Lung Cancer Radiotherapy: Simulation and Analysis Based on a Multi-component Mathematical Model

Wen-song Hong (1350881200@qq.com)
Guangdong Second Provincial General Hospital https://orcid.org/0000-0002-6655-0393
Shun-guan Wang
Guangdong Second Provincial General Hospital
Gang-qing Zhang
Guangdong Second Provincial General Hospital

Research

Keywords: Lung Cancer, Radiotherapy (RT), Multi-component Mathematical Model (MCM)

Posted Date: October 28th, 2020

DOI: https://doi.org/10.21203/rs.3.rs-96690/v1

Lung Cancer Radiotherapy: Simulation and Analysis Based on a Multi-component Mathematical Model

Hong Wen-song*, Wang Shun-guan & Zhang Gang-qing

Radiotherapy Department of Guangdong Second Provincial General Hospital, Guangzhou, 510317, People's Republic of China

*Correspondence: 1350881200@qq.com

Lung Cancer Radiotherapy: Simulation and Analysis based on a Multi-component Mathematical Model

Hong Wen-song*, Wang Shun-guan & Zhang Gang-qing

Radiotherapy Department of Guangdong Second Provincial General Hospital, Guangzhou, 510317, People's Republic of China

*Correspondence: 1350881200@qq.com

Abstract

Background: Lung cancer has been one of the most deadly illnesses all over the world and radiotherapy can be an effective approach for treating lung cancer. Now, mathematical model has been extended to many biomedical fields to give a hand for analysis, evaluation, prediction and optimization.

Methods: In this paper, we propose a multi-component mathematical model for simulating the lung cancer growth as well as radiotherapy treatment for lung cancer. The model is digitalized and coded for computer simulation and the model parameters are fitted with many research and clinical data to provide accordant results along with the growth of lung cancer cells in vitro.

Results: Some typical radiotherapy plans such as stereotactic body radiotherapy, conventional fractional radiotherapy and accelerated hypo-fractionated radiotherapy are simulated, analyzed and discussed. The results show that our mathematical model can perform the basic work for analysis and evaluation of the radiotherapy plan.

Conclusion: It will be expected that in the near future, mathematical model will be a valuable tool for optimization in personalized medical treatment.

Keywords: Lung Cancer; Radiotherapy (RT); Multi-component Mathematical Model (MCM)

1 | Background

Lung cancer may be one of the most deadly killers in our world. According to the global cancer statistics 2018, it was estimated that there were about 2 million new

lung cancer cases as well as 1.7 million death cases in 2018 all over the world, both incidence and mortality stood in the first place [1]. In the subtype, non-small cell lung cancer (NSCLC) was in the absolute dominance (85%). Although there were many new technologies for diagnosis and treatment of lung cancer, the five year survival was still in a very low level (10-20%) [2].

Radiotherapy (RT) is a valuable approach for lung cancer treatment, especially for local advanced lung cancer [3-4]. A serial of clinical evidences elucidate that radiotherapy combined with chemotherapy or immunotherapy may improve the local control of lung cancer [5-7]. In recent years, a special radiotherapy method, named stereotactic body radiotherapy (SBRT), has been introduced to alternative treatment for early stage inoperable NSCLC [8-10]. In SBRT, a lot of small radiation beams are delivered exactly to the tumor target in one or several fractions. Many international cooperative group trails have confirmed that SBRT can return high rates of tumor control without severe toxicity [11-12].

Mathematical model has been utilized to expound the physiological and pathological processing of human being for a long time. For example, as early as 1960s, Priore made an attempt to evaluate the human tumor response to chemotherapy with a mathematical model [13]. In this decade, mathematical models were extended to many fields of medical research dramatically. In 2015, Michor and his colleagues provided detail analysis on mathematical modeling for cancer treatment improvement [14]. In addition, a serial of papers about mathematical modeling for precision medicine, impact of vaccine and prediction of cancer drug resistance were presented by many researchers [15-17]. Because of the complicacy of physiology and pathology, there were a lot of different mathematical representations for emulating the realistic processing, such as logistic model, ordinary differential equation (ODE) model, stochastic differential equation (SDE), and so on. As the superiority of simplicity and stability, the ODE model has been widely used in the fields of infection control, pharmacodynamics, as well as tumor metabolism [18-21]. In our past work, we have developed a mathematical model based on ODE for tumor

radiotherapy [22], So， The model in this paper is elicited in ODE format.

In this paper, we constitute an ODE model for emulating the processing of tumor growth and tumor radiotherapy. It is supposed in our model that the tumor colony, even in the same colony, may have very different features such as growth speed, apoptosis time, as well as drug resistance and radiation sensitivity, so a hypothesis of multi-component structure should be eligible [23]. In order to lead some further applications to clinical research, we feed our model parameters with the data refined from many clinical studies of lung cancer, furthermore, numerical simulation and analysis were performed based on own developed computer codes.

The paper is organized as following: firstly, the tumor growth model and tumor radiotherapy model are listed in detail. Then, the outputs of numerical simulation were figured out with corresponding analysis and explanation. Finally, a discussion is worked out.

2 | Methods

2.1 | Tumor growth model

Many mathematical models of tumor growth have been applied in basic or clinical research [24], among which Logistic Model (LM) and Gompertz Model (GM) may be the most popular. LM is formulated as:

$$\frac{\mathrm{dV}}{\mathrm{dt}} = \mathrm{aV}\left(1 - \frac{\mathrm{V}}{\mathrm{K}}\right) \tag{1}$$

Where V, a function of time t, is the tumor volume, $\frac{\mathrm{d}}{\mathrm{dt}}$ is the derivative formula with respect to t. Both a and K are constant related to tumor proliferation kinetics and carrying capacity, respectively.

GM was proposed first by Benjamin Gompertz in 1925 [25]. The model is described as:

$$\frac{\mathrm{dV}}{\mathrm{dt}} = \mathrm{aV} - \mathrm{bVlnV} \tag{2}$$

Where a, b are coefficients.

It can be deduced that because of the carrying capacity K in (1), the leap for Gompertz model will be larger.

As we know, the tumor growth is impacted by many natural factors, such as

nutrient, the tumor cell cycle and even the contest between the neighbor tumor cells. Also in the same tumor colony, the cells may be at different state and have different growth rate, for example, active tumor, quiescent cells, etc. So we can conclude the following model rationally (Fig. 1 and formula (3)):

Fig. 1. Illustration of multi-component model of tumor growth

$$\begin{cases} \frac{dV_1}{dt} = a_1 V_1\left(1-\frac{V_1}{K_1}\right) + p_{Q1}V_Q - (p_{1Q}+p_{1ND})V_1 \\ \frac{dV_2}{dt} = a_2 V_2\left(1-\frac{V_2}{K_2}\right) + p_{Q2}V_Q - (p_{2Q}+p_{2ND})V_2 \\ \vdots \\ \frac{dV_m}{dt} = a_m V_m\left(1-\frac{V_m}{K_m}\right) + p_{Qm}V_Q - (p_{mQ}+p_{mND})V_m \\ \frac{dV_Q}{dt} = (p_{1Q}V_1 + p_{2Q}V_2 + \cdots + p_{mQ}V_m) - (p_{Q1}+p_{Q2}+\cdots+p_{Q} \\ \frac{dV_{ND}}{dt} = p_{1ND}V_1 + p_{2ND}V_2 + \cdots + p_{mND}V_m + p_{QND}V_Q - \eta V_{ND} \\ m = 1, 2, \ldots, M \end{cases} \tag{3}$$

Where, V_m, volume of the active tumor T_m mentioned in the Fig.1. η is the clear rate of non-dividing cells into blood. Here we prefer to the LM tumor growth model.

2.2 | Tumor radiotherapy model

The most popular model for tumor radiotherapy may be Linear-quadratic (LQ) model [26]. In LQ model, it is assumed that the X-ray can break the double-stranded DNA of the tumor cells and lead to the death of them. The probability of the tumor cell death is related to the dose of the given X-rays, while the survival probability of the tumor cells can be described as:

$$S = e^{-\alpha D - \beta D^2} \tag{4}$$

Where S is the probability of survival tumor cells, D is single radiation dose, e is the natural constant, and α, β are the parameters relating to the radiation sensitivity, which is represented as α/β. For using in this paper, we rewrite formula (4) in an ODE formulation:

$$\frac{dV}{dt} = -(\alpha D + 2\beta D^2)V \quad (5)$$

Here, D is the radiation dose rate. Because X-ray acts as breaking the double-stranded DNA and stopping proliferation of the cells, it can impact the active and quiescent cells only, but not the non-dividing cells. Then, the single dose radiotherapy model can be:

$$\begin{cases} \frac{dV_1}{dt} = a_1 V_1\left(1 - \frac{V_1}{K_1}\right) + p_{Q1}V_Q - (p_{1Q} + p_{1ND})V_1 - (\alpha_1 D + 2\beta_1 D^2)V_1 \\ \frac{dV_2}{dt} = a_2 V_2\left(1 - \frac{V_2}{K_2}\right) + p_{Q2}V_Q - (p_{2Q} + p_{2ND})V_2 - (\alpha_2 D + 2\beta_2 D^2)V_2 \\ \vdots \\ \frac{dV_m}{dt} = a_m V_m\left(1 - \frac{V_m}{K_m}\right) + p_{Qm}V_Q - (p_{mQ} + p_{mND})V_m - (\alpha_m D + 2\beta_m D^2)V_m \\ \frac{dV_Q}{dt} = (p_{1Q}V_1 + p_{2Q}V_2 + \cdots + p_{mQ}V_m) - (p_{Q1} + p_{Q2} + \cdots + p_{Qm} + p_{QND})V_Q - (\alpha_Q D \\ \frac{dV_{ND}}{dt} = p_{1ND}V_1 + p_{2ND}V_2 + \cdots + p_{mND}V_m + p_{QND}V_Q - \eta V_{ND} \\ m = 1, 2, \ldots, M \end{cases} \quad (6)$$

Now in the routine radiotherapy practice, the radiation dose may be divided into many fractions, for example, a larger dose fractional radiotherapy may have several fractions, while normal fractional radiotherapy may take 30 times in one treatment course, and each fraction may take only several or dozens of minutes for radiation. To simulate this process, a piecewise integration equation is presented here:

$$V_1 = \sum_{i=1}^{L}\left(\begin{array}{c}\int_{t_0}^{t_F}\left(a_1 V_{1i}\left(1 - \frac{V_{1i}}{K_1}\right) + p_{Q1}V_{Qi} - (p_{1Q} + p_{1ND})V_{1i}\right)dt \\ -\left(\int_{t_0}^{t_R}\left((\alpha_1 D_i + 2\beta_1 D_i^{\,2})V_{1i}\right)dt\right)\end{array}\right) \quad (7)$$

Where L is the total fraction number in one radiotherapy course, $(t_0,\ t_F)$ is the time interval between each two fractions, $(t_0,\ t_R)$ is the radiation time, the subscript i in V_{1i}, V_{Qi}, D_i indicates that V_1, V_Q, and D are in the i^{th} fraction, respectively. According to formula (6), the equations of V_1, V_2, V_m, and V_Q can be built In the same way like V_1.

2.3 | Parameters of the model

To simplify the simulation process, we set the parameter M in (6) to 2, then, the active tumor cell colony is comprised of 2 kinds, T_1 and T_2 with the volume V_1, and V_2, respectively, and also it is assumed that the dose rate D_i in each fraction be

a constant D.

Much research has been done for fitting the tumor model parameters with clinical data [27-28]. In 2013, Benzekry et al. recorded a serial of comprehensive experiments for several classical mathematical models for tumor growth [29], in their paper, the parameters in many mathematical models include LM and GM for lung and breast cancer are been fitted with the experimental data. As a key reference, their lung data was extracted for estimating and fitting the parameters of our tumor growth model, also we refined our model parameters according to the dada of the volume double time of lung cancer in some studies [30-31].

The parameters in LQ mode is mainly about the value of α and β. It was recommended in many paper that the value of α/β for lung cancer can be taken from 10 to 20 for clinical use [32-33], moreover, in paper[34], the value of α/β, estimated from 1294 data of non-small cell lung cancer patients treated with stereotactic body radiotherapy, could be in the range of 12 - 16. We referred their papers for fitting the parameters of LQ model registered in this paper.

In order to give the quantitative assessment of the radiotherapy effectiveness, a treatment ratio is introduced as:

Treatment ratio = Tumor volume after RT/Tumor volume before RT

This is the metric for evaluating the treatment effect of RT, the lower is the better.

The crucial model parameters in this paper are listed in table 1.

2.4 | Programming and processing

The computer programming codes are developed for simulating and processing. The development tools are Matlab R2018a (Mathworks Corporation, Natick, MA, USA) and Visual Studio Professional 2012(Microsoft Corporation, Redmond, Washington, USA).

3 | Numerical simulation and analysis

3.1 | Analysis of tumor growth model

The simulation results of GM, LM and our MCM are all plotted in Fig. 2. As references, any experimental data extracted from the studies of the growth of A549 cell lines, which belong to human NSCLC [35], are also presented here. The results reveal that all

the models present a good coincidence at the beginning of the tumor growth. In some research, the experiments of tumor growth had given the evidence that GM and LM could return the perfect curves along with the experimental data during the first 20 days, but in the following days, their fitting power would be more and more poor [29]. Because of the simple representations and unchangeable coefficients, it might be the essential inextricability for these models to hold the real data entirely. While in our MCM, some parameters can be adjusted easily for adapting the curves as much as possible to the real data (A549 in Fig. 2A).

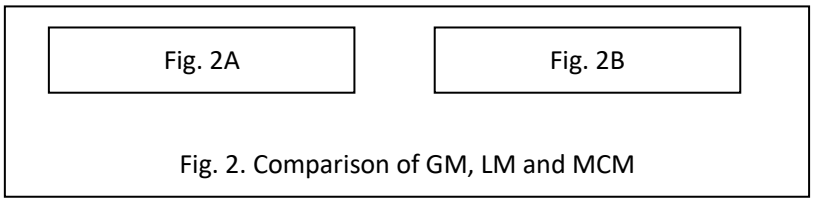

Fig. 2. Comparison of GM, LM and MCM

3.2 | Analysis of SBRT

In 2018, an evidence-based guideline was produced by the American Society for Radiation Oncology (ASTRO) on treatment for early stage NSCLC patient with SBRT [36]. In additional, many clinical trials were performed to compare the treatment results between SBRT and surgery. For example, the data of post-treatment mortality after SBRT and surgery drawn out by William A etc. gave a supportive evidence that SBRT might have lower mortality than surgery [18].

There are many fractional dose approaches for SBRT treatment. The fraction may be 1 to 10 and the dose per fraction may be 7Gy to 23.5Gy, according to the tumor size, tumor place, and so on. Some typical values from the references are picked out to analysis the results through our MCM (Fig. 3).

From the simulating results, we can find that all the four plans have the perfect feedback on tumor control. Among them, 48Gy/4Fr and 60Gy/8Fr may be better, but the dose per fraction of 12Gy or total dose of 60Gy will cause more toxicity to the normal tissues. The rest two plans have similar scores of tumor control enough for clinical practice, so it may be the most reasonable plan for 50Gy/5Fr to SBRT.

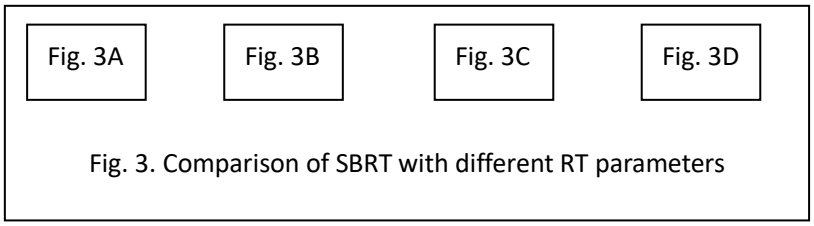

Fig. 3. Comparison of SBRT with different RT parameters

3.3 | Analysis of conventional fractional RT（CFRT）

CFRT has a long history for lung cancer treatment, especially for advanced one. From anterior-posterior two fields RT, multi-fields conformal RT to intensity-modulated RT (IMRT), CFRT plays a crucial role in the improvement of lung cancer therapy. Although there are not any evidences that CFRT can improve the survival rate of lung cancer significantly, it has the effectiveness in local control and symptom relief, moreover, it can give the patients an alternative approach to help them to struggle against the cancer. In 2013, Aileen b. etc. found in their surveys that many patients with incurable lung cancer released more positive expectations about RT [37].

In the clinical practice, CFRT may has about 30~35 fractions and 1.8~2.2Gy per fraction, 5 fractions per week. ASTRO also recommended in the guideline in 2015 that for treatment of locally advanced NSCLC with curative-intent, the RT dose-fractionation should be 60Gy given in 2Gy per fraction [3]. But in the simulating result (Fig. 4), we can find that although the plan of 60Gy/30Fr can do well to higher α/β tumor T_2 (Fig. 4A), its control power to low α/β tumor T_1 may be incompetent, even the total dose rises to 70Gy (Fig. 4B), while if we raise the dose per fraction to 2.5Gy (Fig. 4C), the result may improve significantly. It should be an encouraging hint for us to get better tumor control by changing only the dose per fraction while keeping the same total dose of RT, this may be the theoretical support to hypo-fractionated RT (HFRT).

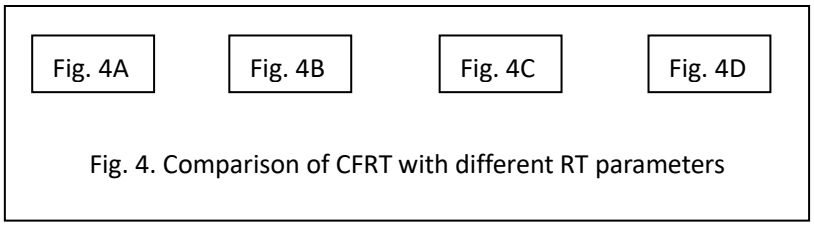

Fig. 4. Comparison of CFRT with different RT parameters

3.4 | Analysis of accelerated hypo-fractionated RT

Along with the development of RT technique, there are many innovations in CFRT for

lung cancer, such as HFRT. It was reported that the proliferation of tumor cells of NSCLC could accelerate in 3-4weeks after the beginning of RT [38], in order to minimize the impact of the proliferation, the dose per fraction was recommended to rise to 2.5 to 3.0Gy, then the total treatment time decreased correspondently, here, HFRT was elicited. But larger single dose could cause more harm to normal tissue, so, it was rational to reduce the dose per fraction as well as increase the fractions per day. Usually the plan was 1.2~1.5Gy per fraction while 2 fractions per day, 5 days a week, but the plan was not mandatory, there was also an HFRT plan containing 1.5Gy per fraction while 3 fractions a day [39]. Amount of research reported that HFRT could achieve local control improvement without increasing toxicity [40-42], however, there was still no comprehensive comparative outcome of the different HFRT plans.

As showing in Fig. 5A and comparing with Fig. 4B, when we only change the RT fractions from 1 per day to 2 per day, we will receive a perfect response that the treatment ratio about T_1 drops dramatically from 0.240 to 0.0065. It can be concluded from Fig. 5 that if we can find out the proliferation of the surrounding normal tissues of the tumor, we can reach an optimization of HFRT just for adjusting the fraction gap of HFRT.

Fig. 5A Fig. 5B Fig. 5C Fig. 5D

Fig. 5. Comparison of HFRT with different RT parameters

4 | Discussion

In modern medicine, it seems that the medical researchers may always on the way to toss a coin in cancer treatment. In a randomized controlled trail (RCT), we have to close our eyes to decide who belong to the test group or to the control group. Moreover, because there is only one choice for a certain patient, it is unclear that weather the treatment effectiveness of the two group is different or not for him. The only word we can say is merely “probability”. To the patient group, the word may be correct, but to an individual, it just means a gamble. Maybe in the era of personalized medicine, the first thing we will do is to reduce the usage frequency of the coin, even

throw it away. Mathematical model may be a light for helping us to tear the darkness.

Everything may have its own rules, without exception. The most important thing should be that how accurate and simple we can describe the rules. For tumor metabolism, with a proper mathematical model and any partial data, we can analyze the past of the tumor as well as its future development. For example, in our MCM, once the model is reconstructed with the in vivo data, we can work out a serial of specific parameters to give the evaluation and prediction of the tumor growth, in addition, we can also build a bridge between the tumor and the blood residue, because the non-dividing tumor cells (T_m) will be cleared and broken down in to the blood eventually. If some biochemicals taken from the blood test are confirmed to come from a curtain tumor, then the tumor features can be further analyzed according to the biochemicals and the tumor mathematical model. This is to say that we can do quantitive analysis about all the active tumor (T_1, T_2 and T_m) through the blood test of the patients.

As we know, it will be a more complicated and time-consuming work to find a new approach for treatment of a specific illness. We have to repeat a serial of endless experiments until a result, maybe a failure result is returned. Will there be a shortcut? Perhaps mathematical model may be the one. For tumor radiotherapy, with the support of mathematical model, as soon as the treatment hypothesis is proposed, we can give it the first feasible evaluation about the total treatment dose, the dose per fraction as well as the time gap between two fractions, also we can receive some reasonable advices from the model to optimize the treatment. The huge experiments are no more needed and what we have to do is waiting the answers from the computer.

As a beneficial attempt, we use our MCM to explain the dominant approaches of lung cancer radiotherapy. To SBRT, our model returns the similar results as current clinical approaches as well as recommends a feasible plan (50Gy/5Fr) for clinical reference. To CFRT, our model shows that a perfect tumor control cannot be reached with normal dose per day (2Gy) despite of high total dose, while with higher dose per

day (for example, 2.5Gy) and normal total dose, the tumor control becomes better! Consequently, it is necessary to make an improvement from CFRT to HFRT or accelerated HFRT. An accordant conclusion is also proposed by some clinical trail [43-44]. But this may be a dream far away from the reality. Although the artificial intelligence (AI) becomes hotter and hotter in recent years, there still has a very long and roundabout way to reach the goals of the clinical application of the mathematical model. For our MCM, the main problem may be the extraction of parameters such as T_1, T_2 and T_m, as well as α and β. Anyway, the future is desirable. It must be the most imperative study for us to determine which kind of the model will be enough for explaining the biophysiological process of the tumor and the interaction between the tumor and radiation ray. It is also a heavy work to gather and analyze the experimental and clinical data for the parameters optimization of the models. These may be our coming work.

5 | Conclusions

Tumor growth is a very complicated process. Naturally, a single tumor cell model may be too rough to explain the tumor metabolism. In our MCM, two different kinds of tumor cells are considered to analyze and evaluate the radiotherapy approaches for lung cancer treatment. The result shows that MCM has make a successful step on clinical evaluation. It should be a valuable study for further research.

Abbreviations

RT: Radiotherapy; MCM: Multi-component Mathematical Model; NSCLC: Non-small Cell Lung Cancer; SBRT: Stereotactic Body Radiotherapy; ODE: Ordinary Differential Equation; SDE: Stochastic Differential Equation; LM: Logistic Model; GM: Gompertz Model; LQ: Linear-quadratic; ASTRO: American Society for Radiation Oncology; CFRT: Conventional Fractional RT; HFRT: Hypo-fractionated RT; RCT: Randomized Controlled Trail.

Ethical Approval and Consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of supporting data

Additional information is available from the corresponding author on reasonable request.

Competing interests

Not applicable.

Funding

Not applicable.

Authors' contributions

WSg checked and approved the study.

ZGq designed, checked and approved the study.

HWs designed, wrote, revised and approved the manuscript.

Acknowledgements

Not applicable.

Authors' information

Not applicable.

Reference

1. Freddie B, Jacques F, Isabelle S, et al. Global Cancer Statistics 2018: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA CANCER J CLIN. 2018; 68: 394–424.
2. Richard DN, Fei S, Jon DE, et al. Lung cancer. British Medical Journal. 2019; 365: 1725-1729.
3. Andrea B, Sarah T, Gregg F, et al. Definitive and Adjuvant Radiotherapy in Locally Advanced Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Clinical Practice Guideline Endorsement of the American Society for Radiation Oncology Evidence-Based Clinical Practice Guideline. Journal of Clinical Oncology. 2015; http://jco.ascopubs.org/cgi/doi/10.1200/JCO.2014.59.2360.
4. Aileen BC, Angel C, Jane CW, et al. Palliative Radiation Therapy Practice in Patients with Metastatic Non–Small-Cell Lung Cancer: A Cancer Care Outcomes Research and Surveillance Consortium (CanCORS) Study. Journal of Clinical Oncology. 2013;

31 (5): 558-564.

5. Jeffrey DB, Kyounghwa B, Mary VG, et al. Primary Analysis of the Phase II Component of a Phase I/II Dose Intensification Study Using Three-Dimensional Conformal Radiation Therapy and Concurrent Chemotherapy for Patients With Inoperable Non‐Small-Cell Lung Cancer: RTOG 0117. Journal of Clinical Oncology. 2010; 28 (14): 2475-2480.
6. Kathryn CA, Gregory JR. Systemic Therapy for Locally Advanced and Metastatic Non–Small Cell Lung Cancer A Review. JAMA. 2019; 322(8): 764-774.
7. Chiara L, Niki K, Alessandra B, et al. Combination of immunotherapy with chemotherapy and radiotherapy in lung cancer: is this the beginning of the end for cancer? Therapeutic Advances in Medical Oncology. 2018; 10: 1–12.
8. Mao-Bin M, Huan-Huan W, Nicholas GZ, et al. Risk‐adapted stereotactic body radiation therapy for central and ultra-central early-stage inoperable non-small cell lung cancer. Cancer Science. 2019; 00: 1‐12.
9. Vivek V, Charles BS. Approaches to stereotactic body radiation therapy for large (⩾ 5 centimeter) non-small cell lung cancer. Translational Lung Cancer Research. 2019; 8(1): 70-77.
10. Andrew B, Andrea B. Stereotactic body radiotherapy for centrally located stage I non-small cell lung cancer. Translational Lung Cancer Research. 2019; 8(1): 58-69.
11. Christopher C, Daniel W, Caroline C, et al. A Systematic Review and Meta-Analysis of Stereotactic Body Radiation Therapy versus Surgery for Patients with Non-Small Cell Lung Cancer. J Thorac Cardiovasc Surg. 2019; 157(1): 362–373.
12. William AS, Michael RB, Robert AM, et al. Post-Treatment Mortality After Surgery and Stereotactic Body Radiotherapy for Early-Stage Non–Small-Cell Lung cancer. Journal of Clinical Oncology. 2018; 36 (7): 642-651.
13. Priore, RL. Using a mathematical model in the evaluation of human tumor response to chemotherapy. J Natl Cancer Inst. 1966; 37(5): 635-47.
14. Franziska M, Kathryn B. Improving Cancer Treatment via Mathematical Modeling: Surmounting the Challenges is Worth the Effort. Cell. 2015; 163(5): 1059–1063.

15. Dominique B, Joseph C, Bruno L, et al. Computational oncology mathematical modelling of drug regimens for precision medicine. Nature Reviews Clinical Oncology. 2016; 13 (4): 242-254.
16. Katherine EA, Erin IL, Sarah RD, et al. Use of mathematical modelling to assess the impact of vaccines on antibiotic resistance. 2017; http://dx.doi.org/10.1016/S1473-3099(17)30478-4.
17. Xiaoqiang S, Bin H. Mathematical modeling and computational prediction of cancer drug resistance. Briefings in Bioinformatics. 2018; 19(6): 1382–1399.
18. Roberts PA, Huebinger RM, Keen E, et al. Mathematical model predicts anti-adhesion-antibiotic-debridement combination therapies can clear an antibiotic resistant infection. PloS Computational Biology. 2019; 15 (7): e1007211.
19. Wilson AM, Reynolds KA, Canales RA. Estimating the effect of hand hygiene compliance and surface cleaning timing on infection risk reductions with a mathematical modeling approach. American Journal of Infection Control. 2019; 47 (12): 1453-1459.
20. Ciccolini J, Barbolosi D, Meille C, et al. Pharmacokinetics and Pharmacodynamics-Based Mathematical Modeling Identifies an Optimal Protocol for Metronomic Chemotherapy. Cancer Research. 2017; 77 (17): 4723-4733.
21. Ledzewicz U, Sch?ttler H. Application of mathematical models to metronomic chemotherapy: What can be inferred from minimal parameterized models? Cancer Letters. 2017; 401: 74-80.
22. Hong WS, Zhang GQ. Simulation analysis for tumor radiotherapy based on three‐component mathematical models. J Appl Clin Med Phys. 2019; 20 (3): 22‒26.
23. Jamal-Hanjani M, Wilson GA, McGranahan, N, et al. Tracking the Evolution of Non–Small-Cell Lung Cancer. The New England Journal of Medicine. 2017; 376 (22): 2109-2121.
24. West GB, Brown JH, Enquist BJ. A general model for ontogenetic growth. Nature. 2001; 413: 628–631.

25. José SD. Gompertz model: resolution and analysis for tumors. J Math Modell Appl. 2012; 1: 70–77.
26. McMahon, SJ. The linear quadratic model: usage, interpretation and challenges. Physics in Medicine & Biology. 2018; 64 (1): 01TR01.
27. Anne T, Rick D. Estimating tumor growth rates in vivo. The Bulletin of Mathematical Biophysics. 2015; 77(10): 1934–1954.
28. Leith H, Benjamin ME, Timothy FC, et al. Patient-specific characterization of the invasiveness and proliferation of low-grade gliomas using serial MR imaging and a mathematical model of tumor growth. Oncology Reports. 2015; 33: 2883-2888.
29. Benzekry S, Lamont C, Beheshti A, et al. Classical Mathematical Models for Description and Prediction of Experimental Tumor Growth. PLoS Comput Biol. 2014; 10 (8): e1003800. doi:10.1371/journal.pcbi.1003800.
30. Kai O, Kimihiro S, Seshiru N, et al. The impact of histology and ground-glass opacity component on volume doubling time in primary lung cancer. Journal of Thoracic Disease. 2018; 10 (9): 5428-5434.
31. Rui Z, Bojiang C, Yongzhao Z, et al. Volume doubling time of lung adenocarcinomas considering epidermal growth factor receptor mutation status of exon 19 and 21: three-dimensional volumetric evaluation. Journal of Thoracic Disease. 2017; 9(11): 4387-4397.
32. Alexander C, Sijin W, Zhongxing L, et al. What Would Be the Most Appropriate α/β Ratio in the Setting of Stereotactic Body Radiation Therapy for Early Stage Non-Small Cell Lung Cancer? BioMed Research International. 2013, http://dx.doi.org/10.1155/2013/391021.
33. Feng L, An T, Percy L, et al. Tumor Control Probability Modeling for Stereotactic Body Radiation Therapy of Early-Stage Lung Cancer Using Multiple Bio-physical Models. Radiotherapy Oncology. 2017; 122(2): 286–294.
34. Klement RJ., Sonke JJ., Allgäuer M, et al. Estimation of the α/β ratio of non-small cell lung cancer treated with stereotactic body radiotherapy. Radiotherapy and Oncology, https://doi.org/10.1016/j.radonc.2019.07.008.
35. Jung JR, Jun-Won Y, Euna K, et al. Dual effects of human adipose tissue-derived

mesenchymal stem cells in human lung adenocarcinoma A549 xenografts and colorectal adenocarcinoma HT-29 xenografts in mice. Oncology Reports. 2015; 34: 1733-1744.

36. Bryan JS, Megan ED, Erin BK, et al. Stereotactic Body Radiotherapy for Early-Stage Non–Small-Cell Lung Cancer: American Society of Clinical Oncology Endorsement of the American Society for Radiation Oncology Evidence-Based Guideline [J]. Journal of Clinical Oncology. 2018; 36 (7): 710-719.

37. Aileen BC, Angel C, Jane CW, et al. Expectations About the Effectiveness of Radiation Therapy Among Patients With Incurable Lung Cancer. Journal of Clinical Oncology. 2013; 31 (21): 2730-2735.

38 Fowler JF, Chappell R. Non-small cell lung tumors repopulate rapidly during radiation therapy. Int J Radiat Oncol Biol Phys. 2000; 46: 516–517.

39. Omar SD, Susan VH, Emma H, et al. Accelerated hypo-fractionated Radiotherapy for non small cell lung cancer: Results from 4 UK centres. Radiotherapy and Oncology. 2013; 109: 8–12.

40. Zheng-Fei Z, Min F, Kai-Liang W, et al. A phase II trial of accelerated hypofractionated three-dimensional conformal radiation therapy in locally advanced non-small cell lung cancer. Radiotherapy and Oncology. 2011; 98: 304–308.

41. Dongryul O, Yong CA, BoKyong K, et al. Hypofractionated Three-Dimensional Conformal Radiation Therapy Alone for Centrally Located cT1-3N0 Non–Small-Cell Lung Cancer. Journal of Thoracic Oncology. 2013; 8: 624-629.

42. James JU, Xiaofei W, Jeffrey AB, et al. Phase I Study of Accelerated Hypofractionated Radiotherapy with Concurrent Chemotherapy for Stage III Non-Small-Cell Lung Cancer: CALGB 31102 (Alliance). Int J Radiat Oncol Biol Phys. 2018; 101(1): 177–185.

43. Michelle I, Aaron TW, Margaret H, et al. (2019): Hypofractionated vs. conventional radiation therapy for stage III non-small cell lung cancer treated without chemotherapy, Acta Oncologica, DOI: 10.1080/0284186X.2019.1675907.

44. Hany S, Patrick C, Latifa Y, et al. Accelerated Hypofractionated Radiotherapy For

Early-stage Non-small-cell Lung cancer: Long-term Results. Int J Radiat Oncol Biol Phys. 2011; 79 (2): 459–465.

Competing interests

No competing interests.

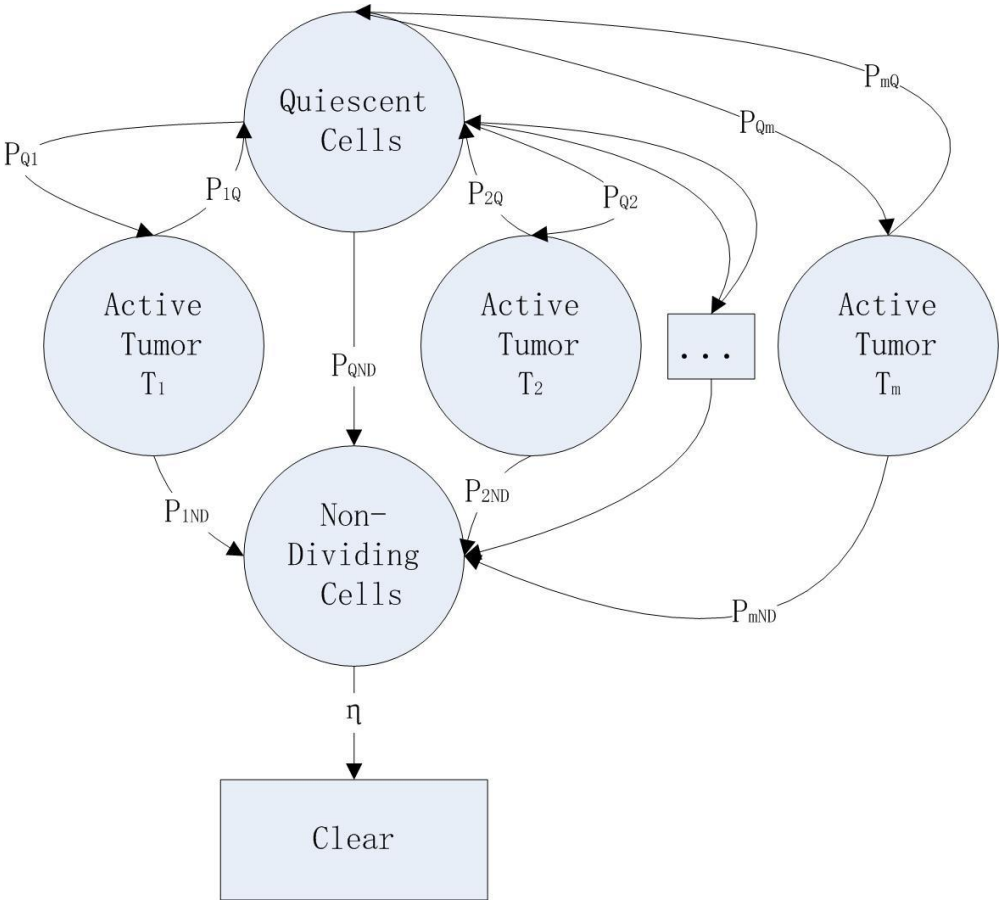

Fig. 1. Illustration of multi-component model of tumor growth

It is assumed that there are different tumor cells in the tumor colony: the quiescent cells, which suspend dividing and can change to active tumors and non-dividing cells; non-dividing cells, which are dead and waiting to be cleared into the blood; active tumors: which can divide normally and can change to quiescent cells and non-dividing cells, and the active tumor also have different types, $T_1, T_2, \cdots T_m$

p_{ij} is the probability of cell i changing to cell j.

η is the clear rate.

Tab. 1. Crucial parameters of models

Model	Parameter	Unit
GM	a = 0.743, b = 0.0792	day^{-1}
LM	a = 0.502	day^{-1}
	K = 1297	mm^3
MCM	a_1 = 0.862, a_2 = 0.501	day^{-1}
	K_1 = 1397, K_2 = 1174	mm^3

	p_{Q1} = 0.1, p_{1Q} = 0.2, p_{1ND} = 0.2, p_{Q2} = 0.1, p_{2Q} = 0.2, p_{2ND} = 0.2, p_{QND} = 0.09, η = 0.4	day^{-1}
L-Q	$\alpha_1 = 0.194, \alpha_2 = 0.3705, \alpha_Q = 0.3$	Gy^{-1}
	$\beta_1 = 0.063, \beta_2 = 0.02335, \beta_Q = 0.15$	Gy^{-2}

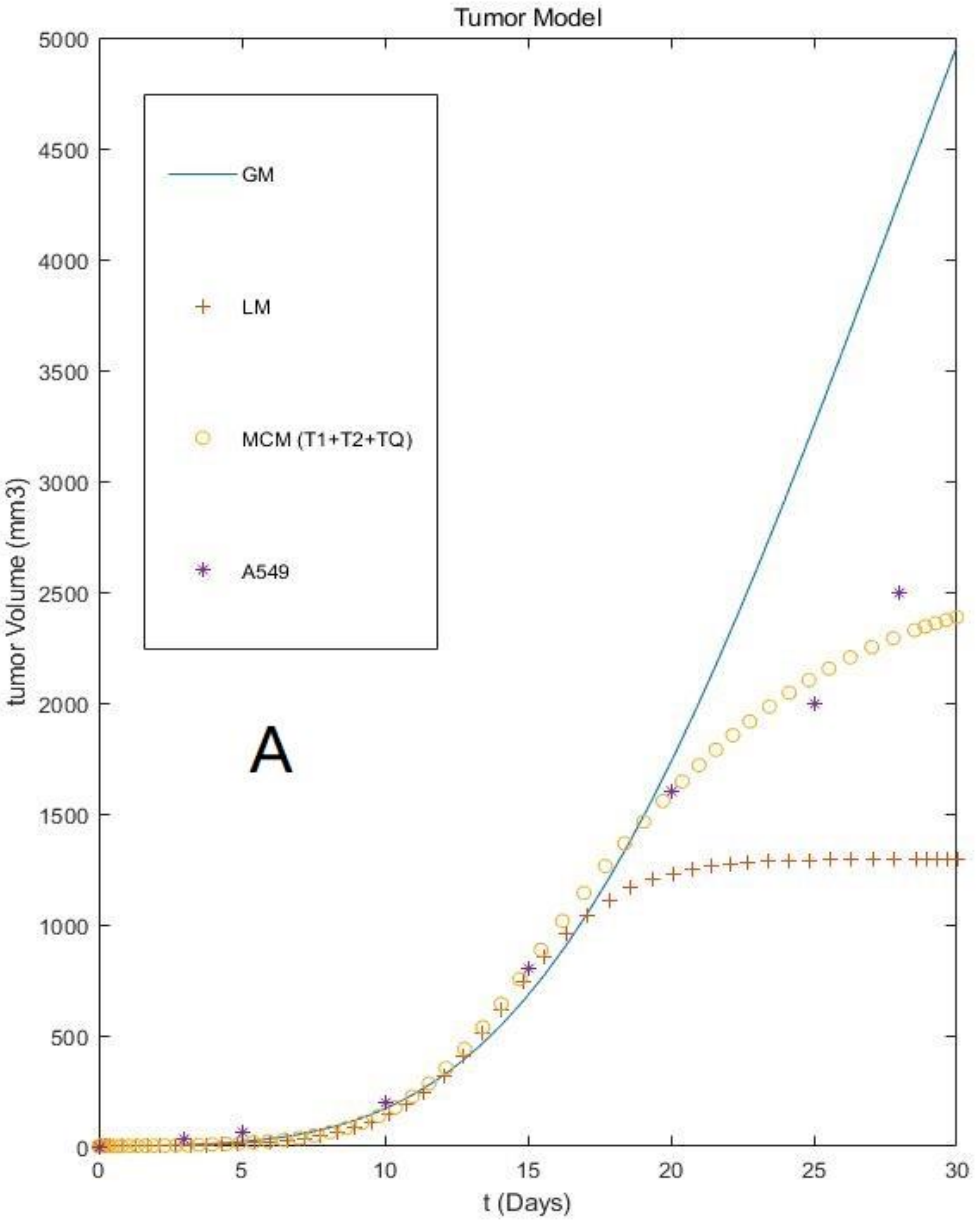

Fig. 2A: Tumor Model-A

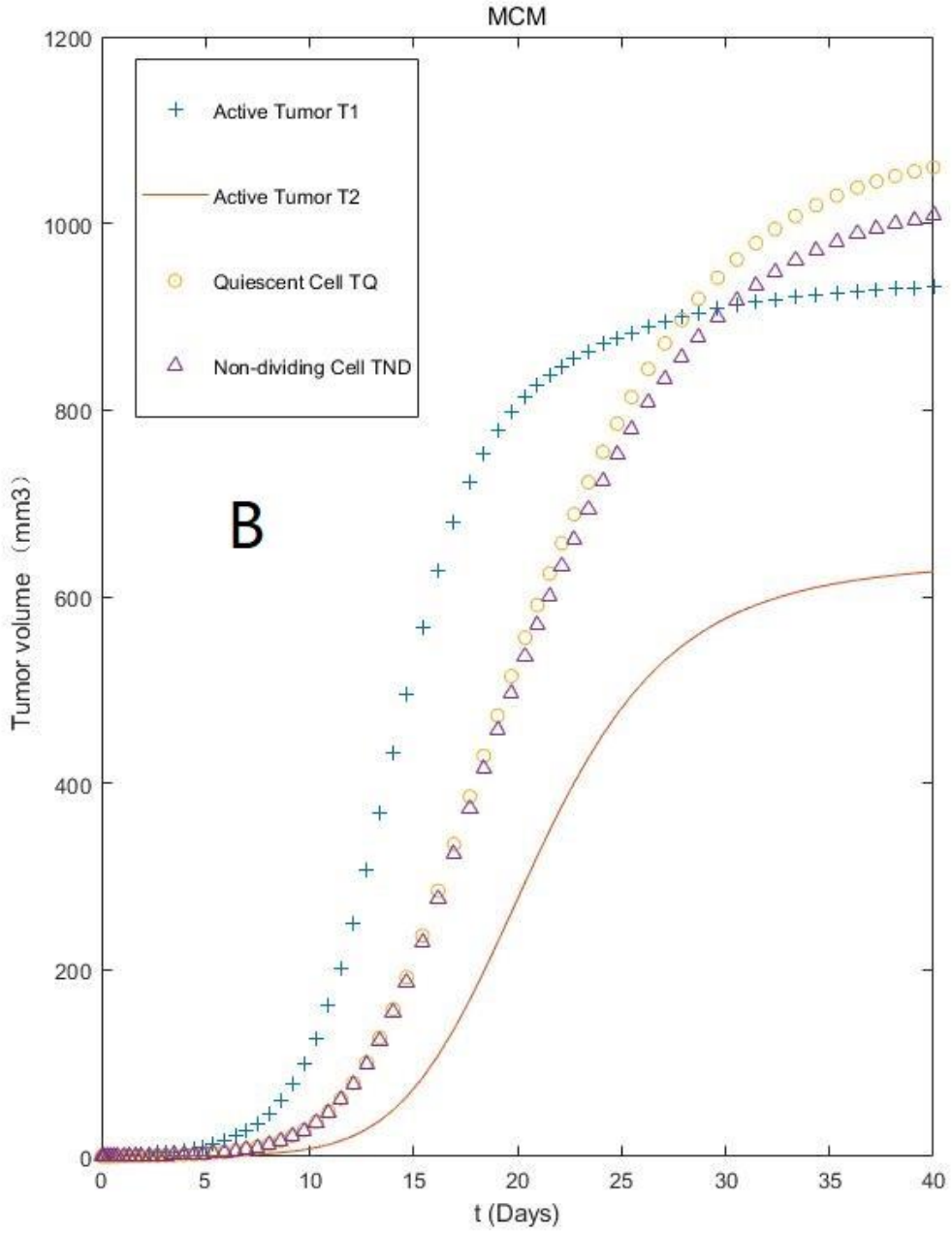
MCM
Active Tumor T1
Active Tumor T2
Quiescent Cell TQ
Non-dividing Cell TND
B
Tumor volume （mm3）
t (Days)
0
200
400
600
800
1000
1200
0
5
10
15
20
25
30
35
40

Fig. 2B: MCM-B

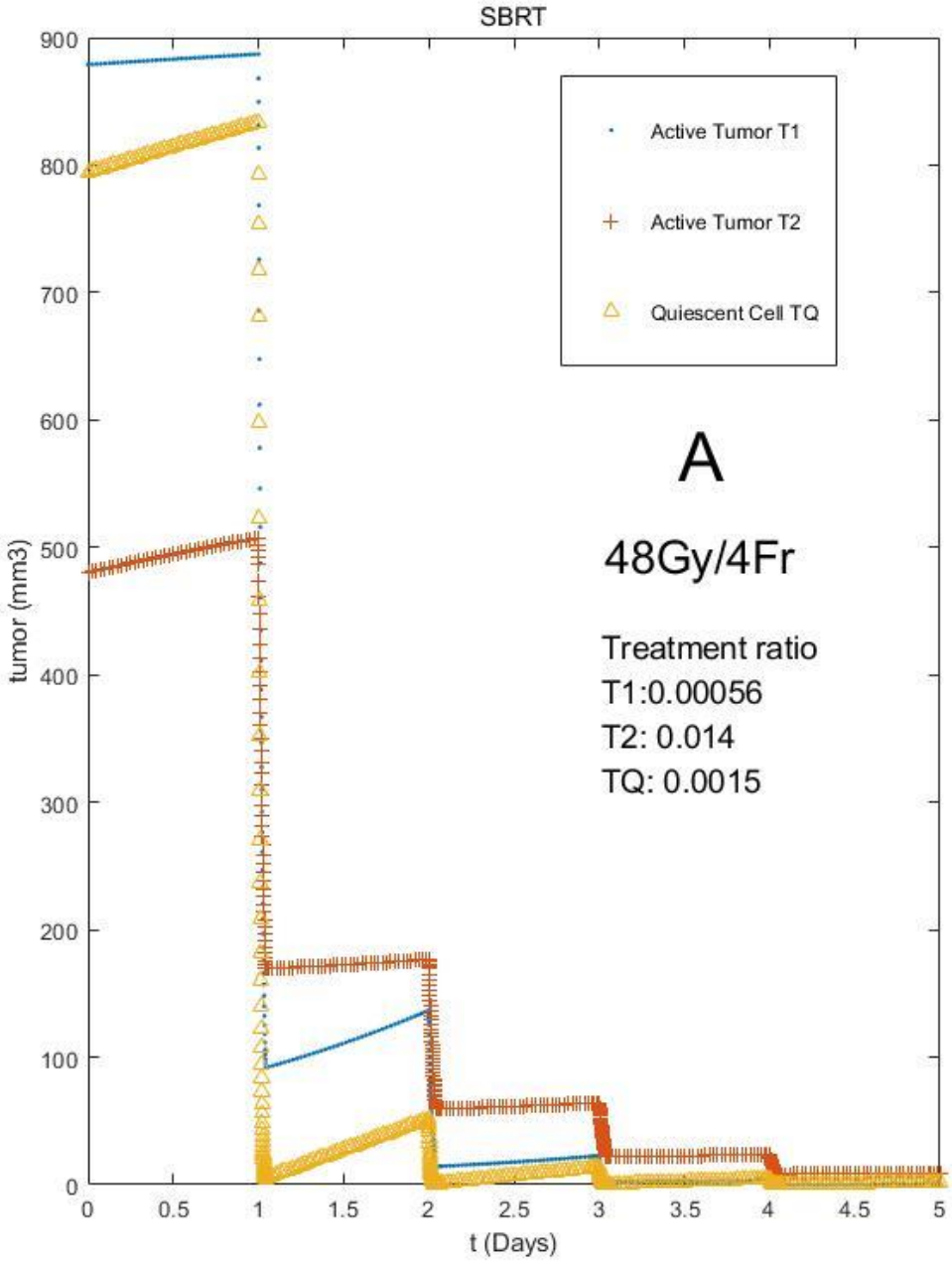
SBRT
Active Tumor T1
Active Tumor T2
Quiescent Cell TQ
A
48Gy/4Fr
Treatment ratio
T1:0.00056
T2: 0.014
TQ: 0.0015
tumor (mm3)
t (Days)
0
100
200
300
400
500
600
700
800
900
0
0.5
1
1.5
2
2.5
3
3.5
4
4.5
5

Fig. 3A: SBRT-A

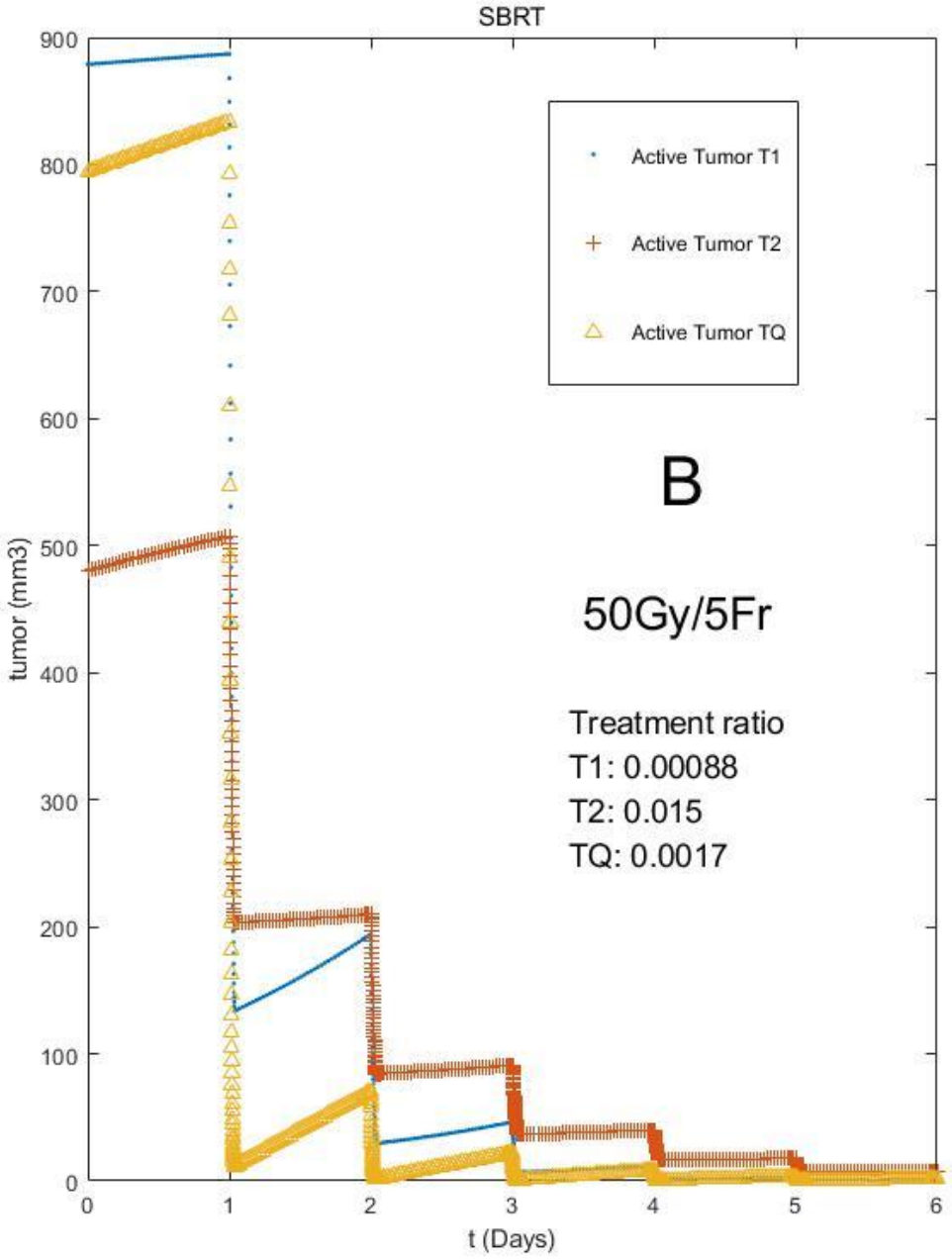
SBRT
Active Tumor T1
Active Tumor T2
Active Tumor TQ
B
50Gy/5Fr
Treatment ratio
T1: 0.00088
T2: 0.015
TQ: 0.0017
tumor (mm3)
t (Days)
0
100
200
300
400
500
600
700
800
900
0
1
2
3
4
5
6

Fig. 3B: SBRT-B

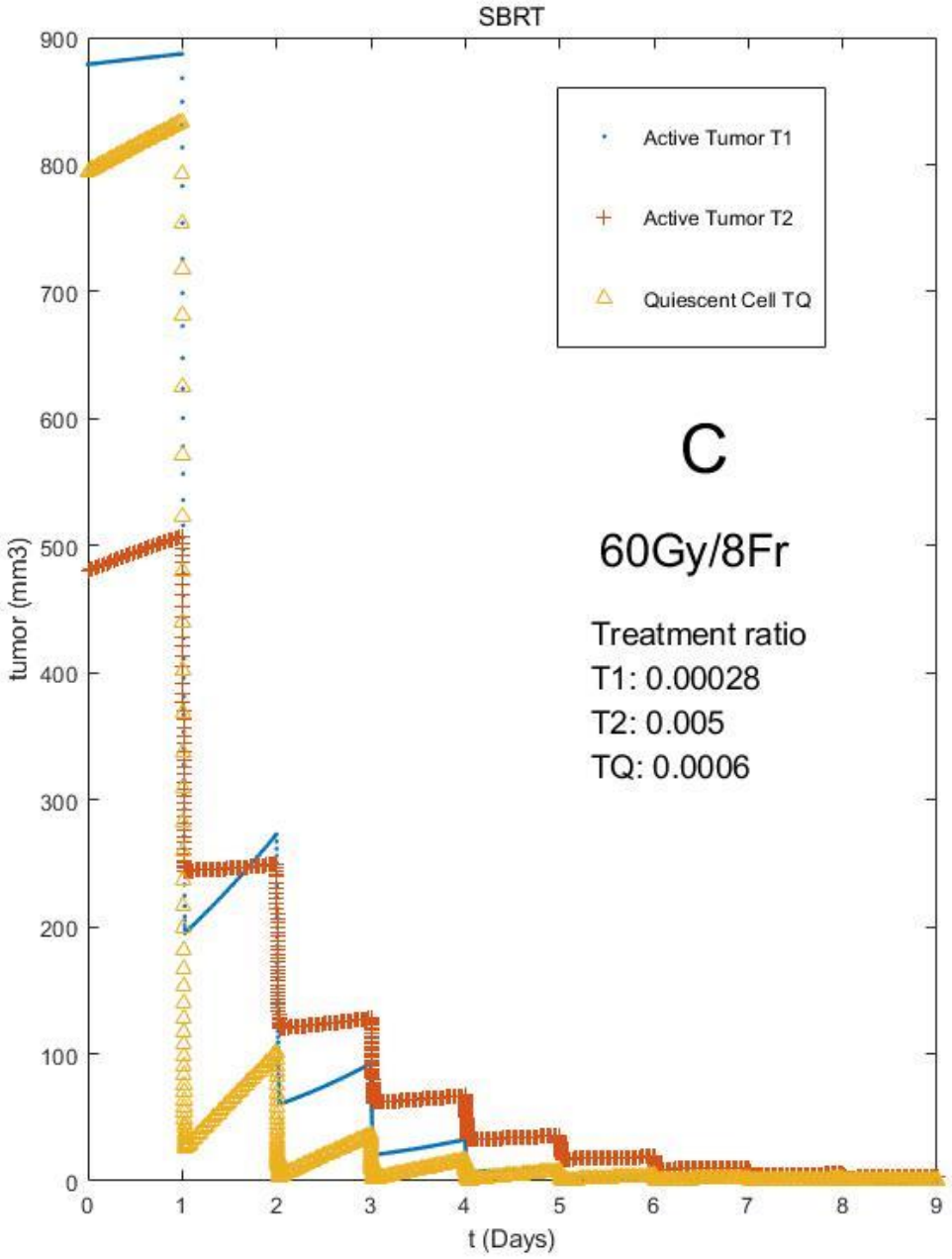
SBRT
Active Tumor T1
Active Tumor T2
Quiescent Cell TQ
C
60Gy/8Fr
Treatment ratio
T1: 0.00028
T2: 0.005
TQ: 0.0006
tumor (mm3)
t (Days)
0
100
200
300
400
500
600
700
800
900
0
1
2
3
4
5
6
7
8
9

Fig. 3C: SBRT-C

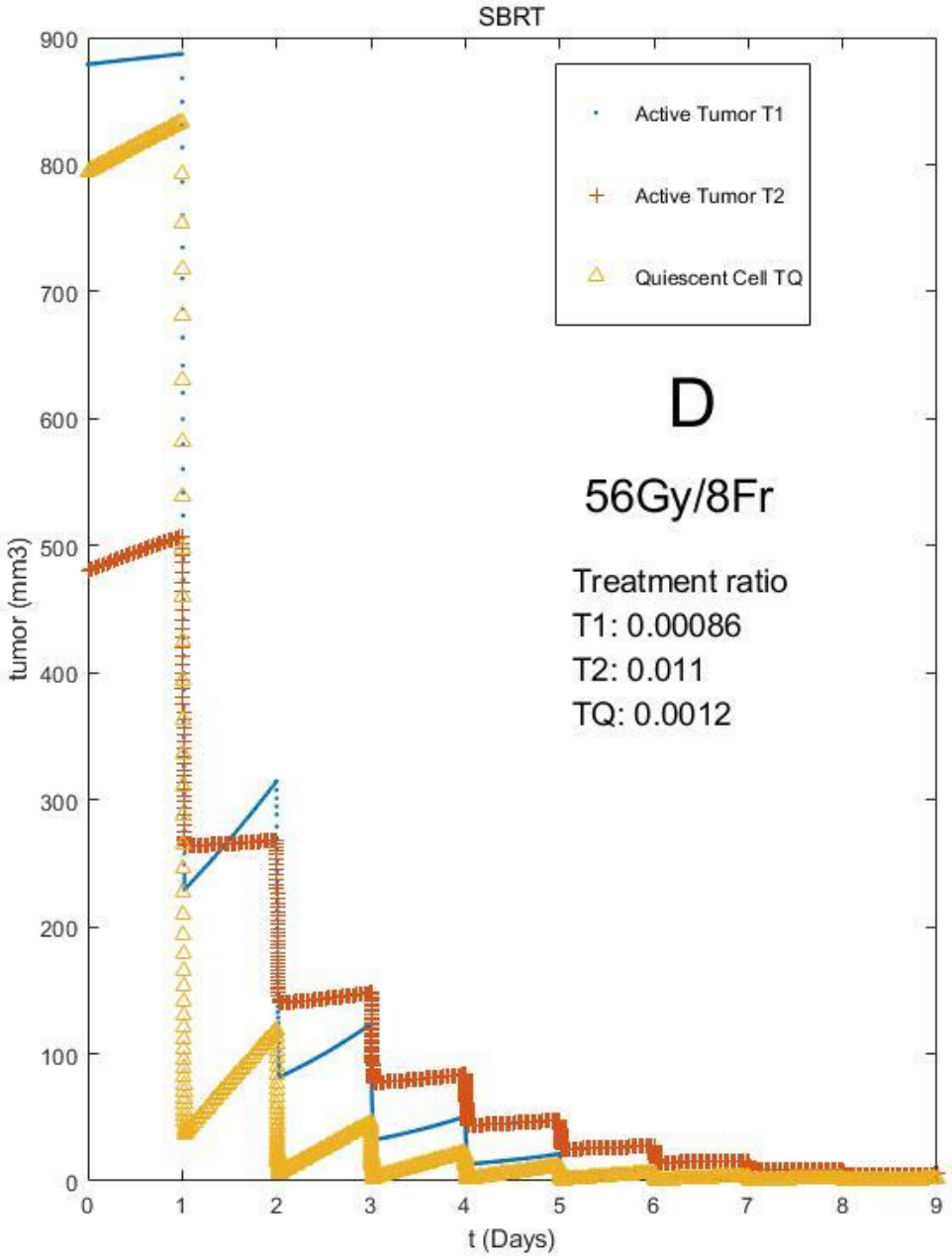
SBRT
Active Tumor T1
Active Tumor T2
Quiescent Cell TQ
D
56Gy/8Fr
Treatment ratio
T1: 0.00086
T2: 0.011
TQ: 0.0012
tumor (mm3)
t (Days)
0
100
200
300
400
500
600
700
800
900
0
1
2
3
4
5
6
7
8
9

Fig. 3D: SBRT-D

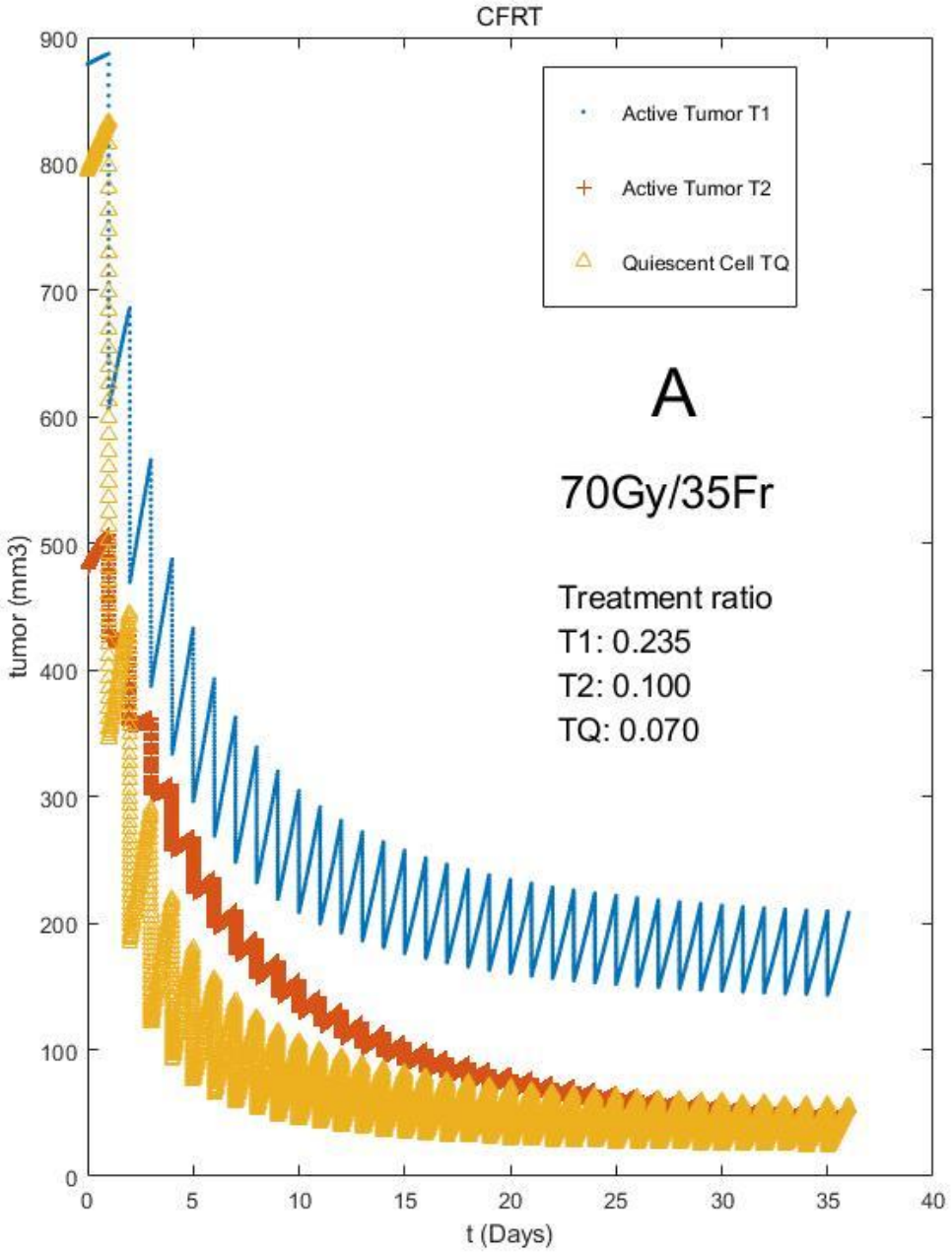
CFRT
Active Tumor T1
Active Tumor T2
Quiescent Cell TQ
A
70Gy/35Fr
Treatment ratio
T1: 0.235
T2: 0.100
TQ: 0.070
tumor (mm3)
t (Days)
0
100
200
300
400
500
600
700
800
900
0
5
10
15
20
25
30
35
40

Fig. 4A: CFRT-A

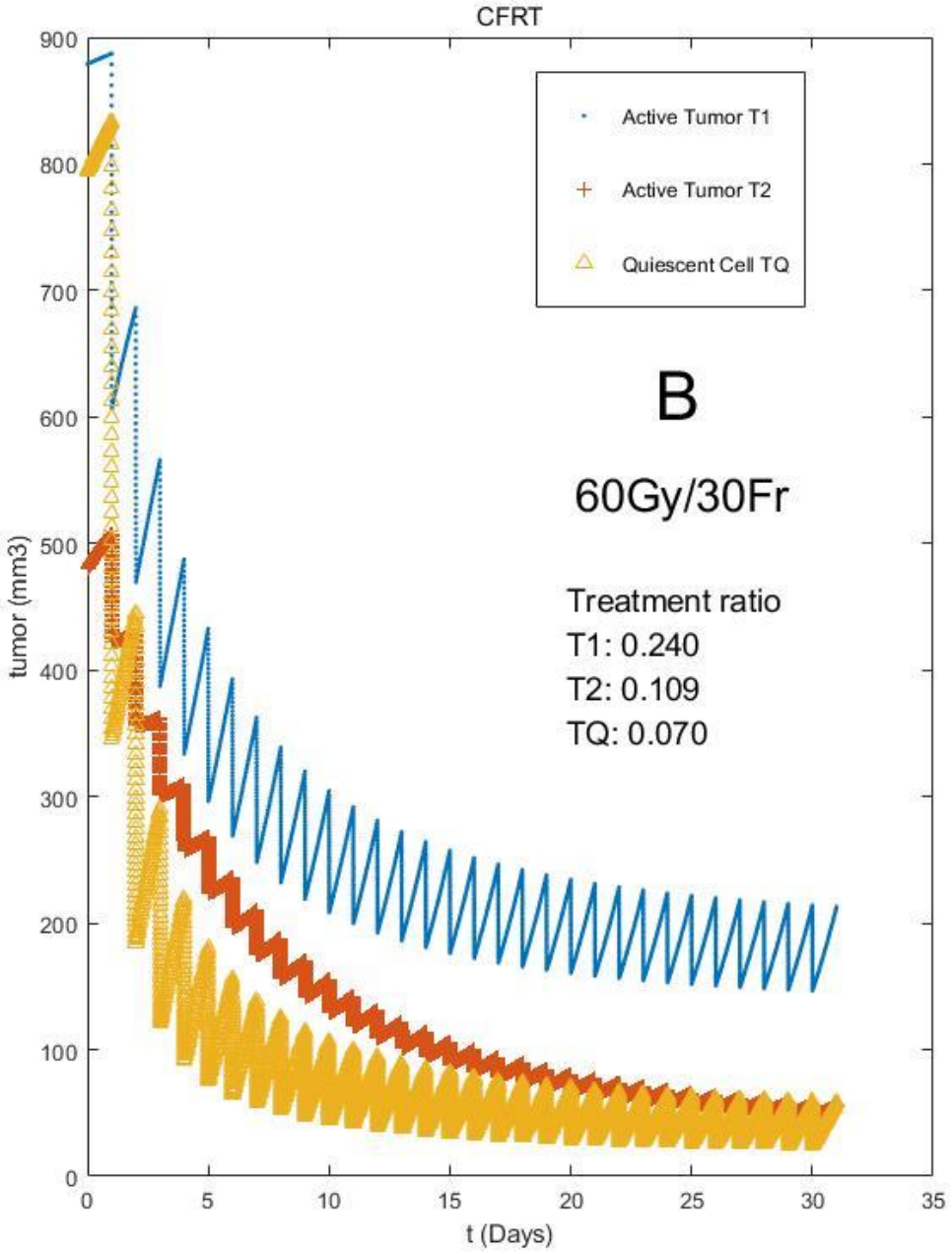
CFRT
Active Tumor T1
Active Tumor T2
Quiescent Cell TQ
B
60Gy/30Fr
Treatment ratio
T1: 0.240
T2: 0.109
TQ: 0.070
tumor (mm3)
t (Days)
0
100
200
300
400
500
600
700
800
900
0
5
10
15
20
25
30
35

Fig. 4B: CFRT-B

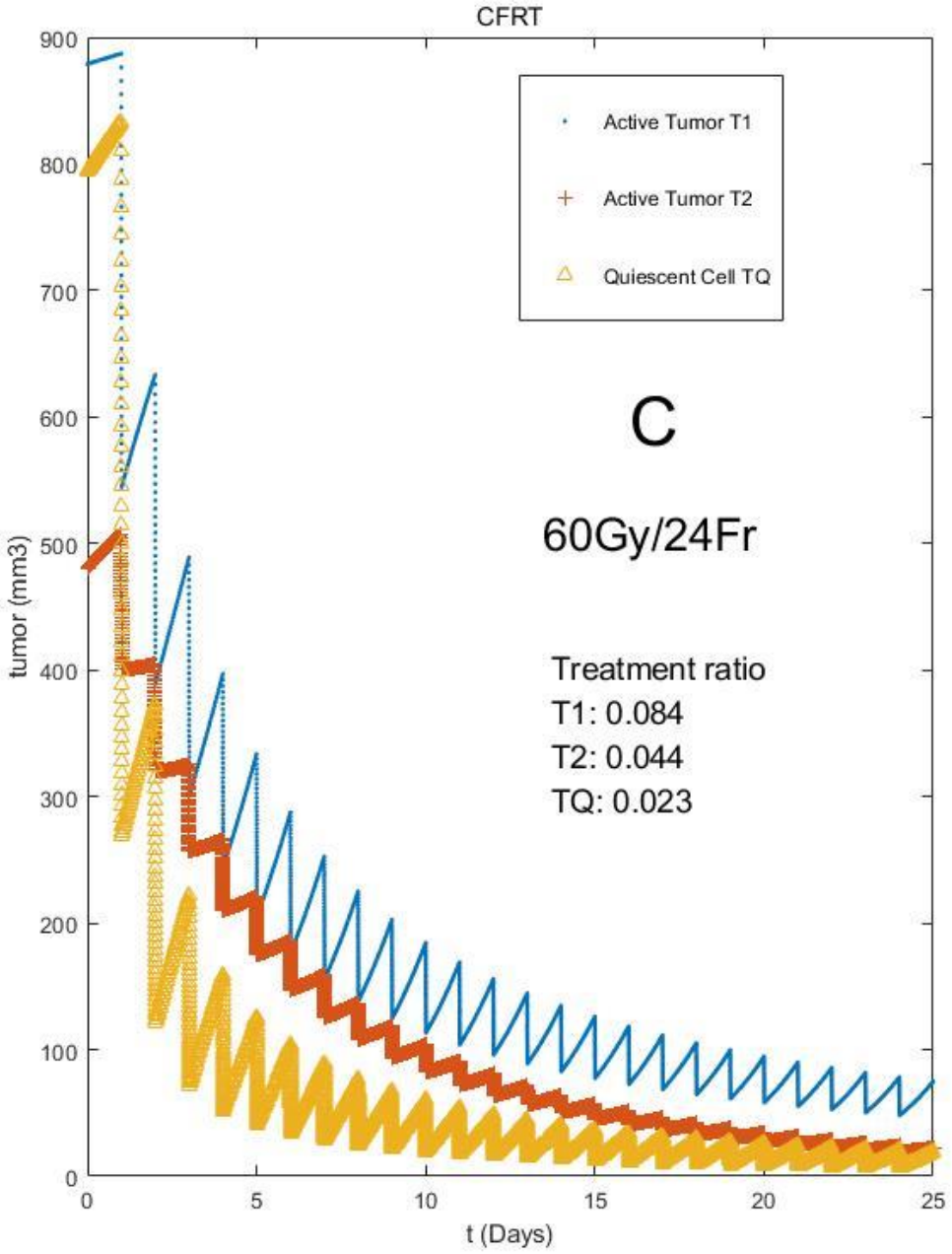
CFRT
Active Tumor T1
Active Tumor T2
Quiescent Cell TQ
C
60Gy/24Fr
Treatment ratio
T1: 0.084
T2: 0.044
TQ: 0.023
tumor (mm3)
t (Days)
0
100
200
300
400
500
600
700
800
900
0
5
10
15
20
25

Fig. 4C: CFRT-C

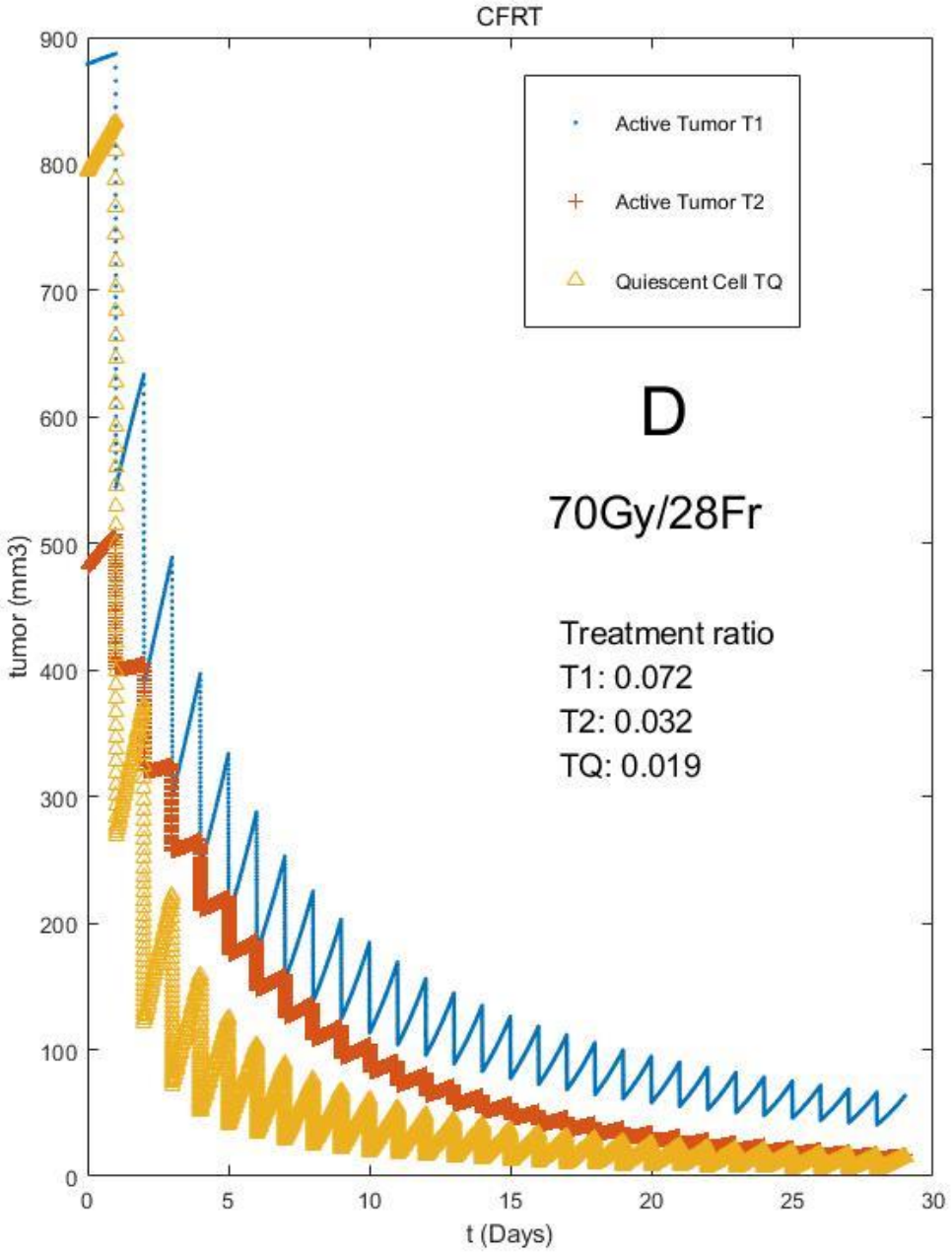
CFRT
Active Tumor T1
Active Tumor T2
Quiescent Cell TQ
D
70Gy/28Fr
Treatment ratio
T1: 0.072
T2: 0.032
TQ: 0.019
tumor (mm3)
t (Days)
0
100
200
300
400
500
600
700
800
900
0
5
10
15
20
25
30

Fig. 4D: CFRT-D

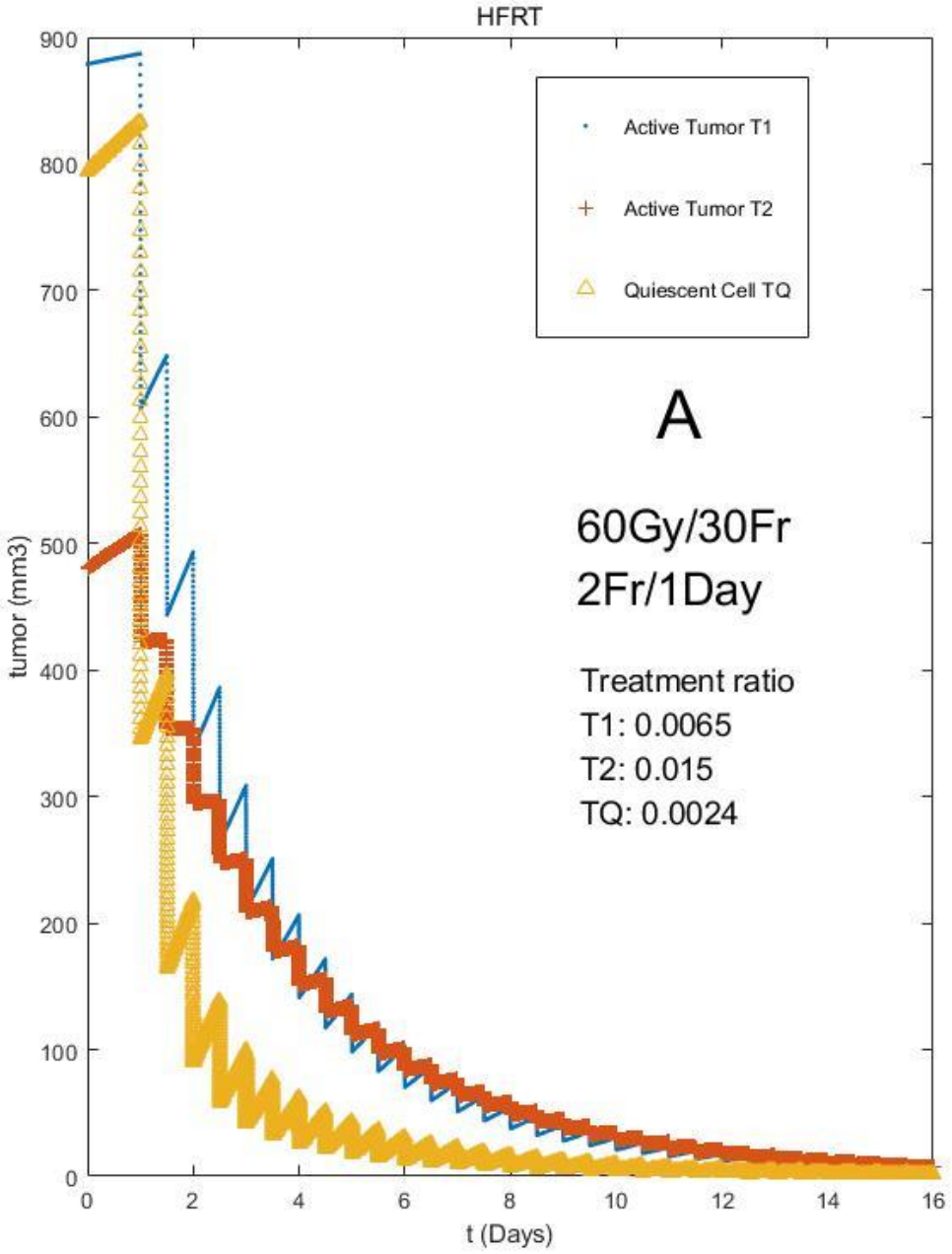
HFRT
Active Tumor T1
Active Tumor T2
Quiescent Cell TQ
A
60Gy/30Fr
2Fr/1Day
Treatment ratio
T1: 0.0065
T2: 0.015
TQ: 0.0024
tumor (mm3)
t (Days)
0
100
200
300
400
500
600
700
800
900
0
2
4
6
8
10
12
14
16

Fig. 5A: HFRT-A

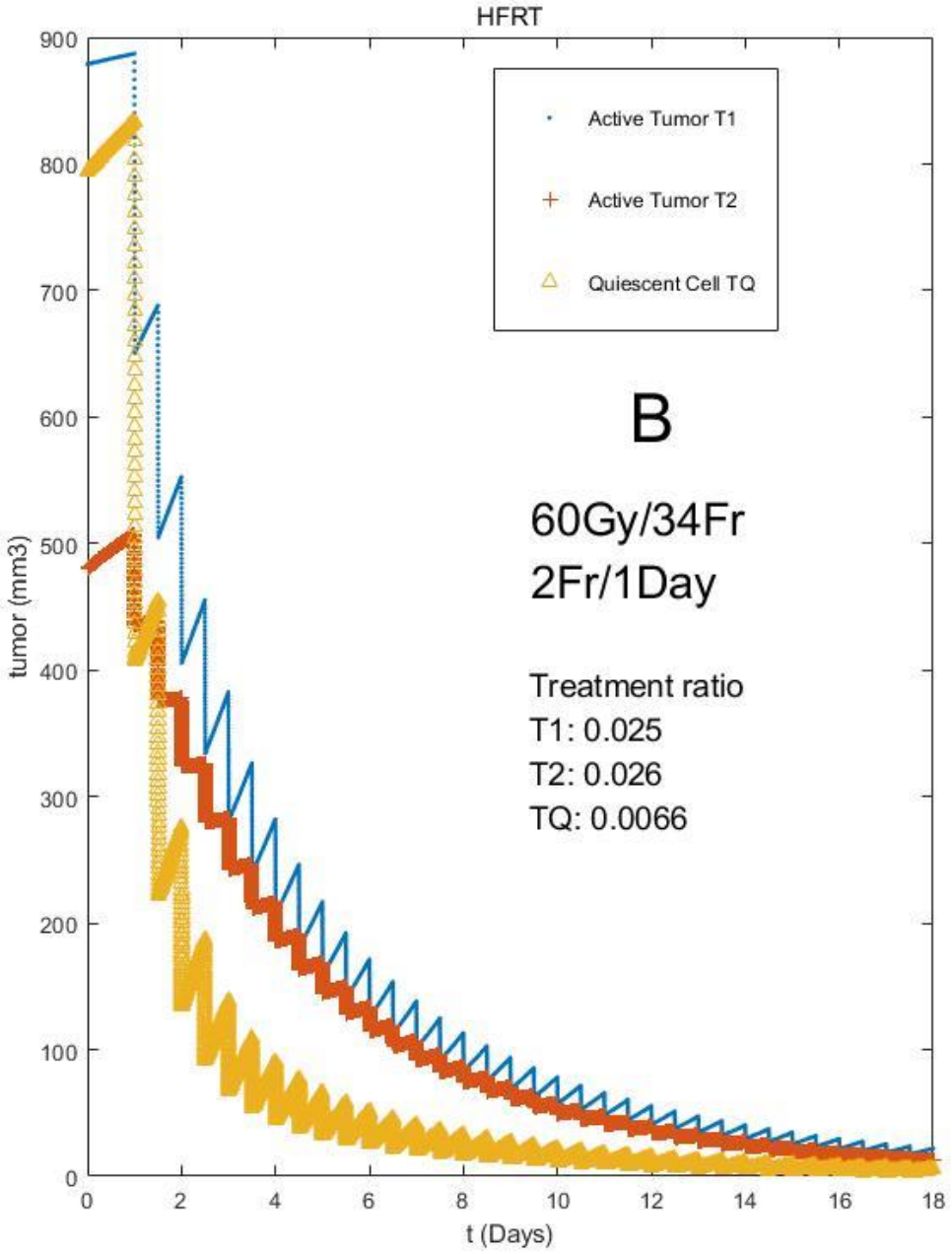
HFRT
Active Tumor T1
Active Tumor T2
Quiescent Cell TQ
B
60Gy/34Fr
2Fr/1Day
Treatment ratio
T1: 0.025
T2: 0.026
TQ: 0.0066
tumor (mm3)
t (Days)
0
100
200
300
400
500
600
700
800
900
0
2
4
6
8
10
12
14
16
18

Fig. 5B: HFRT-B

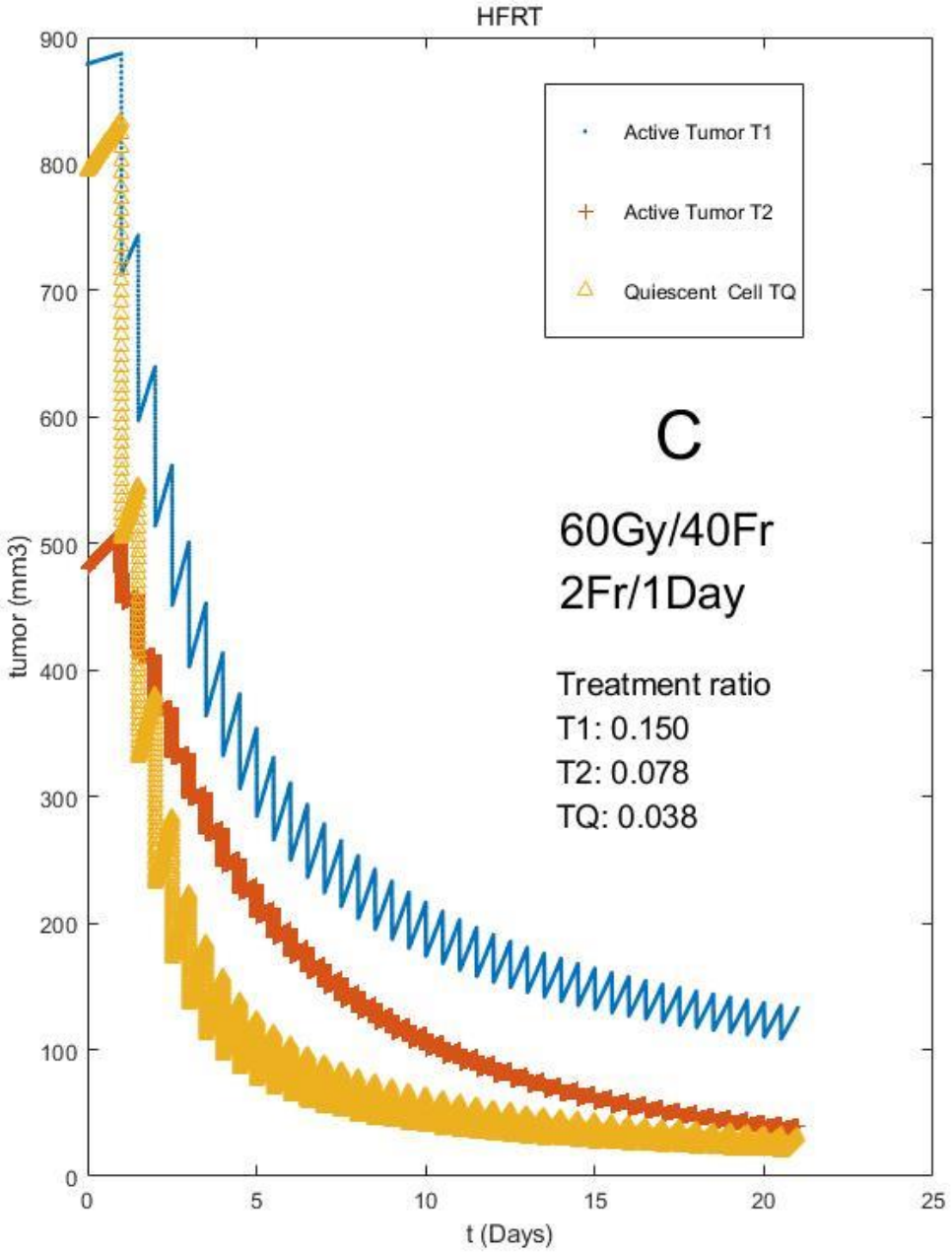
HFRT
Active Tumor T1
Active Tumor T2
Quiescent Cell TQ
C
60Gy/40Fr
2Fr/1Day
Treatment ratio
T1: 0.150
T2: 0.078
TQ: 0.038
tumor (mm3)
t (Days)
0
100
200
300
400
500
600
700
800
900
0
5
10
15
20
25

Fig. 5C: HFRT-C

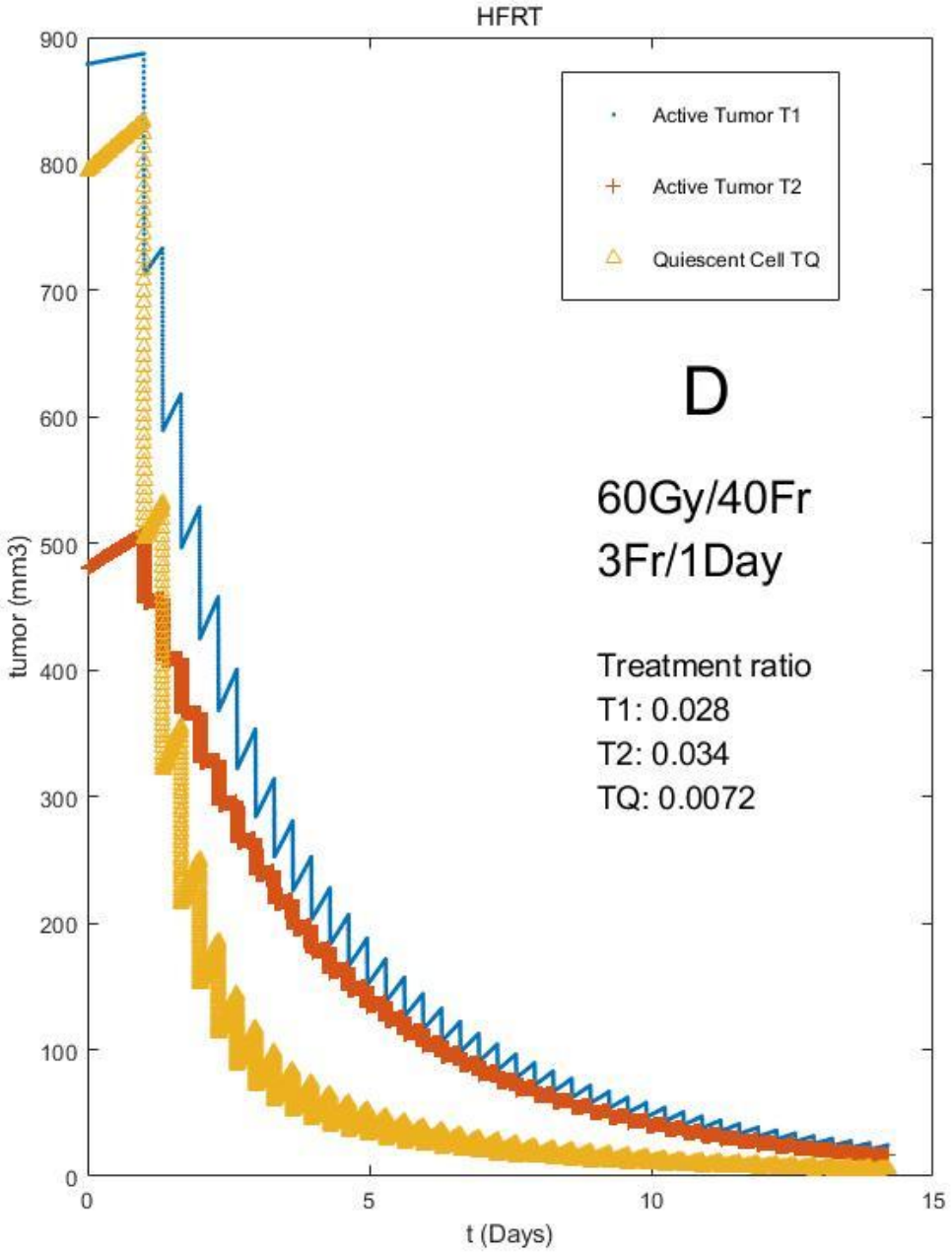
HFRT
Active Tumor T1
Active Tumor T2
Quiescent Cell TQ
D
60Gy/40Fr
3Fr/1Day
Treatment ratio
T1: 0.028
T2: 0.034
TQ: 0.0072
tumor (mm3)
t (Days)
900
800
700
600
500
400
300
200
100
0
0
5
10
15

Fig. 5D: HFRT-D

Figures

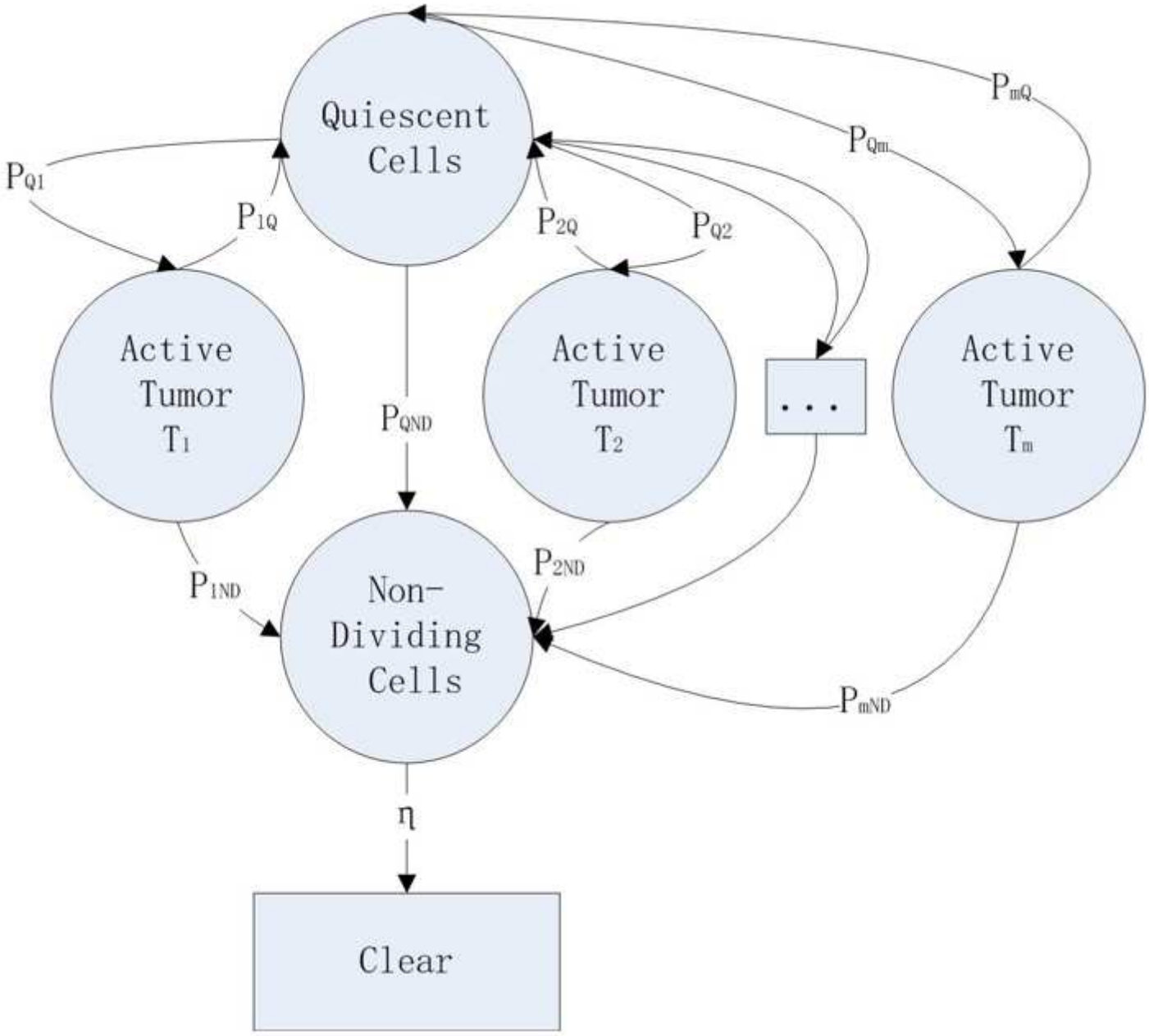

Figure 1

Illustration of multi-component model of tumor growth. It is assumed that there are different tumor cells in the tumor colony: the quiescent cells, which suspend dividing and can change to active tumors and non-dividing cells; non-dividing cells, which are dead and waiting to be cleared into the blood; active tumors: which can divide normally and can change to quiescent cells and non-dividing cells, and the active tumor also have different types, T_1,T_2,… T_m p_ij is the probability of cell i changing to cell j. η is the clear rate.

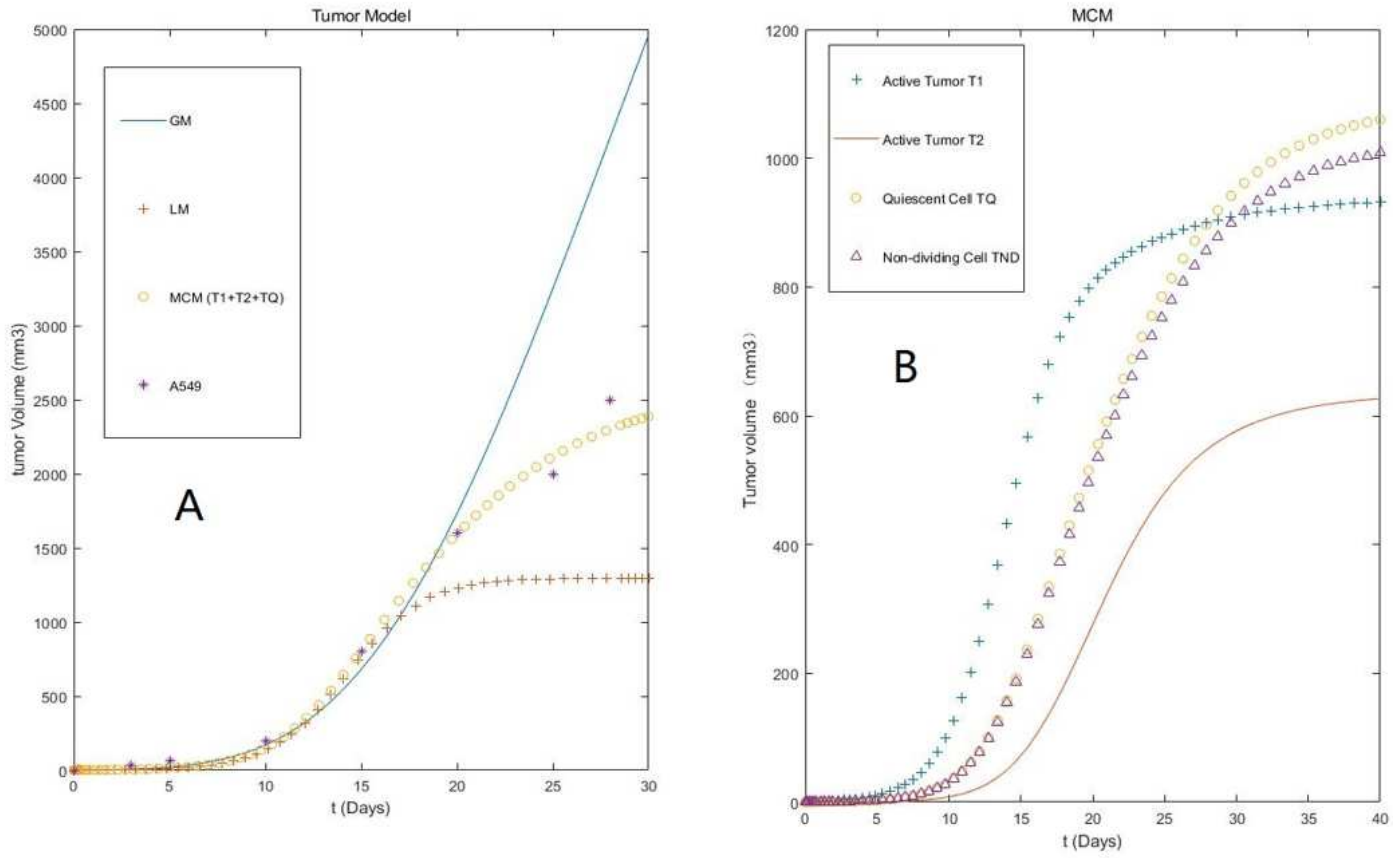

Figure 2

Comparison of GM, LM and MCM A) Tumor Model-A B) MCM-B

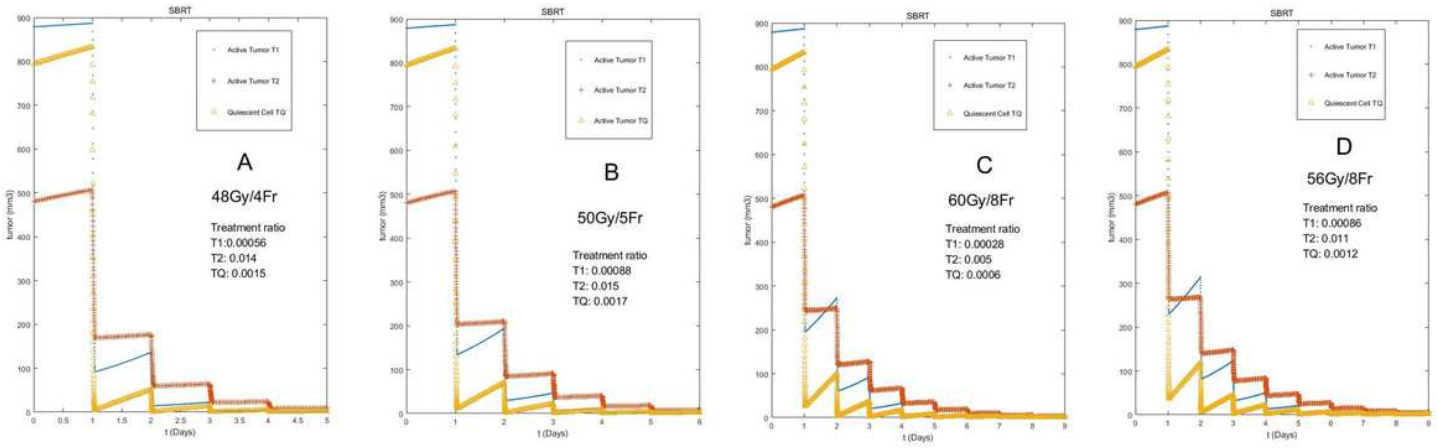

Figure 3

Comparison of SBRT with different RT parameters A)SBRT-A B)SBRT-B C)SBRT-C D)SBRT-D

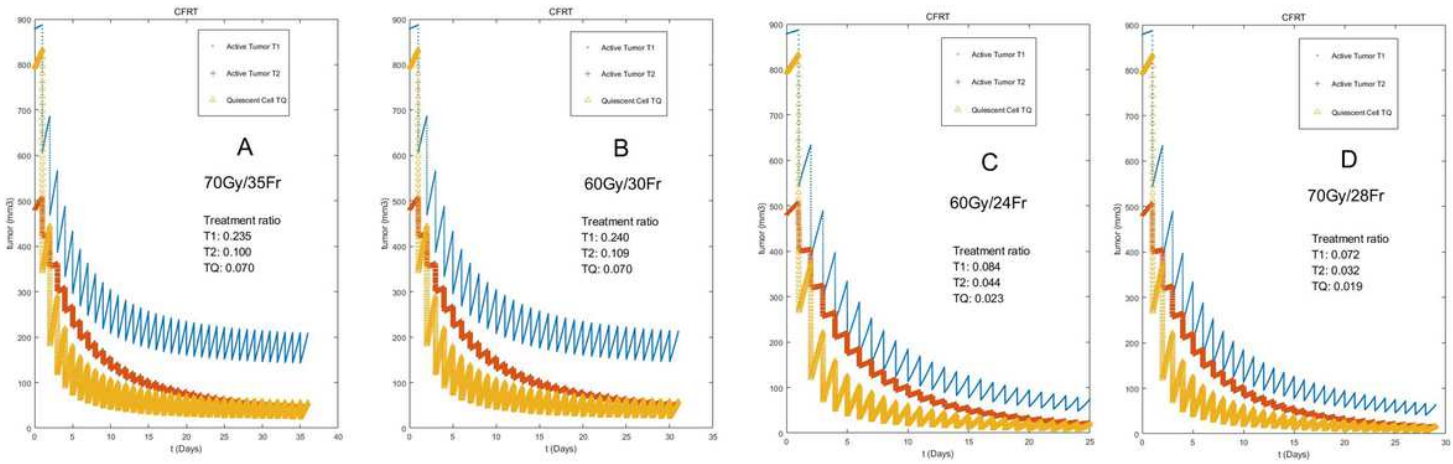

Figure 4

Comparison of CFRT with different RT parameters A)CFRT-A B)CFRT-B C)CFRT-C D)CFRT-D

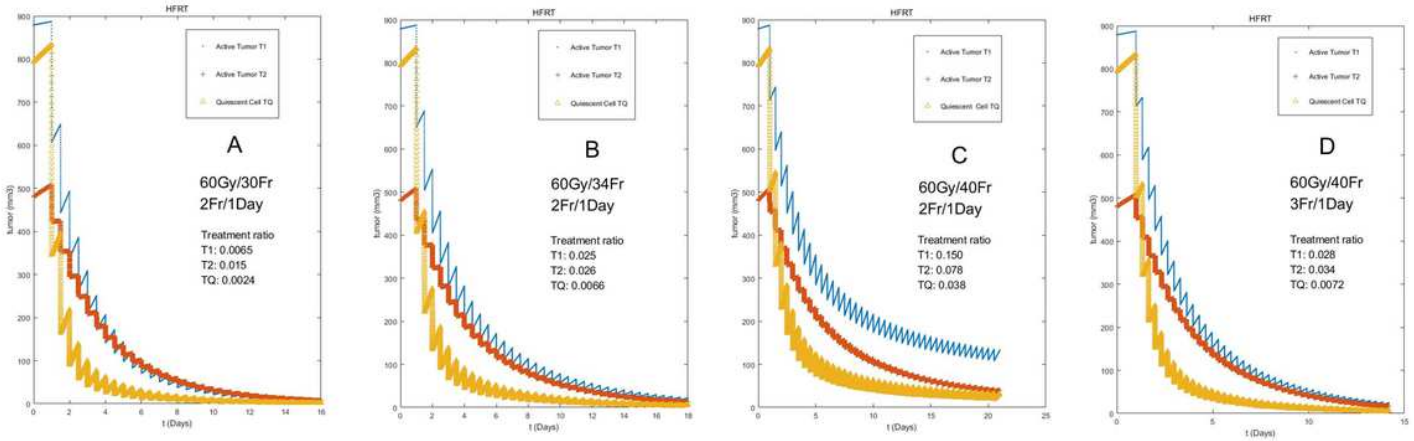

Figure 5

Comparison of HFRT with different RT parameters A)HFRT-A B)HFRT-B C)HFRT-C D)HFRT-D