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

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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
l 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. 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%).

Radiotherapy (RT) is a valuable approach for lung cancer treatment, especially for local advanced lung cancer. A serial of clinical evidences elucidate that radiotherapy combined with chemotherapy or immunotherapy may improve the local control of lung cancer. In recent years, a special radiotherapy method, named stereotactic body radiotherapy (SBRT), has been introduced to alternative treatment for early stage inoperable NSCLC. 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.

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. 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. 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. 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. In our past work, we have developed a mathematical model based on ODE for tumor
radiotherapy\textsuperscript{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 \textsuperscript{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\textsuperscript{24}, among which Logistic Model (LM) and Gompertz Model (GM) may be the most popular. LM is formulated as:

\[
\frac{dV}{dt} = aV \left(1 - \frac{V}{K}\right)
\]  

(1)

Where $V$, a function of time $t$, is the tumor volume, $\frac{d}{dt}$ 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\textsuperscript{25}. The model is described as:

\[
\frac{dV}{dt} = aV - bV\ln V
\]  

(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)):

\[
\begin{align*}
\frac{dV_1}{dt} &= a_1 V_1 \left(1 - \frac{V_1}{K_1}\right) + pQ_1 V_Q - (p_{1Q} + p_{1ND}) V_1 \\
\frac{dV_2}{dt} &= a_2 V_2 \left(1 - \frac{V_2}{K_2}\right) + pQ_2 V_Q - (p_{2Q} + p_{2ND}) V_2 \\
&\vdots \\
\frac{dV_m}{dt} &= a_m V_m \left(1 - \frac{V_m}{K_m}\right) + pQ_m V_Q - (p_{mQ} + p_{mND}) V_m \\
\frac{dV_Q}{dt} &= (p_{1Q} V_1 + p_{2Q} V_2 + \cdots + p_{mQ} V_m) - (p_{Q1} + p_{Q2} + \cdots + p_{Qm}) V_Q \\
\frac{dV_{ND}}{dt} &= p_{1ND} V_1 + p_{2ND} V_2 + \cdots + p_{mND} V_m + p_{QND} V_Q - \eta V_{ND}
\end{align*}
\]

\[m = 1, 2, \ldots, M\]

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

Where, \( V_m \), volume of the active tumor \( T_m \) mentioned in the Fig.1. \( \eta \) 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 \(^2\). 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:

\[S = e^{-\alpha D - \beta D^2}\]

Where \( S \) is the probability of survival tumor cells, \( D \) is single radiation dose, \( e \) is the natural constant, and \( \alpha, \beta \) are the parameters relating to the radiation sensitivity, which is represented as \( \alpha/\beta \). For using in this paper, we rewrite formula (4) in an ODE formulation:
\[
\frac{dV}{dt} = -(\alpha D + 2\beta D^2)V
\]

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:

\[
\begin{align*}
\frac{dv_1}{dt} &= a_1 V_1 \left(1 - \frac{V_1}{K_1}\right) + p_{Q1} V_Q - (p_{1Q} + p_{1ND}) V_1 - (\alpha_1 D + 2\beta_1 D^2) V_1 \\
\frac{dv_2}{dt} &= a_2 V_2 \left(1 - \frac{V_2}{K_2}\right) + p_{Q2} V_Q - (p_{2Q} + p_{2ND}) V_2 - (\alpha_2 D + 2\beta_2 D^2) V_2 \\
\vdots \\
\frac{dv_m}{dt} &= a_m V_m \left(1 - \frac{V_m}{K_m}\right) + p_{Qm} V_Q - (p_{mQ} + p_{mND}) V_m - (\alpha_m D + 2\beta_m D^2) V_m \\
\frac{dv_{ND}}{dt} &= (p_{1Q} V_1 + p_{2Q} V_2 + \cdots + p_{mQ} V_m) - (p_{Q1} + p_{Q2} + \cdots + p_{Qm} + p_{QND}) V_Q - (\alpha D V_{ND}) \\
\end{align*}
\]

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:

\[
V_{1i} = \sum_{i=1}^{L} \left( \int_{t_0}^{t_{Ri}} \left( a_{1i} V_{1i} \left(1 - \frac{V_{1i}}{K_{1i}}\right) + p_{Q1i} V_{Qi} - (p_{1Qi} + p_{1ND}) V_{1i} \right) dt \right) - \left( \int_{t_0}^{t_{Ri}} \left( (\alpha_{i} D_i + 2\beta_i D^2) V_{ai}\right) dt \right)
\]

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 \cite{27-28}. In 2013, Benzekry et al. recorded a serial of comprehensive experiments for several classical mathematical models for tumor growth \cite{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 data of the volume double time of lung cancer in some studies \cite{30-31}.

The parameters in LQ mode is mainly about the value of $\alpha$ and $\beta$. It was recommended in many paper that the value of $\alpha/\beta$ for lung cancer can be taken from 10 to 20 for clinical use \cite{32-33}, moreover, in paper \cite{34}, the value of $\alpha/\beta$, 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:

\[
\text{Treatment ratio} = \frac{\text{Tumor volume after RT}}{\text{Tumor volume before RT}}
\]

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 \cite{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).

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.
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.

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. But in the simulating result (Fig. 4), we can find that although the plan of 60Gy/30Fr can do well to higher $\alpha/\beta$ tumor T2 (Fig. 4A), its control power to low $\alpha/\beta$ tumor T1 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).

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 3-4 weeks 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 3.0 Gy, 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 1.2~1.5 Gy per fraction while 2 fractions per day, 5 days a week, but the plan was not mandatory, there was also an HFRT plan containing 1.5 Gy 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](image)

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 trial (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 into 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 quantitative 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.\textsuperscript{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 $\alpha$ and $\beta$. 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.

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**Authors' contributions**
WSg checked and approved the study.
ZGq designed, checked and approved the study.
HWs designed, wrote, revised and approved the manuscript.

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**Competing interests**

No competing interests.
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$^3$ |

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$_2$, ⋯ T$_m$
$p_{ij}$ is the probability of cell i changing to cell j.
$\eta$ is the clear rate.
\[ p_{Q1} = 0.1, p_{1Q} = 0.2, p_{1ND} = 0.2, \quad \text{day}^{-1} \]
\[ p_{Q2} = 0.1, p_{2Q} = 0.2, p_{2ND} = 0.2, \]
\[ p_{QND} = 0.09, \quad \eta = 0.4 \]

| 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
Fig. 2B: MCM-B
Fig. 3A: SBRT-A

A

48Gy/4Fr

Treatment ratio
T1: 0.00056
T2: 0.014
TQ: 0.0015
Fig. 3B: SBRT-B

50Gy/5Fr

Treatment ratio
T1: 0.00088
T2: 0.015
TQ: 0.0017
Fig. 3C: SBRT-C

C

60Gy/8Fr

Treatment ratio
T1: 0.00028
T2: 0.005
TQ: 0.0006
Fig. 4A: CFRT-A

A
70Gy/35Fr

Treatment ratio
T1: 0.235
T2: 0.100
TQ: 0.070
Fig. 4B: CFRT-B
Fig. 4C: CFRT-C
Fig. 4D: CFRT-D

D

70Gy/28Fr

Treatment ratio
T1: 0.072
T2: 0.032
TQ: 0.019
Fig. 5A: HFRT-A

60Gy/30Fr
2Fr/1Day

Treatment ratio
T1: 0.0065
T2: 0.015
TQ: 0.0024
Fig. 5B: HFRT-B
Fig. 5C: HFRT-C

C

60Gy/40Fr
2Fr/1Day

Treatment ratio
T1: 0.150
T2: 0.078
TQ: 0.038
Fig. 5D: HFRT-D

D

60Gy/40Fr
3Fr/1Day

Treatment ratio
T1: 0.028
T2: 0.034
TQ: 0.0072