.3032	0.0400	4.00	1.74
6	0.1253	0.0205	2.05	4.06

3.2 Case 2: Radiation Protocols with Varying Doses but Without Repopulation

The solutions of Case 2 were shown in Fig 7-12. The figures showed the final populations of the normal and cancer cells with varying doses ranging from 1.0 Gy to 6.0 Gy and interval 0.01 Gy for 20 fractions to avoid repopulation.

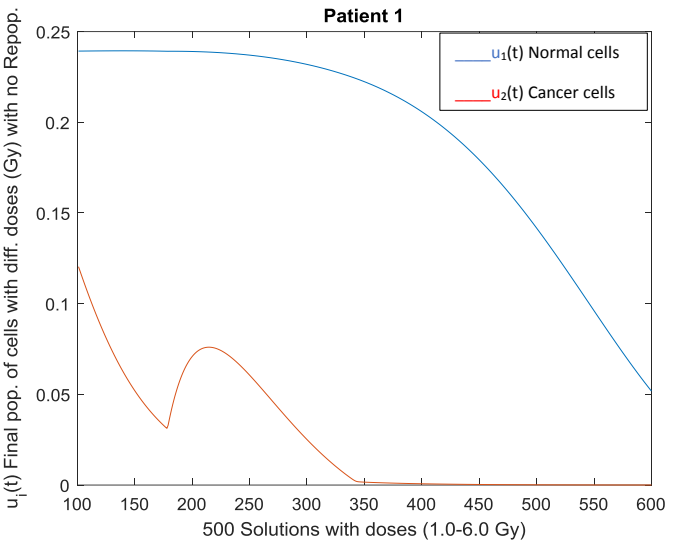

Fig 7: Final pop. of the normal and cancer cells for 1.0-6.0 Gy for Patient 1 (20 fractions)

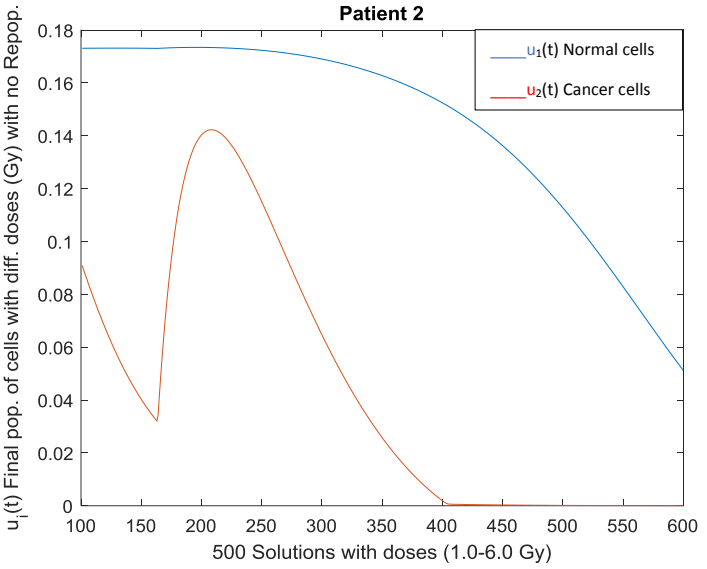

Fig 8: Final pop. of the normal and cancer cells for 1.0-6.0 Gy for Patient 2 (20 fractions)

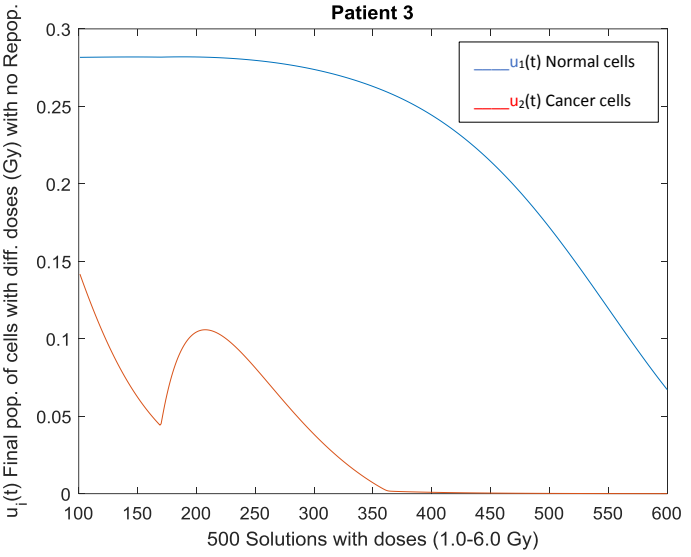

Fig 9: Final pop. of the normal and cancer cells for 1.0-6.0 Gy for Patient 3 (20 fractions)

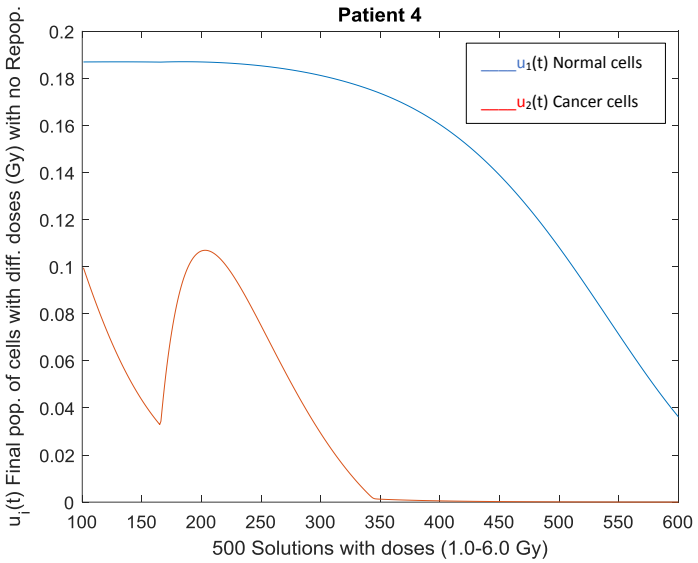

Fig 10: Final pop. of the normal and cancer cells for 1.0-6.0 Gy for Patient 4 (20 fractions)

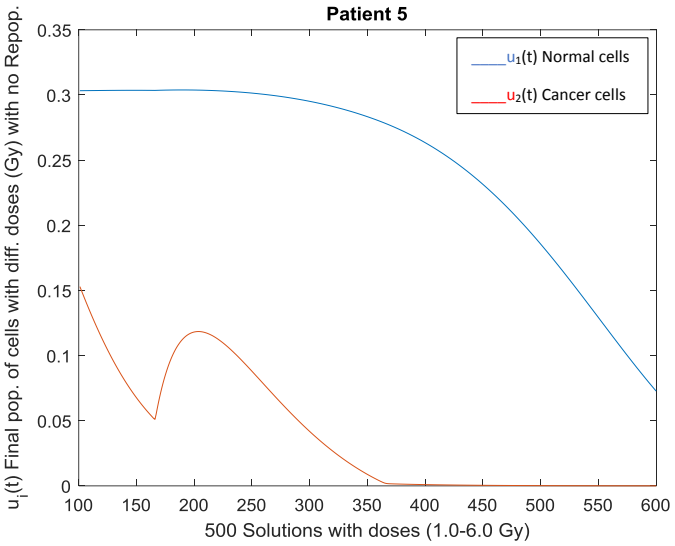

Fig 11: Final pop. of the normal and cancer cells for 1.0-6.0 Gy for Patient 5 (20 fractions)

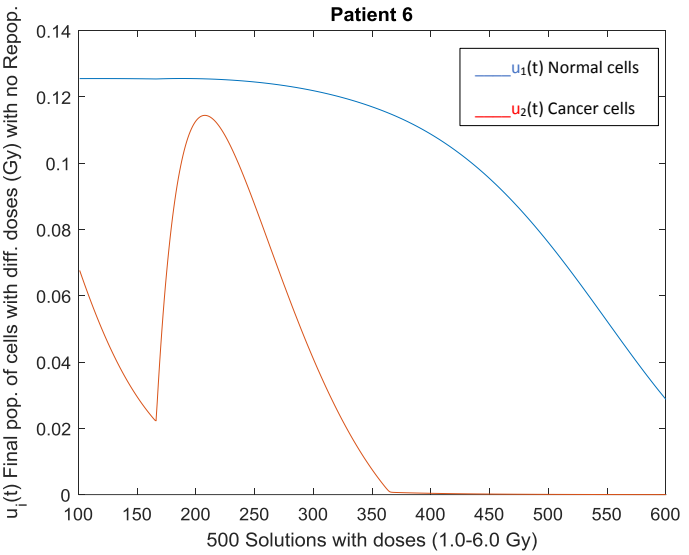

Fig 12: Final pop. of the normal and cancer cells for 1.0-6.0 Gy for Patient 6 (20 fractions)

3.3 Case 3: Radiation Protocols with the Same Doses for Some Number of Fractions

The results of the simulated cancer treatments with a different number of fractions were presented in Tables 7-12. The results included the number of days for treatment T_d, the total treatment time T, the number of fractions n, the scaled final populations of normal and cancer cells, the percentages of cancer treatments, and the percentages of normal cells damage.

Table 7: Patient 1 with 2 Gy but different number of fractions ($\mu = 0.1993$)

Number of treatment days T_d	Total treatment time T	Number of fractions	Scaled final pop. of Normal cells	Scaled final pop. of Cancer cells	Percentage of Cancer Treatment	Percentage of Normal cells damage
35	375	25	0.2387	0.0358	85.1452	0.9544
36	390	26	0.2387	0.0317	86.8465	0.9544
37	405	27	0.2386	0.0278	88.4647	0.9959
38	420	28	0.2386	0.0242	89.9585	0.9959
39	435	29	0.2386	0.0211	91.2448	0.9959
40	450	30	0.2386	0.0206	91.4108	0.9959
43	465	31	0.2386	0.0207	91.4108	0.9959
44	480	32	0.2385	0.0206	91.4108	1.0373
45	495	33	0.2385	0.0206	91.4108	1.0373
46	510	34	0.2385	0.0205	91.4938	1.0373
47	525	35	0.2385	0.0205	91.4938	1.0373

Table 8: Patient 2 with 2 Gy but different number of fractions ($\mu = 0.1863$)

Number of treatment days T_d	Total treatment time T	Number of fractions	Scaled final pop. of Normal cells	Scaled final pop. of Cancer cells	Percentage of Cancer Treatment	Percentage of Normal cells damage
35	375	25	0.1729	0.0861	50.5172	0.6322
36	390	26	0.1729	0.0815	53.1609	0.6322
37	405	27	0.1729	0.0771	55.6897	0.6322
38	420	28	0.1728	0.073	58.046	0.6897
39	435	29	0.1728	0.0691	60.2874	0.6897
40	450	30	0.1728	0.0654	62.4138	0.6897
43	465	31	0.1727	0.0561	67.7586	0.7471
44	480	32	0.1727	0.053	69.5402	0.7471
45	495	33	0.1727	0.0501	71.2069	0.7471
46	510	34	0.1726	0.0473	72.8161	0.8046
47	525	35	0.1726	0.0446	74.3678	0.8046

Table 9: Patient 3 with 1.8 Gy but different number of fractions ($\mu = 0.1588$)

Number of treatment days T_d	Total treatment time T	Number of fractions	Scaled final pop. of Normal cells	Scaled final pop. of Cancer cells	Percentage of Cancer Treatment	Percentage of Normal cells damage
35	375	25	0.2817	0.0568	80.0000	0.8100
36	390	26	0.2816	0.0498	82.4648	0.8451
37	405	27	0.2816	0.0433	84.7535	0.8451
38	420	28	0.2815	0.0381	86.5845	0.8803
39	435	29	0.2815	0.038	86.6197	0.8803
40	450	30	0.2815	0.038	86.6197	0.8803
43	465	31	0.2815	0.0383	86.5141	0.8803
44	480	32	0.2815	0.0382	86.5493	0.8803
45	495	33	0.2815	0.0382	86.5493	0.8803
46	510	34	0.2815	0.0382	86.5493	0.8803
47	525	35	0.2814	0.0381	86.5845	0.9155

Table 10: Patient 4 with 1.8 Gy but different number of fractions (μ=0.1532)

Number of treatment days T_d	Total treatment time T	Number of fractions	Scaled final pop. of Normal cells	Scaled final pop. of Cancer cells	Percentage of Cancer Treatment	Percentage of Normal cells damage
35	375	25	0.1869	0.0645	65.6915	0.5851
36	390	26	0.1869	0.0572	69.5745	0.5851
37	405	27	0.1868	0.0502	73.2979	0.6383
38	420	28	0.1868	0.0436	76.8085	0.6383
39	435	29	0.1868	0.0373	80.1596	0.6383
40	450	30	0.1867	0.0314	83.2979	0.6915
43	465	31	0.1867	0.0265	85.9043	0.6915
44	480	32	0.1867	0.0265	85.9043	0.6915
45	495	33	0.1867	0.0264	85.9574	0.6915
46	510	34	0.1867	0.0264	85.9574	0.6915
47	525	35	0.1867	0.0264	85.9574	0.6915

Table 11: Patient 5 with 1.8 Gy but different number of fractions (μ=0.1566)

Number of treatment days T_d	Total treatment time T	Number of fractions	Scaled final pop. of Normal cells	Scaled final pop. of Cancer cells	Percentage of Cancer Treatment	Percentage of Normal cells damage
35	375	25	0.3035	0.0775	74.6732	0.817
36	390	26	0.3035	0.0705	76.9608	0.817
37	405	27	0.3034	0.0638	79.1503	0.8497
38	420	28	0.3033	0.0575	81.2092	0.8824
39	435	29	0.3033	0.0515	83.1699	0.8824
40	450	30	0.3032	0.0459	85.0000	0.915
43	465	31	0.3032	0.0417	86.3725	0.915
44	480	32	0.3032	0.0416	86.4052	0.915
45	495	33	0.3032	0.0416	86.4052	0.915
46	510	34	0.3031	0.0416	86.4052	0.9477
47	525	35	0.3031	0.0415	86.4379	0.9477

Table 12: Patient 6 with 1.8 Gy but different number of fractions (μ=0.1508)

Number of treatment days T_d	Total treatment time T	Number of fractions	Scaled final pop. of Normal cells	Scaled final pop. of Cancer cells	Percentage of Cancer Treatment	Percentage of Normal cells damage
35	375	25	0.1255	0.0612	51.4286	0.3968
36	390	26	0.1254	0.0536	57.4603	0.4762
37	405	27	0.1254	0.0464	63.1746	0.4762
38	420	28	0.1254	0.0396	68.5714	0.4762
39	435	29	0.1253	0.0332	73.6508	0.5556
40	450	30	0.1253	0.027	78.5714	0.5556
43	465	31	0.1253	0.0211	83.254	0.5556
44	480	32	0.1253	0.0181	85.6349	0.5556
45	495	33	0.1253	0.0181	85.6349	0.5556
46	510	34	0.1253	0.0181	85.6349	0.5556
47	525	35	0.1253	0.0181	85.6349	0.5556

3.4 Case 4: Radiation Protocols of the Six Patients with the Same Regression Equation

The cancer treatments of the six patients were simulated with the same regression equation. The regression equation was given by equation (8) [18] and was obtained from the average of all the radiation protocols obtained from the BED. Also, the scaled final populations of the cancer cells were converted to volumes and compared to the clinical values in Table 2. The errors in volumes and the results of radiation protocols were presented in Table 13.

$$\mu = 0.1478d - 0.104. \tag{8}$$

Table 13: Results of radiation protocols of the six patients with the same regression equation

Patient	Scaled final pop. of Normal cells	Scaled final pop. of Cancer cells	Simulated final tumor vol.cm^3	Error cm^3
1	0.239	0.0719	7.19	3.6
2	0.1727	0.0601	6.01	2.6
3	0.2816	0.0375	3.75	1.92
4	0.1867	0.0246	2.46	1.9
5	0.3032	0.0419	4.19	1.55
6	0.1253	0.0169	1.69	4.42

3.5 Numerical Optimization

The optimal solution for the radiotherapy cancer treatment model is the solution with the best cancer treatment and the least damage to normal cells. From the simulated results shown in Fig 1-12, these optimal solutions occurred at the minimum turning points. Furthermore, the points of complete cancer treatment where the cancer cells population became zero were obtained. After these points, the cancer treatment ceased, and the normal cells damage became more severe with increased doses. The optimal solutions and the complete cancer treatment solutions were presented in Tables 14-17.

Table 14: Optimal cancer treatment solutions for Case 1

Patient	Dosel (Gy)	Number of fractions	Scaled final pop. of Normal cells	Scaled final pop. of tumor vol.cm^3	Simul. final Cancer cells	Percentage of Cancer Treatment	Percentage of Normal cells damage
1	1.93	25	0.2388	0.0238	2.38	90.116	0.9055
2	1.75	25	0.1729	0.0264	2.64	84.8138	0.6111
3	1.83	25	0.2815	0.0348	3.48	87.764	0.8881
4	1.84	28	0.1867	0.0234	2.34	87.5339	0.7174
5	1.84	28	0.3031	0.037	3.70	87.9033	0.944
6	1.77	25	0.1253	0.0177	1.77	85.9403	0.5468

Table 15: Complete cancer treatment solutions for Case 1

Patient	Dosel (Gy)	Number of fractions	Scaled final pop. of Normal cells	Scaled final pop. of tumor vol.cm^3	Simul. final Cancer cells	Percentage of Cancer Treatment	Percentage of Normal cells damage
1	5.50	25	0.0845	0.00	0.00	100	64.9342
2	5.54	25	0.0724	0.00	0.00	100	58.41
3	5.66	25	0.0886	0.00	0.00	100	68.812
4	5.27	28	0.0753	0.00	0.00	100	59.934
5	5.66	28	0.0888	0.00	0.00	100	70.975
6	5.18	25	0.0624	0.00	0.00	100	50.5029

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Table 16: Optimal cancer treatment solutions for Case 2 without repopulation

Patient	Dosel (Gy)	Number of fractions	Scaled final pop. of Normal cells	Scaled final pop. of tumor vol.cm^3	Simul. final Cancer cells	Percentage of Cancer Treatment	Percentage of Normal cells damage
1	1.78	20	0.2392	0.0313	3.13	87.0239	0.7580
2	1.63	20	0.1731	0.0320	3.20	81.5827	0.5339
3	1.69	20	0.2818	0.0442	4.42	84.4259	0.7849
4	1.65	20	0.1869	0.0330	3.30	82.4705	0.5727
5	1.66	20	0.3035	0.0511	5.11	83.3115	0.8121
6	1.66	20	0.1254	0.0223	2.23	82.3218	0.4514

Table 17: Complete cancer treatment solutions for Case 2 without repopulation

Patient	Dosel (Gy)	Number of fractions	Scaled final pop. of Normal cells	Scaled final pop. of tumor vol.cm^3	Simul. final Cancer cells	Percentage of Cancer Treatment	Percentage of Normal cells damage
1	5.59	20	0.0877	0.0000	0.00	100	63.6091
2	5.63	20	0.0746	0.0000	0.00	100	57.1373
3	5.75	20	0.0925	0.0000	0.00	100	67.431
4	5.39	20	0.0796	0.0000	0.00	100	57.668
5	5.79	20	0.0956	0.0000	0.00	100	68.7728
6	5.26	20	0.0641	0.0000	0.00	100	49.1639

4 Discussion

The results of the simulations were analyzed mathematically and interpreted in the following subsections according to different cases.

4.1 Case 1: Radiation Protocols with the Same Number of Fractions but Varying Doses

The doses were varied 500 times from 1.0 Gy to 6.0 Gy but the number of fractions of the patients was unaltered. From the error results presented in Table 6, the least error of 0.1 cm^3 was obtained with Patient 1 while the highest error of 4.06 cm^3 was obtained with Patient 6, and the remaining errors were less than 2.0 cm^3. Since these errors were minimal, it can be concluded that the results of the simulations shown in Fig 1-6 were better predictions of the different radiation protocols. From these predictions, the expected outcomes of radiotherapy processes are derived. These expected outcomes included the final populations of the cancer cells, from which the final tumor volumes can be obtained, and the final populations of the normal cells, from which the normal cells damage can be obtained.

4.2 Case 2: Radiation Protocols with Varying Doses but Without Repopulation

In this case, the doses were also varied 500 times from 1.0 Gy to 6.0 Gy but the number of fractions was fixed at 20 for the patients to avoid repopulation of the cancer cells. The simulations were done with the six regression equations and the results were presented in Fig 7-12. The results showed the final populations of the cells from which the final tumor volumes and the volumes occupied by the normal cells can be derived. Since it was shown that the errors obtained with the six regression equations were minimal, the simulated final populations of cells were approximate solutions for the 500 radiation protocols. From the simulated results, it was deduced that reducing the number of fractions to 20 to avoid repopulation of cancer cells was less productive in terms of cancer treatments. For instance, a dose of 2 Gy and 25 fractions produced simulated final tumor volumes of 3.49 cm^3, 10.03 cm^3, 6.73 cm^3, 5.57 cm^3, 6.82 cm^3, and 7.34 cm^3 for the six patients respectively while a dose of 2 Gy and 20 fractions produced simulated final tumor volumes of 7.09 cm^3, 14.03 cm^3, 10.43 cm^3, 10.67 cm^3, 11.81 cm^3, and 11.28 cm^3.

4.3 Case 3: Radiation Protocols with the Same Doses but Different Number of Fractions

In this case, the number of fractions was varied from 25 to 35 for each of the patients. The results of the simulations were presented in Tables 6-11. From the simulated results, it can be concluded that after a certain number of fractions, the cancer treatment becomes slow or dormant with an increasing number of fractions. For instance, the cancer treatment becomes dormant after 29 fractions for Patient 1, after 28 fractions for Patient 3, after 31 fractions for Patient 4, after 31 fractions for Patient 5, after 32 fractions for Patient 6, and becomes slow after 31 fractions for Patient 2. Also, there was a slow increase in the normal cells damage as the number of fractions increased. From these results, it can be concluded that increasing the number of fractions may not necessarily increase the effectiveness of radiotherapy. The most realistic solution is to obtain the optimal radiotherapy cancer treatment solution.

4.4 Case 4: Radiation Protocols of the Six Patients with a Single Regression Equation

Also, the single regression equation (8) was used to simulate the cancer treatment processes of the six patients with the radiation protocol shown in Table 2. Therefore, for this case, 6 solutions were obtained where each solution was the final population of the normal and cancer cells. Similarly, the accuracy of the results was investigated by using the errors in the final tumor volumes. The errors, shown in Table 13, were the differences between the simulated final tumor volumes and the clinical tumor volumes presented in Table 2. The least error was 1.55 cm^3 with Patient 5 while the highest error was 4.42 cm^3 with Patient 6. This showed that the model predicted better results with the separate regression equations than with the single regression equation. However, the errors in the results obtained with the single regression equation (8) were not large. Therefore, the radiotherapy cancer treatment process can also be simulated with a single regression equation.

4.5 Optimal Cancer Treatment Solutions

The optimal cancer treatment solutions are the radiation protocols that gave the most effective treatment with minimal normal cells damage. Graphically, these points were the minimum turning points in Fig 1-6. The corresponding optimal radiation protocols for Case 1 were presented in

Table 14. From the simulated results, the best cancer treatment was achieved for Patient 1 with 1.93 Gy and 25 fractions which produced a 90.116 % cancer treatment with corresponding normal cells damage of 0.9055 %. The remaining patients' optimal cancer treatments were above 84 % and normal cells damage below 0.944 %. Also, for Case 2, shown in Fig 7-12 where the number of fractions was fixed at 20 fractions, the optimal radiation protocols were presented in Table 16. The best cancer treatment was also achieved for Patient 1 with 1.78 Gy and 20 fractions which produced 87.0239 % cancer treatment with corresponding normal cells damage of 0.7580 %. The remaining patients' cancer treatments were above 81 % and normal cells damage below 0.8121 %. Therefore, the radiation protocols for Case 1 produced better optimal results than Case 2 radiation protocols.

4.6 Complete Cancer Treatment Solutions

The complete cancer treatment solutions are the radiation protocols that gave zero cancer cells population. The results of the complete cancer treatments were presented in Table 15 for Case 1 radiation protocols and Table 17 for Case 2 radiation protocols. For the Case 1 radiation protocols, the fractionated doses of between 5.18 Gy and 5.66 Gy produced complete cancer treatment but with normal cells damage of between 50.5029 % and 70.975 %. Also, for the Case 2 radiation protocols, the doses of between 5.26 Gy and 5.79 Gy produced 100 % cancer treatment but with normal cells damage of between 49.1639 % and 68.7728 %. This implied that once the fractionated dose is above 5 Gy all the cancer cells will be destroyed but the normal cells damage will be severe. Furthermore, from the simulated results, shown in Fig 1-12, increasing the fractionated dose beyond 5 Gy will rapidly cause more damage to the patient. Therefore, once the complete cancer treatment is detrimental to the patient's health, the best and most realistic option is to seek the optimal treatment solution. After obtaining the optimal treatment solution, the remaining tumor volume can be eliminated with other treatment methods like chemotherapy.

Lastly, the simulation of the radiotherapy cancer treatment process with the use of a mathematical model is of great significance in medical sciences. The clinical data available to the medical practitioner are the tumor volumes that form the initial values or cells populations for the model. The radiation protocols for the cancer treatment procedures comprise of the fractionated doses and the number of fractions. The expected outcomes of the treatment procedures are the final tumor volumes and the normal cells damage. Ordinarily, these expected outcomes can only be known after the treatments or through clinical trials or the use of animal models. But with the use of the model equations (2) and (3), the treatment processes can be simulated, and the expected outcomes can be approximated. Although the results of the simulations were not equal to those of the clinical data, they were shown to be close to the clinical data with minimal errors. Therefore, the model is suitable as a predictive tool for different treatment procedures. These treatment protocols might include varying the fractionated doses or varying the number of fractions. From this study, medical practitioners are exposed to an optimal radiotherapy treatment procedure.

5 Conclusions

In this article, a radiotherapy cancer treatment model was used to simulate different treatment procedures. The different treatment simulations were divided into four cases. The four cases included the radiation protocols with varying doses, the radiation protocols without repopulation of cancer cells, the radiation protocols with a different number of fractions, and the radiation protocols simulated with a single regression equation for the Caputo fractional derivative. The

simulated results had minimal errors when compared with clinical data, making the predictions reliable for use. The simulated radiation protocols were analyzed and the optimal cancer treatment procedures were presented. Also, complete cancer treatment solutions were presented, and it was shown that these complete treatment solutions were accompanied by high percentages of normal cells damage. As a result, optimal cancer treatment solutions should be administered. Although the radiation parameters and values used for the simulations were specifically for uterine cervical cancer, this model is also appropriate and can be extended to simulate the treatment of other types of cancers, which is the subject of further research works.

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