Journal of Applied Mathematics and Computing (2023) 69:1819–1843
https://doi.org/10.1007/s12190-022-01813-z

ORIGINAL RESEARCH

Mathematical models and dynamic behaviors of cancer treatment by continuous and pulsed radiotherapy

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Received: 31 July 2022 / Revised: 20 September 2022 / Accepted: 20 October 2022 /
Published online: 6 November 2022

Abstract
In this study, two mathematical models are introduced to describe treatment of cancer by continuous and pulsed radiotherapy. In the continuous radiotherapy model, we determine all of the equilibrium points and conduct a thorough examination of the stability of these equilibria. Criterions of the radiation dose that guarantee the cancer to be eradicated or take a positive balance with normal cells are provided. In the pulsed radiotherapy model, conditions of the existence and stability of cancer win periodic solution, cancer eradication periodic solution and coexistent periodic solution are derived. Meanwhile, numerical simulations to the effect of radiation dose on the cure and spread of the cancer are carried out. A brief conclusion is presented, as well as a few intriguing subjects for additional investigation are discussed.

Keywords Radiotherapy · Cure · Coexistence · Cancer eradication periodic solution · Cancer win periodic solution

1 Introduction

Cancer is a fatal disease that affects people all over the world and is difficult to treat. Surgery, chemotherapy, radiotherapy and immunotherapy are four typical treatment options in clinical practice. As a result of the intersection of mathematics and medicine, many researchers have begun to utilize mathematical models to describe the cancer progression and its treatments, and have discovered a wealth of interesting insights

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about cancer [1–6]. This study will theoretically and numerically simulate cancer treatment using continuous and pulsed radiotherapy, as well as investigate its dynamical behaviors.

As the first line of treatment, radiotherapy has been shown to be an effective weapon in the fight against certain types of cancer [7, 8]. Radiation therapy uses radiation to kill malignant cells. This treatment is designed to target cells that quickly replicate, such as those found in cancer [9]. Michor and Beal [10] pointed out that mathematical modeling can be applied to improve cancer treatment as well as provide mechanistic insights. There have been a large number of studies that focus on cancer treatment by radiotherapy via methods of mathematical models [3, 5, 11–15]. Belostotski in [3] created a control theory model for radiotherapy treatment of cancer based on the Lotka-Volterra competition system. He regarded radiation therapy as a harvesting-type control term and equated the radiation-induced harvesting with the reduction of cancer cell concentration, considered four different types of treatment delivery, constant, linear, feedback and periodic, and investigated the cure or treatment of corresponding systems. As to the hypothesis in [3] that the effect of radiation on normal cells is zero, Freedman and Belostotski [11] improved the model by allowing the radiation affects the normal cells to some extent while radiotherapy, established sufficient conditions on the cure state to the four radiation delivery control mechanisms. Liu and Yang focused on cancer treatment with period radiotherapy [5, 12], presented period radiotherapy ODE models and studied their dynamic behaviors such as the coexistence of the normal and cancer cells, the existence and globally asymptotic stability of the positive periodic solution, the cancer eradication periodic solution and the cancer win periodic solution. Farayola et al. [13, 14] formulated Caputo Fractional derivative models to simulate cancer treatment process by radiotherapy, and gave the population changes in the cells and the final volumes of the normal and cancer cells in their results. Pang et al. [15] developed an impulsive differential equation model to describe tumor growth treated by radiotherapy and investigated the influence on the effect of tumor radiotherapy from the reoxygenation of hypoxic cells and the radiosensitivity of radiotherapy.

Though lots of mathematical models have been presented and studied on the cancer treatment with radiotherapy, there is still much basic and impressed work worth to carry out. This paper aims to establish mathematical models to the cancer treatment by continuous and pulsed radiotherapy and analyze their dynamical behaviors. Based on ideas and rules of paper [3], we provide a cancer treatment model with continuous radiotherapy. We calculate the four equilibrium points of the model and make a comprehensive analysis on the stabilities of these four equilibrium points. To the pulsed radiotherapy, we reconsider the period radiotherapy model in paper [12]. We investigate the existence and stability of boundary periodic solutions and positive periodic solution by applying new methods that are different with the methods in [5, 12]. Moreover, we conduct numerical simulations to discuss in depth the effect of radiation dose on the cure or spread of the cancer.

The organization of the remaining part is as follows. In Sect. 2, we present tumor growth model without treatment and give a useful Lemma. A theoretically comprehensive analysis on the existence and stability of the equilibrium points to the continuous radiotherapy treatment model is done in Sect. 3. In Sect. 4, we investigate the pulsed

Table 1 Definition of variables and parameters

$\dot{x}$	dx/dt
x_1	The concentration of the normal cells in the given tissue
x_2	The concentration of the cancer cells in the given tissue
α_1	The proliferation coefficient of the normal cells
α_2	The proliferation coefficient of the cancer cells
K_1	The allowed maximum concentration of the normal cells in the given tissue (carrying capacity)
K_2	The allowed maximum concentration of the cancer cells in the given tissue (carrying capacity)
β_1	Competition coefficient from cancer to normal cells
β_2	Competition coefficient from normal to cancer cells

radiotherapy cancer treatment model theoretically and numerically. Finally, we conclude this paper and provide an interesting problem for further study.

2 The model without treatment

Considering a piece of bodily tissue that contain cancer cells, we model the interaction between normal and cancer cells as a competition for tissue resources and take the following Lotka-Volterra competition type [16–18]:

$$\begin{cases} \dot{x}_1 = \alpha_1 x_1\left(1 - \dfrac{x_1}{K_1}\right) - \beta_1 x_1 x_2, \\ \dot{x}_2 = \alpha_2 x_2\left(1 - \dfrac{x_2}{K_2}\right) - \beta_2 x_1 x_2. \end{cases} \tag{2.1}$$

The definition of variables and parameters is given in Table 1.

According to the biological interpretation, we assume that $x_1(0) \geq 0$, $x_2(0) \geq 0$, α_i, K_i, β_i are all positive constants for $i = 1, 2$. For model (2.1), the following well-known results had been proved in [19, 20].

Lemma 2.1 *The model (2.1) always has a trivial equilibrium $\bar{E}_0(0, 0)$ and two semi-trivial equilibria $\bar{E}_1(K_1, 0)$ and $\bar{E}_2(0, K_2)$. Denote $\Delta = \alpha_1\alpha_2 - \beta_1\beta_2 K_1 K_2$, suppose that*

(i) $\Delta < 0$,

(i1) *if $\alpha_2 - \beta_2 K_1 > 0$, then $\bar{E}_0$ is an unstable node, $\bar{E}_1$ is a saddle point and $\bar{E}_2$ is a stable focus;*

(i2) *if $\alpha_1 - \beta_1 K_2 > 0$, then $\bar{E}_0$ is an unstable node, $\bar{E}_1$ is a stable focus and $\bar{E}_2$ is a saddle point;*

(i3) *if $\alpha_2 - \beta_2 K_1 < 0$ and $\alpha_1 - \beta_1 K_2 < 0$, then $\bar{E}_0$ is an unstable node, $\bar{E}_1$ and $\bar{E}_2$ are stable focuses, model (2.1) has a unique positive equilibrium $\bar{E}^*(x_1^*, x_2^*)$ which is a saddle point, where*

$$\bar{x}_1^* = \frac{\alpha_2}{K_2}\frac{\alpha_1 - \beta_1 K_2}{\Delta}, \qquad \bar{x}_2^* = \frac{\alpha_1}{K_1}\frac{\alpha_2 - \beta_2 K_1}{\Delta};$$

(ii) $\Delta > 0$,

(ii1) *if* $\alpha_2 - \beta_2 K_1 < 0$, *then* $\bar{E}_0$ *is an unstable node,* $\bar{E}_1$ *is a stable focus and* $\bar{E}_2$ *is a saddle point;*

(ii2) *if* $\alpha_1 - \beta_1 K_2 < 0$, *then* $\bar{E}_0$ *is an unstable node,* $\bar{E}_1$ *is a saddle point and* $\bar{E}_2$ *is a stable focus;*

(ii3) *if* $\alpha_2 - \beta_2 K_1 > 0$ *and* $\alpha_1 - \beta_1 K_2 > 0$, *then* $\bar{E}_0$ *is an unstable node,* $\bar{E}_1$ *and* $\bar{E}_2$ *are saddle points, model (2.1) has a unique positive equilibrium* $\bar{E}^*(x_1^*, x_2^*)$ *which is globally asymptotically stable in the interior of the first quadrant.*

Remark 2.1 From Lemma 2.1,
(1) $\bar{E}_0$ is always an unstable node, i.e., normal and cancer cells will never go extinct simultaneously for any positive initial concentration of normal cells;
(2) If the interior positive equilibrium $\bar{E}^*$ does not exist, then $\bar{E}_1$ is a stable focus and $\bar{E}_2$ is a saddle point (or exchange the stability), i.e., either the normal cells win the competition and the cancer cells go extinct, or the cancer cells win the competition and spread for all positive initial concentrations of normal and cancer cells;
(3) If there is an interior positive equilibrium $\bar{E}^*$ of the model, then either it is globally asymptotically stable in the interior of the first quadrant or it is a saddle point, at this moment, $\bar{E}_1$ and $\bar{E}_2$ are stable focuses with stabilities depending on the location of the initial values $x_1(0)$ and $x_2(0)$ in the first quadrant, i.e., either the normal and cancer cells coexist or one of them wins the competition, which depends on the initial concentrations of the normal and cancer cells.

As we all know, in the absence of treatment, most cancer will win the competition and spread, i.e., $\bar{E}_2(0, K_2)$ is one globally stable equilibrium of model (2.1) for any positive initial value. Criteria from Lemma 2.1 (also can refer to [16]) for this to happen are

$$\alpha_1 < \beta_1 K_2 \qquad \text{and} \qquad \alpha_2 > \beta_2 K_1. \tag{2.2}$$

Throughout the rest of this paper, we assume that (2.2) holds.

In the following, we will modify model (2.1) by adding continuous or pulsed radiotherapy and analyze their dynamical behaviors. Meanwhile, we will discuss the medical meanings of these mathematical results.

3 Treatment by continuous radiotherapy

In this section, we consider the continuous application of radiotherapy, without pause or interruption. We aims to make a theoretically comprehensive analysis on the treatment by continuous radiotherapy which has not been done before, even if we know this continuous radiation therapy may not be often used in real clinical treatment for protecting the patient's physical condition under the radiation.

To incorporate the effect of the radiation in model (2.1), we assume that the administration of radiation removes a large amount of cancer cells and a small amount of normal cells from the system. Here, the terms "large" and "small" are used as a relation to the appropriate cell population at a particular location in the organism. Radiotherapy

is in fact a control mechanism on the rates of change of the concentrations of cancer and normal cells by harvesting them. Model (2.1) is modified under the continuous radiotherapy to take the form

$$\begin{cases} \dot{x}_1 = \alpha_1 x_1\Big(1 - \dfrac{x_1}{K_1}\Big) - \beta_1 x_1 x_2 - \varepsilon\gamma x_1, \\ \dot{x}_2 = \alpha_2 x_2\Big(1 - \dfrac{x_2}{K_2}\Big) - \beta_2 x_1 x_2 - \gamma x_2, \end{cases} \tag{3.1}$$

where γ is the radiation dose and $\varepsilon\gamma$ is the proportion of the radiation to the normal cells, $0 < \varepsilon \leq 1$ ($\varepsilon = 0$ is the ideal, but impossible to achieve in a practical scenario). Rewrite model (3.1) as

$$\begin{cases} \dot{x}_1 = (\alpha_1 - \varepsilon\gamma)x_1\Big[1 - \dfrac{x_1}{K_1(1 - \frac{\varepsilon\gamma}{\alpha_1})}\Big] - \beta_1 x_1 x_2, \\ \dot{x}_2 = (\alpha_2 - \gamma)x_2\Big[1 - \dfrac{x_2}{K_2(1 - \frac{\gamma}{\alpha_2})}\Big] - \beta_2 x_1 x_2. \end{cases} \tag{3.2}$$

The rest of this section will analyze the equilibria and stabilities of model (3.2) as the change of radiation dose γ under assumption (2.2).

There are four possible nonnegative equilibria for model (3.2), namely $E_0(0, 0)$, $E_1(K_1(1-\varepsilon\gamma/\alpha_1), 0)$, $E_2(0, K_2(1-\gamma/\alpha_2))$ and $E^*(x_1^*, x_2^*)$. E_0, the null state, always exists. If the inequalities $\alpha_1 > \varepsilon\gamma$ and $\alpha_2 > \gamma$ hold, the boundary equilibria E_1 and E_2 exist. The interior equilibrium E^*, if exists, will be

$$\begin{aligned} x_1^* &= \frac{K_1\alpha_2(\alpha_1 - \varepsilon\gamma) - K_1K_2\beta_1(\alpha_2 - \gamma)}{\Delta}, \\ x_2^* &= \frac{-K_1K_2\beta_2(\alpha_1 - \varepsilon\gamma) + \alpha_1K_2(\alpha_2 - \gamma)}{\Delta}, \end{aligned} \tag{3.3}$$

where Δ still denotes the expression $\alpha_1\alpha_2 - \beta_1\beta_2K_1K_2$.

Applying Lemma 2.1, we analyze model (3.2) theoretically. Meanwhile, we conduct numerical simulations to verify the results and to make the results more visible. We use the non-dimensional number 1 to represent the carrying capacity of normal and cancer cell populations [3]. Therefore, the initial conditions should satisfy $x_1(0) \leq 1, x_2(0) \leq 1$. We take initial values $(x_1(0), x_2(0))$ as $(0.1, 0.8)$, $(0.25, 0.05)$, $(0.25, 1)$, $(0.5, 0.7)$, $(0.6, 0.05)$, $(0.75, 0.4)$, $(0.9, 0.95)$, $(1, 0.2)$ respectively. Table 2 shows the parameters that are taken. The reasonable of the parameters can be referred to papers [3, 9, 21, 22]. But note that they do not come from any real cell populations.

Case I: $\Delta < 0$.

We first analyze (I1)-(I3) under assumptions $\alpha_1 > \varepsilon\gamma$ and $\alpha_2 > \gamma$.

(I1) $(\alpha_2 - \gamma) - \beta_2K_1(1 - \varepsilon\gamma/\alpha_1) > 0$, then E_0 is an unstable node, E_1 is a saddle point, E_2 is a stable focus and E^* does not exist. Now we consider the value of parameter γ. It follows from the assumption of (I1) that $(\alpha_1 - \beta_2K_1\varepsilon)\gamma < \alpha_1(\alpha_2 - \beta_2K_1)$. Obviously, it always holds for $\alpha_1 - \beta_2K_1\varepsilon \leq 0$ because of $\alpha_2 > \beta_2K_1$. Then we have $\alpha_1/\varepsilon \leq \beta_2K_1 < \alpha_2$ and $\gamma < \min\{\alpha_1/\varepsilon, \alpha_2\} = \alpha_1/\varepsilon$. When $\alpha_1 - \beta_2K_1\varepsilon > 0$,

Table 2 Values of parameters for continuous radiotherapy

Parameters	Values for $\Delta < 0$	Values for $\Delta > 0$	References
α_1	0.2	0.1	[3, 22]
α_2	0.6	0.45	[3, 21, 22]
K_1	1	1	[3, 9]
K_2	1	1	[3, 9]
β_1	0.5	0.11	[3]
β_2	0.55	0.15	[3]

then $\gamma < \min\{\alpha_1/\varepsilon, \alpha_2, \alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon)\} = \alpha_1/\varepsilon$ for $\alpha_1/\alpha_2 \leq \varepsilon$ and $\gamma < \min\{\alpha_1/\varepsilon, \alpha_2, \alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon)\} = \alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon)$ for $\alpha_1/\alpha_2 > \varepsilon$. Therefore we have $\gamma < \alpha_1/\varepsilon$ holds for all $\varepsilon \geq \alpha_1/\alpha_2$. Finally, for all $\gamma < \alpha_1/\varepsilon$ when $\alpha_1/\alpha_2 \leq \varepsilon \leq 1$ and all $\gamma < \alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon)$ when $\varepsilon < \alpha_1/\alpha_2$, we always have E_2 is a stable focus and there are no other equilibrium points. This indicates that cancer will win the competition and spread when γ take values in these ranges. See Fig. 1A1 and B1.

Remark 3.1 Conditions and results of (I1) can be understood as follows. When $\alpha_1/\alpha_2 \leq \varepsilon \leq 1$, larger proportion of radiation to the normal cells will lead to the extinction of normal cells for all radiation dose $\gamma < \alpha_1/\varepsilon$. However, if we set a smaller spilled proportion of radiation, i.e. $\varepsilon < \alpha_1/\alpha_2$, then the radiation dose γ will satisfy $\gamma < \alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon)$, this implies that less radiation dose can not kill cancer cells successfully. In a word, radiation dose that satisfies condition (I1) can not cure the cancer.

(I2) $(\alpha_1 - \varepsilon\gamma) - \beta_1 K_2(1 - \gamma/\alpha_2) > 0$, then E_0 is an unstable node, E_1 is a stable focus, E_2 is a saddle point and E^* does not exist. From the assumption of (I2), we have $(\alpha_2\varepsilon - \beta_1 K_2)\gamma < \alpha_2(\alpha_1 - \beta_1 K_2)$. Obviously, γ does not exist for $\alpha_2\varepsilon - \beta_1 K_2 \geq 0$ because of the inequality $\alpha_1 < \beta_1 K_2$. When $\alpha_2\varepsilon - \beta_1 K_2 < 0$, then $\alpha_2(\beta_1 K_2 - \alpha_1)/(\beta_1 K_2 - \alpha_2\varepsilon) < \gamma < \min\{\alpha_1/\varepsilon, \alpha_2\}$. However, γ also does not exist for all $\alpha_1/\alpha_2 \leq \varepsilon$ since $\alpha_2(\beta_1 K_2 - \alpha_1)/(\beta_1 K_2 - \alpha_2\varepsilon) - \alpha_2 \geq 0$. Hence, we focus on $\alpha_1/\alpha_2 > \varepsilon$. Now we have $\alpha_2(\beta_1 K_2 - \alpha_1)/(\beta_1 K_2 - \alpha_2\varepsilon) < \gamma < \alpha_2$. This inequality is reasonable as $\alpha_2 - \alpha_2(\beta_1 K_2 - \alpha_1)/(\beta_1 K_2 - \alpha_2\varepsilon) = \alpha_2(\alpha_1 - \alpha_2\varepsilon)/(\beta_1 K_2 - \alpha_2\varepsilon) > 0$. Finally in case (I2) we have E_1 is a stable focus and there are no other equilibrium for all $\alpha_2(\beta_1 K_2 - \alpha_1)/(\beta_1 K_2 - \alpha_2\varepsilon) < \gamma < \alpha_2$ when $\alpha_1/\alpha_2 < \varepsilon$. Medically, the normal cells will win the competition and cancer will be eradicated when $\alpha_2(\beta_1 K_2 - \alpha_1)/(\beta_1 K_2 - \alpha_2\varepsilon) < \gamma < \alpha_2$. See Fig. 1A3 and B3.

Remark 3.2 When $\varepsilon < \alpha_1/\alpha_2$, it is shown that the cancer will win the competition for all $\gamma < \alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon)$ from (I1) and the cancer will be eradicated for all $\alpha_2(\beta_1 K_2 - \alpha_1)/(\beta_1 K_2 - \alpha_2\varepsilon) < \gamma < \alpha_2$ from (I2). Moreover, we notice that $\alpha_2(\beta_1 K_2 - \alpha_1)/(\beta_1 K_2 - \alpha_2\varepsilon) - \alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon) > 0$ under the basic conditions $\alpha_1 < K_2\beta_1, \alpha_2 > K_1\beta_2$ and $\Delta < 0$ when $\varepsilon < \alpha_1/\alpha_2$. Hence, from (I1) and (I2) we can conclude that as the increase of the radiation dose for a smaller radiation spill, the cancer can be cured in their early stages.

(I3) $(\alpha_2 - \gamma) - \beta_2 K_1(1 - \varepsilon\gamma/\alpha_1) < 0$ and $(\alpha_1 - \varepsilon\gamma) - \beta_1 K_2(1 - \gamma/\alpha_2) < 0$, then E_0 is an unstable node, E_1 and E_2 are stable focuses, the unique positive equilibrium $E^*(x_1^*, x_2^*)$ is a saddle point. From the assumption of (I3) we have

$$(\alpha_1 - \beta_2 K_1 \varepsilon)\gamma > \alpha_1(\alpha_2 - \beta_2 K_1) \tag{3.4}$$

and

$$(\alpha_2 \varepsilon - \beta_1 K_2)\gamma > \alpha_2(\alpha_1 - \beta_1 K_2). \tag{3.5}$$

Obviously, γ does not exist when $\alpha_1 - \beta_2 K_1 \varepsilon \leq 0$. When $\alpha_1 - \beta_2 K_1 \varepsilon > 0$, then $\alpha_2 \varepsilon - \beta_1 K_2 < 0$ because of $\Delta < 0$. Hence from (3.4) we have $\gamma > \alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon)$ and (3.5) we have $\gamma < \alpha_2(\alpha_1 - \beta_1 K_2)/(\alpha_2 \varepsilon - \beta_1 K_2)$. Sequently we have $\alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon) < \gamma < \min\{\alpha_1/\varepsilon, \alpha_2, \alpha_2(\alpha_1 - \beta_1 K_2)/(\alpha_2 \varepsilon - \beta_1 K_2)\}$ for $\alpha_1 - \beta_2 K_1 \varepsilon > 0$. If $\alpha_1/\alpha_2 \leq \varepsilon$, then $\alpha_1/\varepsilon \leq \alpha_2$ and $[\alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon)]/(\alpha_1/\varepsilon) = (\alpha_2 - \beta_2 K_1)\varepsilon/(\alpha_1 - \beta_2 K_1 \varepsilon) \geq 1$. Hence, γ does not exist when $\alpha_1/\alpha_2 \leq \varepsilon$. On the other hand, if $\alpha_1/\alpha_2 > \varepsilon$, i.e., $\alpha_1/\varepsilon > \alpha_2$, then $\alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon) < \gamma < \min\{\alpha_2, \alpha_2(\alpha_1 - \beta_1 K_2)/(\alpha_2 \varepsilon - \beta_1 K_2)\} = \alpha_2(\alpha_1 - \beta_1 K_2)/(\alpha_2 \varepsilon - \beta_1 K_2)$ and the existence of γ is guaranteed by $\alpha_2(\alpha_1 - \beta_1 K_2)/(\alpha_2 \varepsilon - \beta_1 K_2) - \alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon) > 0$ for all $\alpha_1/\alpha_2 > \varepsilon$. Notice that $\alpha_1/\alpha_2 > \varepsilon$ also implies $\alpha_1 - \beta_2 K_1 \varepsilon > 0$. Finally, case (I3) means that when $\alpha_1/\alpha_2 > \varepsilon$, E_0 is an unstable node, E_1 and E_2 are stable focuses, $E^*(x_1^*, x_2^*)$ exists and is a saddle point for all $\alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon) < \gamma < \alpha_2(\alpha_1 - \beta_1 K_2)/(\alpha_2 \varepsilon - \beta_1 K_2)$. Medically, when the radiation dose $\alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon) < \gamma < \alpha_2(\alpha_1 - \beta_1 K_2)/(\alpha_2 \varepsilon - \beta_1 K_2)$, the cancer's spread or eradication will depend on the initial concentrations of the two kind cells. See Fig. 1A2 and B2.

Remark 3.3 When $\Delta < 0$, for all $0 < \varepsilon < \alpha_1/\alpha_2$, two radiation doses $\alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon)$ and $\alpha_2(\alpha_1 - \beta_1 K_2)/(\alpha_2 \varepsilon - \beta_1 K_2)$ are very important. We can conclude that the cancer will win the competition for all $\gamma < \alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon)$, the cancer will be cured for all $\alpha_2(\alpha_1 - \beta_1 K_2)/(\alpha_2 \varepsilon - \beta_1 K_2) < \gamma < \alpha_2$ and the cancer's spread or eradication will depend on the initial concentrations of the two kind cells when $\alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon) < \gamma < \alpha_2(\alpha_1 - \beta_1 K_2)/(\alpha_2 \varepsilon - \beta_1 K_2)$.

To the analytical integrality in mathematics, we make the following complementary analysis.

(I4) (a) $0 < \varepsilon < \alpha_1/\alpha_2$. If $\alpha_2 < \gamma < \alpha_1/\varepsilon$, E_2 and E^* do not exist. Moreover, it follows from model (3.3) that $\dot{x}_2(t) \leq (\alpha_2 - \gamma)x_2(t)$, i.e., $\lim_{t \to +\infty} x_2(t) \to 0$, then $\lim_{t \to +\infty} x_1(t) \to K_1(1 - \varepsilon\gamma)/\alpha_1$. This means that E_1 is a globally asymptotically stable boundary equilibrium point, i.e., the cancer will be cured. See Fig. 1A4 and B4. However, if $\gamma > \alpha_1/\varepsilon$, from model (3.2) we have E_1 and E_2 are nonexist, E_0 is a globally stable point and the existence of E^* can not be judged but does not affect the global behavior of E_0. See Fig. 1A5 and B5. (b) $\varepsilon \geq \alpha_1/\alpha_2$. If $0 < \gamma < \alpha_1/\varepsilon$, it follows from (I1) that E_0 and E_1 are unstable points, E^* is nonexist and E_2 is a stable focus, i.e., the cancer will spread. See Fig. 2A6 and B6. If $\alpha_1/\varepsilon \leq \gamma \leq \alpha_2$, applying the same analysis as (a) we have E_1 and E^* do not exist and E_2 is a globally

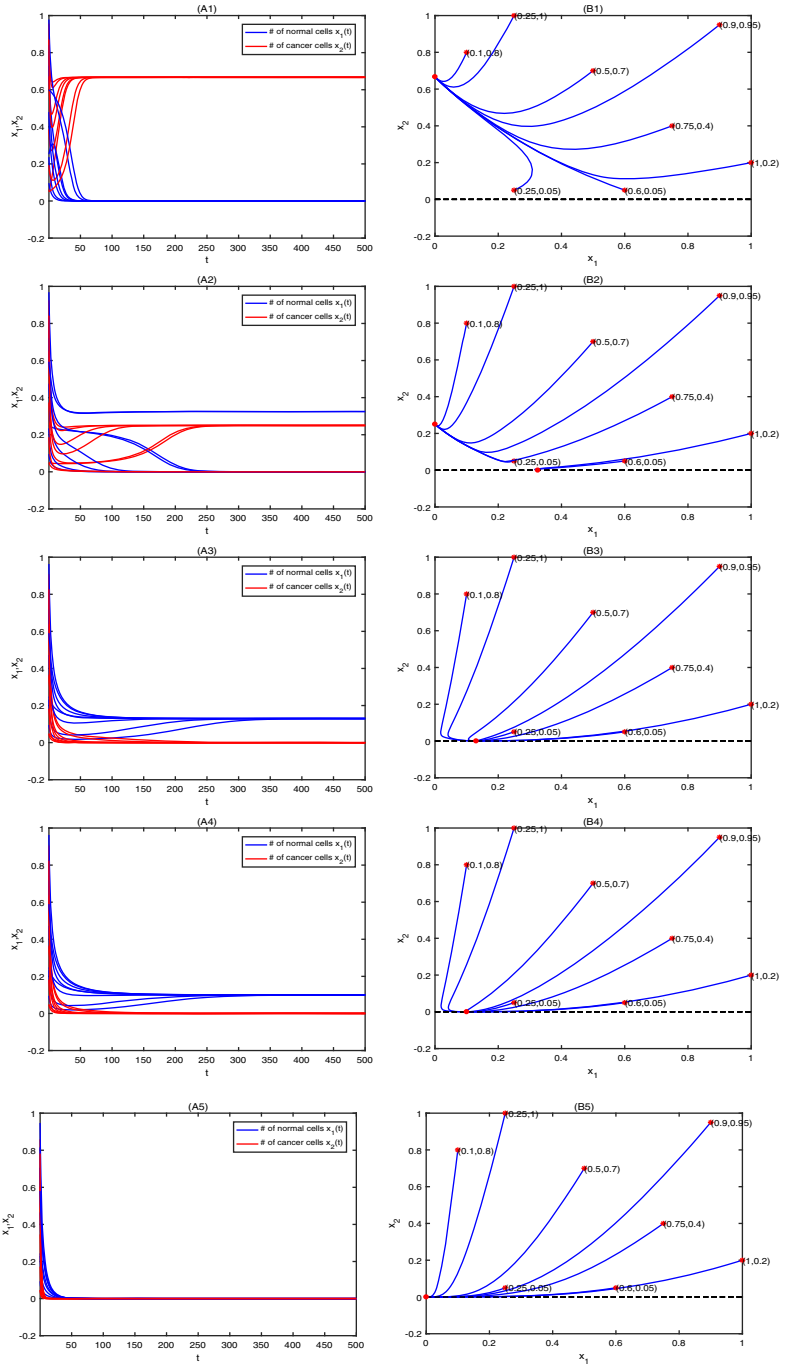

Fig. 1 The time series (t=t(hours)) and the phase of system (3.1) under 8 different initial values, where the radiation spilled rate $\varepsilon = 0.3$ and radiation dose $\gamma = 0.2, 0.45, 0.58, 0.6, 1$ in **A1**,**B1**–**A5**,**B5** respectively. Other parameters are taken from Table 2

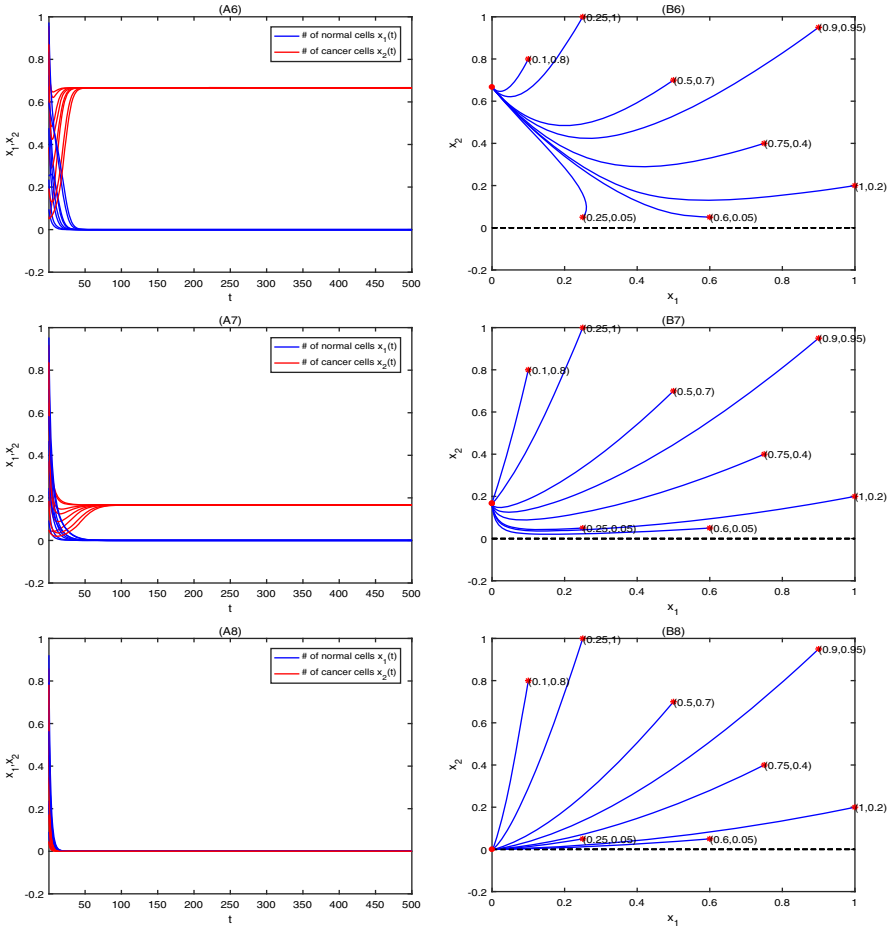

Fig. 2 The time series (t=t(hours)) and the phase of system (3.1) under 8 different initial values, where the radiation spilled rate $\varepsilon = 0.5$ and radiation dose $\gamma = 0.2, 0.5, 1$ in **A6**,**B6**–**A8**,**B8** respectively. Other parameters are taken from Table 2

asymptotically stable boundary equilibrium point, i.e., the cancer will spread. See Fig. 2A7 and B7. Moreover, if $\gamma > \alpha_2$, from model (3.2) we have E_1 and E_2 are nonexist, E_0 is a globally stable point (See Fig. 2A8 and B8) and the existence of E^* can not be judged but does not affect the global behavior of of E_0.

Case II: $\Delta > 0$.

Applying Lemma 2.1, conducting the same analysis as Case I, we have the following results (II1)-(II4). Notice that, (II1)-(II3) are based on the assumptions that $\alpha_1 > \varepsilon\gamma$ and $\alpha_2 > \gamma$.

(II1) $(\alpha_2 - \gamma) - \beta_2 K_1(1 - \varepsilon\gamma/\alpha_1) < 0$. When $0 < \varepsilon < \alpha_1/\alpha_2$, for all $\alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon) < \gamma < \alpha_2$, E^* is nonexist, E_0 is an unstable node, E_1 is a stable focus and E_2 is a saddle point. Medically, the normal cells will win the competition

and cancer will be eradicated for all $\alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1 \varepsilon) < \gamma < \alpha_2$ when $0 < \varepsilon < \alpha_1/\alpha_2$. See Fig. 3A11 and B11.

(II2) $(\alpha_1 - \varepsilon\gamma) - \beta_1 K_2(1 - \gamma/\alpha_2) < 0$. For all $\gamma < \alpha_2(\beta_1 K_2 - \alpha_1)/(\beta_1 K_2 - \alpha_2\varepsilon)$ when $0 < \varepsilon < \alpha_1/\alpha_2$ and all $\gamma < \alpha_1/\varepsilon$ when $\alpha_1/\alpha_2 \leq \varepsilon \leq 1$, we always have E^* is nonexist, E_0 is an unstable node, E_1 is a saddle point and E_2 is a stable focus, medically, the cancer will win the competition and spread. See Fig. 3A9 and B9.

(II3) $(\alpha_2 - \gamma) - \beta_2 K_1(1 - \varepsilon\gamma/\alpha_1) > 0$ and $(\alpha_1 - \varepsilon\gamma) - \beta_1 K_2(1 - \gamma/\alpha_2) > 0$. When $0 < \varepsilon < \alpha_1/\alpha_2$, for all $\alpha_2(\beta_1 K_2 - \alpha_1)/(\beta_1 K_2 - \alpha_2\varepsilon) < \gamma < \alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1\varepsilon)$, E_0 is an unstable node, E_1 and E_2 are saddle points, the unique positive equilibrium $E^*(x_1^*, x_2^*)$ is a globally asymptotically stable point in the interior of the first quadrant, medically, the cancer and normal cells will coexist. See Fig. 3A10 and B10.

(II4) Here, we neglect the restrictions of $\alpha_1 > \varepsilon\gamma$ and $\alpha_2 > \gamma$. (a) $0 < \varepsilon < \alpha_1/\alpha_2$. If $\alpha_2 < \gamma < \alpha_1/\varepsilon$, E_2 and E^* do not exist, E_1 is a globally asymptotically stable boundary equilibrium point, i.e., the cancer can be cured. See Fig. 3A12 and B12. However, if $\gamma > \alpha_1/\varepsilon$, then we have E_1 and E_2 are nonexist, E_0 is a globally stable point and the existence of E^* can not be judged but does not affect the global behavior of E_0. See Fig. 3A13 and B13. (b) $\varepsilon \geq \alpha_1/\alpha_2$. If $0 < \gamma < \alpha_1/\varepsilon$, it follows from (II2) that E_0 and E_1 are unstable points, E^* is nonexist and E_2 is a stable focus, i.e., the cancer will spread. See Fig. 4A14 and B14. If $\alpha_1/\varepsilon < \gamma < \alpha_2$, then E_1 and E^* do not exist and E_2 is a globally asymptotically stable boundary equilibrium point, i.e., the cancer will spread. See Fig. 4A15 and B15. Moreover, if $\gamma > \alpha_2$, obviously, E_1 and E_2 are nonexist, E_0 is a globally stable point (See Fig. 4A16 and B16) and the existence of E^* can not be judged but does not affect the global behavior of E_0.

Remark 3.4 When $\Delta > 0$, from (II1)-(II4) we can conclude that when $0 < \varepsilon < \alpha_1/\alpha_2$, the cancer will win the competition for all $\gamma < \alpha_2(\beta_1 K_2 - \alpha_1)/(\beta_1 K_2 - \alpha_2\varepsilon)$, the cancer will be cured for all $\alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1\varepsilon) < \gamma < \alpha_2$ and the cancer and normal cells will coexist when $\alpha_2(\beta_1 K_2 - \alpha_1)/(\beta_1 K_2 - \alpha_2\varepsilon) < \gamma < \alpha_1(\alpha_2 - \beta_2 K_1)/(\alpha_1 - \beta_2 K_1\varepsilon)$. Moreover, for all $\alpha_2 < \gamma < \alpha_1/\varepsilon$, E_1 is a globally asymptotically stable boundary equilibrium point and the cancer will be cured; for all $\gamma > \alpha_1/\varepsilon$, both the normal and the cancer cells will die out. When $\varepsilon \geq \alpha_1/\alpha_2$. If $0 < \gamma < \alpha_1/\varepsilon$, E_2 is a stable focus and the cancer will spread; if $\alpha_1/\varepsilon < \gamma < \alpha_2$, E_2 is a globally asymptotically stable point and the cancer will spread; if $\gamma > \alpha_2$, both the normal and the cancer cells will die out.

Remark 3.5 From (I4) and (II4), we can conclude that for any $0 < \varepsilon \leq 1$, if $\gamma > \max\{\alpha_1/\varepsilon, \alpha_2\}$, both the normal and the cancer cells will die out. If $\alpha_1/\varepsilon < \gamma < \alpha_2$, the cancer will spread. If $\alpha_2 < \gamma < \alpha_1/\varepsilon$, the cancer will be eradicated.

Based on the above analysis, we finally have the following result.

Theorem 3.1 *System (3.1) has four possible nonnegative equilibria* $E_0(0, 0)$, $E_1(K_1(1 - \varepsilon\gamma/\alpha_1), 0)$, $E_2(0, K_2(1 - \gamma/\alpha_2))$ *and* $E^*(x_1^*, x_2^*)$, *where* x_1^* *and* x_2^* *are given by (3.3). Based on assumption 2.2, we list all the cases on the existence and stability of the equilibrium points in Table 3.*

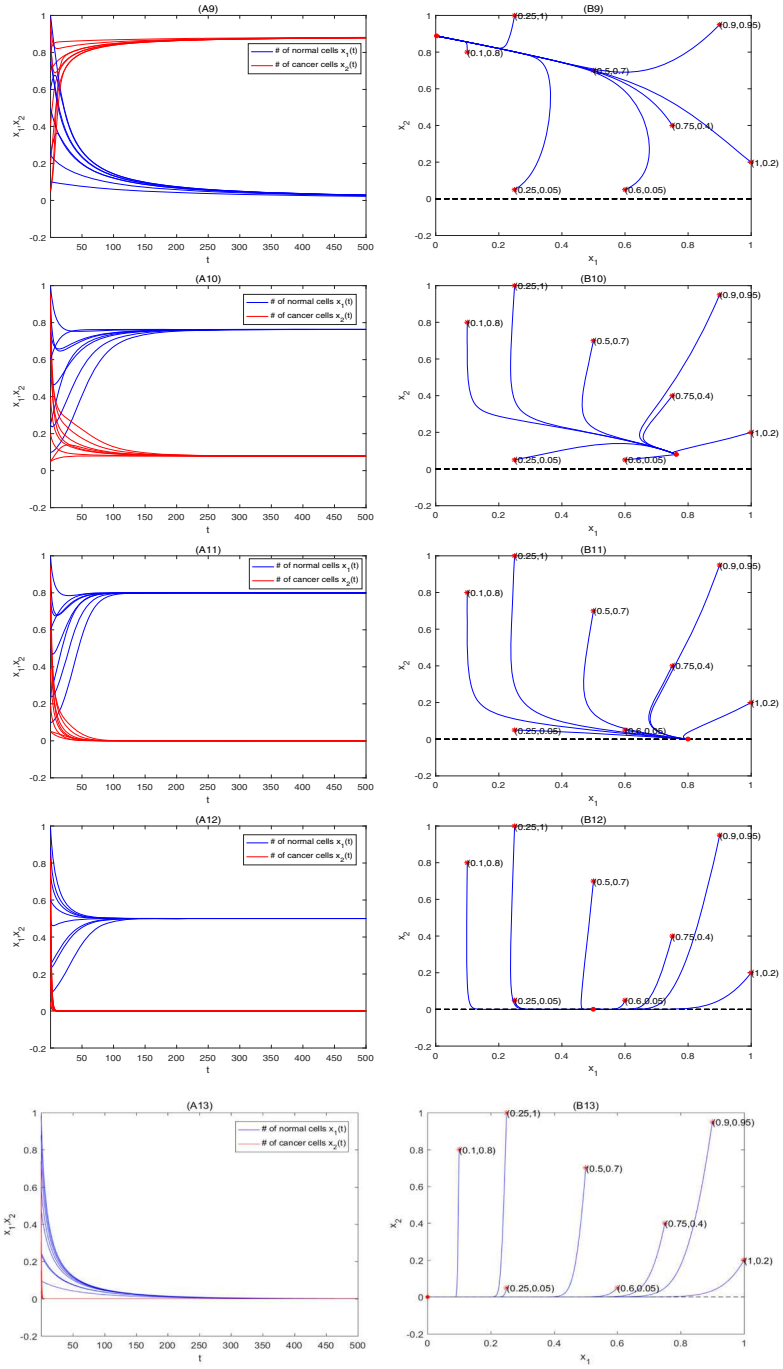

Fig. 3 The time series (t=t(hours)) and the phase of system (3.1) under 8 different initial values, where the radiation spilled rate $\varepsilon = 0.05$ and radiation dose $\gamma = 0.205, 0.3, 0.4, 1, 2.2$ in **A9**,**B9**–**A13**,**B13** respectively. Other parameters are taken from Table 2

Table 3 Constraints of parameters and existence and stability of equilibria

Δ	ε	γ	E_0	E_1	E_2	E^*	H-cells	C-cells	Cases	Figures
$\Delta < 0$	$0 < \varepsilon < \frac{\alpha_1}{\alpha_2}$	$0 < \gamma < \gamma_1$	us	sd	st, foc	–	ext	win	(1)	(A1),(B1)
		$\gamma_1 < \gamma < \gamma_2$	us	st, foc	st, foc	sd	div	div	(2)	(A2),(B2)
		$\gamma_2 < \gamma < \alpha_2$	us	st, foc	sd	–	win	ext	(3)	(A3),(B3)
		$\alpha_2 < \gamma < \alpha_1/\varepsilon$	sd	gs	–	–	win	ext	(4)	(A4),(B4)
		$\alpha_1/\varepsilon < \gamma$	gs	–	–	–	ext	ext	(5)	(A5),(B5)
	$\frac{\alpha_1}{\alpha_2} \le \varepsilon$	$0 < \gamma < \alpha_1/\varepsilon$	us	sd	st, foc	–	ext	win	(6)	(A6),(B6)
		$\alpha_1/\varepsilon < \gamma < \alpha_2$	sd	–	gs	–	ext	win	(7)	(A7),(B7)
		$\alpha_2 < \gamma$	gs	–	–	–	ext	ext	(8)	(A8),(B8)
$\Delta > 0$	$0 < \varepsilon < \frac{\alpha_1}{\alpha_2}$	$0 < \gamma < \bar{\gamma}_1$	us	sd	st, foc	–	ext	win	(9)	(A9),(B9)
		$\bar{\gamma}_1 < \gamma < \bar{\gamma}_2$	us	sd	sd	st, nod	coex	coex	(10)	(A10),(B10)
		$\bar{\gamma}_2 < \gamma < \alpha_2$	us	st, foc	sd	–	win	ext	(11)	(A11),(B11)
		$\alpha_2 < \gamma < \alpha_1/\varepsilon$	sd	gs	–	–	win	ext	(12)	(A12),(B12)
		$\alpha_1/\varepsilon < \gamma$	gs	–	–	–	ext	ext	(13)	(A13),(B13)
	$\frac{\alpha_1}{\alpha_2} \le \varepsilon$	$0 < \gamma < \alpha_1/\varepsilon$	us	sd	st, foc	–	ext	win	(14)	(A14),(B14)
		$\alpha_1/\varepsilon < \gamma < \alpha_2$	sd	–	gs	–	ext	win	(15)	(A15),(B15)
		$\alpha_2 < \gamma$	gs	–	–	–	ext	ext	(16)	(A16),(B16)

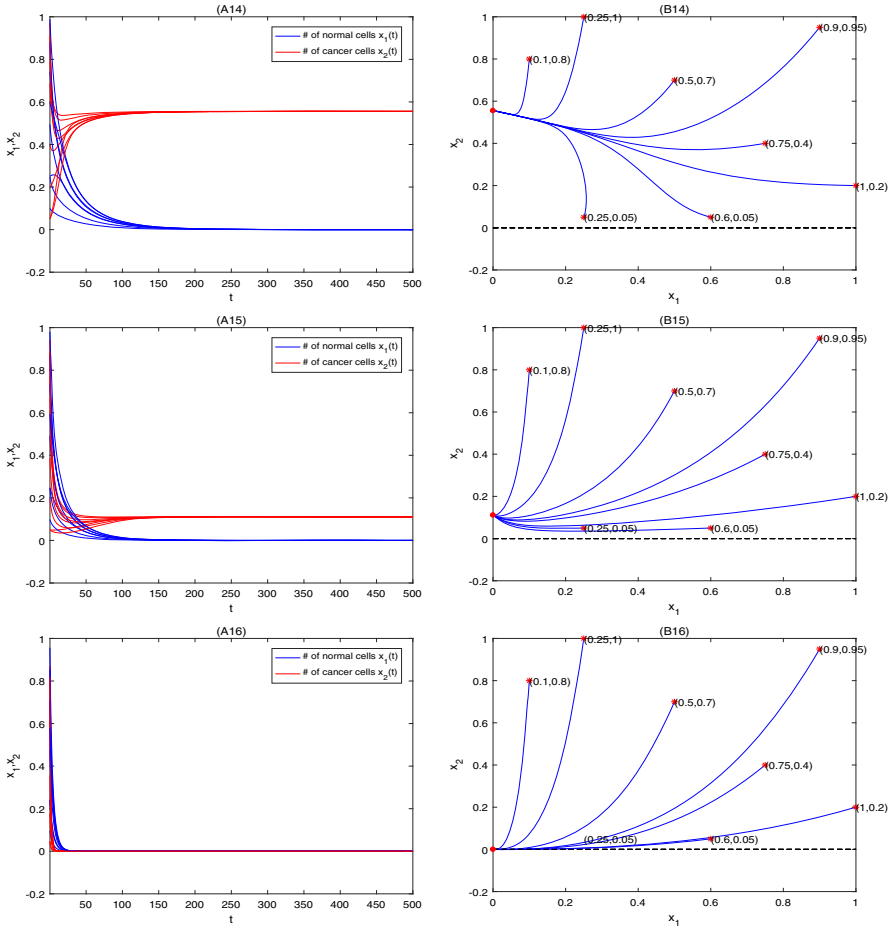

Fig. 4 The time series (t=t(hours)) and the phase of system (3.1) under 8 different initial values, where the radiation spilled rate $\varepsilon = 0.3$ and radiation dose $\gamma = 0.2, 0.4, 1$ in **A14**,**B14**–**A16B16** respectively. Other parameters are taken from Table 2

where $\Delta = \alpha_1\alpha_2 - \beta_1\beta_2 K_1 K_2$,

$$\gamma_1 = \frac{\alpha_1(\alpha_2 - \beta_2 K_1)}{\alpha_1 - \beta_2 K_1 \varepsilon}, \quad \gamma_2 = \frac{\alpha_2(K_2\beta_1 - \alpha_1)}{K_2\beta_1 - \alpha_2\varepsilon},$$
$$\bar{\gamma}_1 = \frac{\alpha_2(K_2\beta_1 - \alpha_1)}{K_2\beta_1 - \alpha_2\varepsilon}, \quad \bar{\gamma}_2 = \frac{\alpha_1(\alpha_2 - \beta_2 K_1)}{\alpha_1 - \beta_2 K_1 \varepsilon},$$

H-cells:=normal cells, C-cells:= cancer cells, st:= stable, us:=unstable, sd:=saddle, foc:=focus, nod:=node, gs:=globally stable, coex:= coexistent, ext:=extinction, div:=depends on initial value, −:=nonexistent.

In reality, we are more concern the cases that cancer is controlled or eradicated. Hence, cases (3),(4),(10), (11) and (12) are of important significance for us. We detail

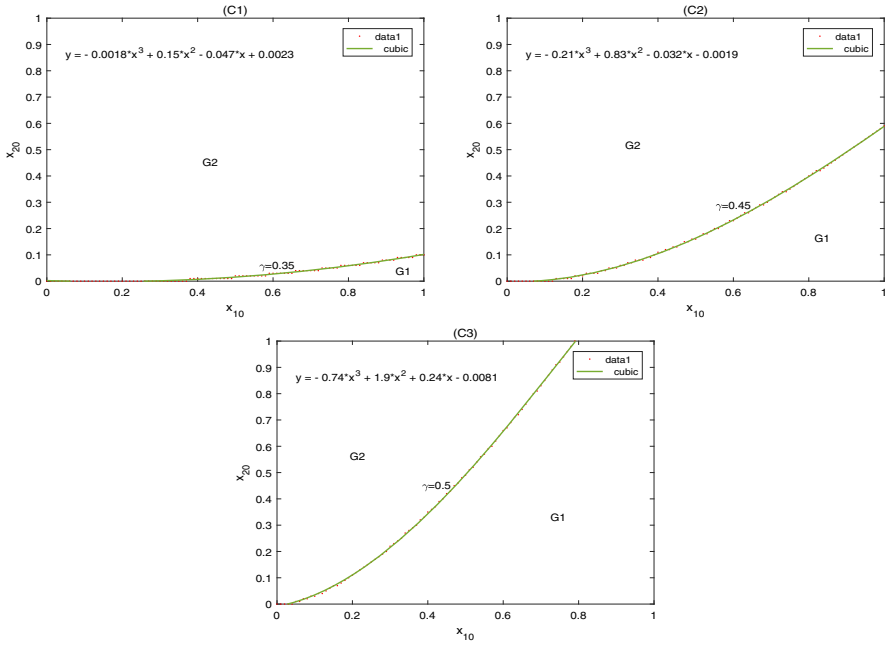

Fig. 5 The dependence of the stability of the cancer eradiation equilibrium point E_1 and cancer win equilibrium point E_2 on the initial values of the normal and cancer cells under three different radiation doses (i.e., $\gamma = 0.35,\ 0.45,\ 0.5$). The cancer will be eradiated if the estimated initial concentrations of the normal and cancer cells are exactly in region G1 and the cancer will spread if the initial values belong to region G2

the range of parameters especially the radiation dose γ on these five cases in Table 4. Here, we should note that condition (2.2) can not be omitted, i.e., cancer will win the competition and spread if there is no treatment.

It is worth noting that when the radiation dose γ satisfies $\gamma_1 < \gamma < \gamma_2$, the cancer's spread or eradication depends on initial concentrations of the normal and cancer cells. Figure 5C1–C3 demonstrate the dependence of the stability of the cancer eradiation equilibrium point E_1 and cancer win equilibrium point E_2 on the initial values of the normal and cancer cells under three different radiation doses (i.e. $\gamma = 0.35,\ 0.45,\ 0.5$). From Figures we see that under parameter settings of case (2), larger radiation dose γ allows larger proportion of cancer cells to normal cells at the initial moments. We provide a boundary curve to the initial value distribution. All solutions that have initial conditions in region G1 will tend to equilibrium point E_1, i.e., the cancer will be eradicated. Otherwise, solutions that have initial conditions in region G2 will tend to equilibrium point E_2 and the cancer will spread at this circumstance. Here, we omit the initial values that cause the solutions to go to the saddle point E^* once are taken. The method to determine the boundary curve is as follows. Firstly, we calculate the value of solution $(x_1(T), x_2(T))$ (where T large enough to judge that $x_1(T) < 10^{-4}$ or $x_2(T) < 10^{-4}$ holds) under each initial value $(x_1(0), x_2(0))$. Secondly, we distinguish which initial values cause the solution of the system to

Table 4 Some important cases in Table 3

Parameters and natural restrictions			Radiation dose and results				
parameters parameters	condition (2.2)	restriction of spilled rate ε	cases of Δ	range of dose γ	results	cases	Figures
	$\alpha_1 < \beta_1 K2$	$0 < \varepsilon < \frac{\alpha_1}{\alpha_2}$	$\Delta > 0$	$\bar{\gamma}_1 < \gamma < \bar{\gamma}_2$	H-cells and C-cells	(10)	(A10),(B10)
α_1					reach to a positive		
α_2					balance		
β_1				$\bar{\gamma}_2 < \gamma < \frac{\alpha_1}{\varepsilon}$	cancer will be	(11)	(A11),(B11)
β_2	$\alpha_2 > \beta_2 K1$				eradicated	(12)	(A12),(B12)
K_1			$\Delta < 0$	$\gamma_2 < \gamma < \frac{\alpha_1}{\varepsilon}$	cancer will be	(3)	(A3),(B3)
K_2					eradicated	(4)	(A4),(B4)

approach the equilibrium point E_1, and which initial values cause the solution to approach the equilibrium point E_2. Thirdly, to the initial values that cause the solution to tend to the equilibrium point E_1, we select the maximal value $\hat{x}_2(0)$ under the same $x_1(0)$. Finally, we apply cubic polynomial to fit the curve by using every point $(x_1(0), \hat{x}_2(0))$ for all $0 \le x_1(0) \le 1$ and obtain the desired function. We point out here that the method is reasonable according to the continuous dependence of the solution on initial values. In clinical, the initial concentrations of the normal and cancer cells can be estimated. The above analysis provide a method that one can predict the tendency of the cancer under different radiation dose once initial values of the normal and cancer cells are given. For example, under parameter settings in case (2), let $\gamma = 0.45$, we can calculate by using the fit function $y = -0.21x^3 + 0.83x^2 - 0.032x - 0.0019$ that $y(0.25) = 0.0387 < 0.05$, $y(0.75) = 0.3524 < 0.4$, $y(0.6) = 0.2323 > 0.05$, $y(1) = 0.5861 > 0.2$. This determine the region G1 or G2 that the initial value belongs to and then predict the final tendency of the solutions that take these initial values. Calculation shows that $(x_1(0), x_2(0)) = (0.25, 0.05)$ or $(0.75, 0.4)$ belongs to region G2 and solutions that have these initial values will go to cancer win equilibrium point E_2 and $(x_1(0), x_2(0)) = (0.6, 0.05)$ or $(1, 0.2)$ belongs to region G1 and the solution will tend to cancer eradicated equilibrium point E_1 once these initial conditions are taken.

4 Treatment by pulsed radiotherapy

Usually, cancer radiotherapy is implemented many times over a period of time. Suppose the time interval between two treatments is of equal. Then we can model the cancer treatment in the form of pulsed radiotherapy with the following switching system.

$$\begin{cases} \left.\begin{aligned} \dot{x}_1 &= \alpha_1 x_1\Big(1 - \frac{x_1}{K_1}\Big) - \beta_1 x_1 x_2 - \varepsilon\gamma x_1 \\ \dot{x}_2 &= \alpha_2 x_2\Big(1 - \frac{x_2}{K_2}\Big) - \beta_2 x_1 x_2 - \gamma x_2 \end{aligned}\right\}, \ t \in [n\omega, n\omega + L)(\text{treatment stage}), \\ \left.\begin{aligned} \dot{x}_1 &= \alpha_1 x_1\Big(1 - \frac{x_1}{K_1}\Big) - \beta_1 x_1 x_2 \\ \dot{x}_2 &= \alpha_2 x_2\Big(1 - \frac{x_2}{K_2}\Big) - \beta_2 x_1 x_2 \end{aligned}\right\}, \ t \in [n\omega + L, (n+1)\omega)(\text{no treatment stage}), \ n = 0, 1, 2..., \end{cases} \tag{4.1}$$

where ω is the time interval between two treatments, $0 < L < \omega$ is the radiation treatment time, i.e., we implement radiation therapy when $t \in [n\omega, n\omega + L)$ while do not when $t \in [n\omega + L, (n+1)\omega)$. n is the radiation times over the period of treatment. In the following analysis, we still assume condition (2.2) holds.

It is easy to see that $x_i(t) \ge 0$ if $x_i(0) \ge 0$ for $i = 1, 2$. In fact, from model (4.1), we can obtain that

$$x_1(t) = x_1(n\omega) \exp\left(\alpha_1\Big(1 - \frac{x_1(s)}{K_1}\Big) - \beta_1 x_2(s) - \varepsilon\gamma\right)$$

for all $t \in [n\omega, n\omega + L)$ and

$$x_1(t) = x_1(n\omega + L) \exp\left(\alpha_1\left(1 - \frac{x_1(s)}{K_1}\right) - \beta_1 x_2(s)\right)$$

for all $t \in [n\omega + L, (n+1)\omega)$. According to the piecewise iteration method and the continuity of solutions, we have $x_1(t) \geq 0$ for any nonnegative initial value $x_1(0) \geq 0$. The same analysis can be done to $x_2(t)$. Next, we will investigate the existences and stabilities of cancer eradication periodic solution, cancer win periodic solution and coexistent periodic solution.

4.1 Existence and global stability of cancer eradication (win) periodic solution

Firstly, let us investigate the existence of cancer eradication periodic solution of system (4.1). Rewrite system (4.1) as

$$\begin{cases} \dot{x}_1 = \alpha_1 x_1\left(1 - \dfrac{x_1}{K_1}\right) - \beta_1 x_1 x_2 - \varepsilon D(t) x_1, \\ \dot{x}_2 = \alpha_2 x_2\left(1 - \dfrac{x_2}{K_2}\right) - \beta_2 x_1 x_2 - D(t) x_2, \end{cases} \tag{4.2}$$

where $D(t)$ is a periodic function with period ω. $D(t) \equiv \gamma > 0$ when $t \in [n\omega, n\omega + L)$(treatment stage) and $D(t) \equiv 0$ when $t \in [n\omega + L, (n+1)\omega)$(no treatment stage) for all $n = 0, 1, 2, \ldots$. Obviously, system (4.2) is ω-periodic. Consider the following subsystem of (4.2) under the case $x_2(t) \equiv 0$

$$\dot{x}_1 = \alpha_1 x_1\left(1 - \frac{x_1}{K_1}\right) - \varepsilon D(t) x_1. \tag{4.3}$$

It is easy to know that system (4.3) admits a unique positive periodic solution $x_1^*(t)$ when $\int_0^\omega [\alpha_1 - \varepsilon D(t)]dt > 0$, i.e., $\alpha_1\omega > \varepsilon\gamma L$. Consequently, system (4.1) has a unique cancer eradiation periodic solution under the condition that $\alpha_1\omega > \varepsilon\gamma L$. In the following, we will prove that this periodic solution is globally asymptotically stable if $\alpha_2\omega < \gamma L$.

For any solution $(x_1(t), x_2(t))$ of system (4.1) with initial values $x_i(0) \geq 0$ $(i = 1, 2)$ that different from $(x_1^*(t), 0)$, there is an integer $n \geq 0$ such that $t \in [n\omega, (n+1)\omega)$. From the second equation of (4.2), we easily obtain

$$\begin{aligned} x_2(t) &\leq x_2(0) \exp\left(\int_0^t [\alpha_2 - D(s)]dt\right) \\ &= x_2(0) \exp\left(\int_0^{n\omega} [\alpha_2 - D(s)]dt + \int_{n\omega}^t [\alpha_2 - D(s)]dt\right) \\ &\leq x_2(0) e^{(\alpha_2+\gamma)\omega} e^{n(\alpha_2\omega - \gamma L)}. \end{aligned}$$

This implies that $x_2(t) \to 0$ as $t \to +\infty$ if $\alpha_2\omega < \gamma L$ holds. Therefore, for any $\eta > 0$, there is $T > 0$ such that $x_2(t) < \eta$ for all $t > T$. Take

$$V(t) = |\ln x_1(t) - \ln x_1^*(t)|,$$

then for $t > T$ we have

$$\begin{aligned}\dot{V}(t) &= \operatorname{sgn}(x_1(t) - x_1^*(t))\Big[\Big(\alpha_1 - \varepsilon D(t) - \frac{\alpha_1}{K_1}x_1(t) - \beta_1 x_2(t)\Big) - \Big(\alpha_1 - \varepsilon D(t) - \frac{\alpha_1}{K_1}x_1^*(t)\Big)\Big] \\ &< -\frac{\alpha_1}{K_1}|x_1(t) - x_1^*(t)| + \beta_1\eta.\end{aligned}$$

Because of the arbitrariness of η, one can obtain

$$\dot{V}(t) \le -\frac{\alpha_1}{K_1}|x_1(t) - x_1^*(t)|. \tag{4.4}$$

If there is $\bar{T} \ge T$ such that $x_1(t) \equiv x_1^*(t)$ for all $t \ge \bar{T}$, the global stability of the periodic solution $(x_1^*(t), 0)$ is then obtained. Otherwise, (4.4) implies that $V(t) \to 0$ as $t \to +\infty$. This also guarantee the global stability of the periodic solution $(x_1^*(t), 0)$. Therefore, we have the following result.

Theorem 4.1 *Suppose that $\alpha_1\omega > \varepsilon\gamma L$, then system (4.1) has a unique cancer eradiation periodic solution. Moreover, if $\alpha_2\omega < \gamma L$, the solution is globally asymptotically stable.*

Since x_2 has a similar expression in the form of x_1 in system (4.1), using the same analytical technique, we have the following result on the cancer win periodic solution.

Theorem 4.2 *Assume that $\alpha_2\omega > \gamma L$, then system (4.1) has a unique cancer win periodic solution. Moreover, if $\alpha_1\omega < \varepsilon\gamma L$, the solution is globally asymptotically stable.*

4.2 Existence and global stability of the coexistent periodic solution

In reality, cancer cells may not be eradicated. The coexistence of cancer cells and normal cells is also of importance and should be concerned. We have the following results about the coexistence of the normal and cancer cells.

Theorem 4.3 *Suppose that*

$$\alpha_1\omega - \varepsilon\gamma L > \frac{\beta_1 K_2}{\alpha_2}(\alpha_2\omega - \gamma L) > 0 \quad \text{and} \quad \alpha_2\omega - \gamma L > \frac{\beta_2 K_1}{\alpha_1}(\alpha_1\omega - \varepsilon\gamma L), \tag{4.5}$$

then system (4.1) has at least one positive periodic solution. Moreover, if

$$\alpha_1 > K_1\beta_2 \quad \text{and} \quad \alpha_2 > K_2\beta_1, \tag{4.6}$$

the positive periodic solution is unique and globally asymptotically stable.

Proof Based on inequalities of (4.5), it is easy to verified that conditions of Corollary 1 in paper [23]. The existence of positive periodic solutions of system (4.1) is now guaranteed. Then, we prove the uniqueness and globally asymptotical stability of the positive periodic solution under conditions of (4.6).

Let $(x_1^*(t), x_2^*(t))$ be a positive periodic solution of system (4.1). Take

$$V(t) = |\ln x_1(t) - \ln x_1^*(t)| + |\ln x_2(t) - \ln x_2^*(t)|,$$

where $(x_1(t), x_2(t))$ is any solution of system (4.1) that different from $(x_1^*(t), x_2^*(t))$. Calculating the derivative of $V(t)$ along system (4.2), we have

$$\begin{aligned}\dot{V}(t) =& \operatorname{sgn}(x_1 - x_1^*)\Big[\Big(\alpha_1 - \varepsilon D(t) - \frac{\alpha_1}{K_1}x_1 - \beta_1 x_2\Big) - \Big(\alpha_1 - \varepsilon D(t) - \frac{\alpha_1}{K_1}x_1^* - \beta_1 x_2^*\Big)\Big] \\ &+ \operatorname{sgn}(x_2 - x_2^*)\Big[\Big(\alpha_2 - D(t) - \frac{\alpha_2}{K_2}x_2 - \beta_2 x_1\Big) - \Big(\alpha_2 - D(t) - \frac{\alpha_2}{K_2}x_2^* - \beta_2 x_1^*\Big)\Big] \\ =& -\frac{\alpha_1}{K_1}|x_1 - x_1^*| - \frac{\alpha_2}{K_2}|x_2 - x_2^*| \\ &+ \operatorname{sgn}(x_1 - x_1^*)(-\beta_1)(x_2 - x_2^*) + \operatorname{sgn}(x_2 - x_2^*)(-\beta_2)(x_1 - x_1^*) \\ \le& -\Big(\frac{\alpha_1}{K_1} - \beta_2\Big)|x_1 - x_1^*| - \Big(\frac{\alpha_2}{K_2} - \beta_1\Big)|x_2 - x_2^*|.\end{aligned}$$

Consequently, from condition (4.6), we have $\dot{V}(t) < 0$ for all $t \ge 0$. By Lyapunov stability theory (see [24, 25]), the positive periodic solution is unique and globally asymptotically stable. □

Note that condition (4.6) does not involve the treatment dose γ, which is undoubtedly an important parameter in the cancer treatment model. In the following, we will establish some new sufficient conditions for the globally asymptotic stability of the positive periodic solution applying a similar method as in [26].

Theorem 4.4 *Suppose that conditions (4.5) hold and let $(x_1^*(t), x_2^*(t))$ be a positive periodic solution to system (4.1). Further, let*

$$b_{11}(t) = \frac{\alpha_1}{K_1}x_1^*(t),\ b_{21}(t) = \beta_2 x_1^*(t),\ b_{22}(t) = \frac{\alpha_2}{K_2}x_2^*(t),\ b_{12}(t) = \beta_1 x_2^*(t), \tag{4.7}$$

if

$$\int_0^\omega \max\Big\{-b_{22}(t) + \frac{(b_{12}(t) + b_{21}(t))^2}{4b_{11}(t)}, -b_{11}(t) + \frac{(b_{12}(t) + b_{21}(t))^2}{4b_{22}(t)}\Big\}dt < 0, \tag{4.8}$$

then $(x_1^*(t), x_2^*(t))$ is globally asymptotically stable.

Proof Let $(x_1(t), x_2(t))$ be any positive solution of system (4.1) with initial values $x_i(0) > 0, i = 1, 2$. It is easy to obtain the permanence of the system, i.e., there exist two constants $M > m > 0$ such that $m < x_i(t) < M$ for $t > 0, i = 1, 2$, under conditions (4.5) (see [26] and the reference cited therein).

Let

$$u_1(t) = \frac{x_1(t)}{x_1^*(t)} - 1, \quad u_2(t) = \frac{x_2(t)}{x_2^*(t)} - 1. \tag{4.9}$$

Obviously, $(u_1(t), u_2(t))$ satisfies differential equations

$$\begin{cases} \dot{u}_1(t) = (1 + u_1(t))\big(- b_{11}(t)u_1(t) - b_{12}(t)u_2(t)\big), \\ \dot{u}_2(t) = (1 + u_2(t))\big(- b_{21}(t)u_1(t) - b_{22}(t)u_2(t)\big), \end{cases} \tag{4.10}$$

where $b_{ij}(t), i, j = 1, 2$ are defined by (4.7). Then the required assertion in the Theorem is equivalent to the statement that

$$\lim_{t\to+\infty} |u_1(t)| = 0 = \lim_{t\to+\infty} |u_2(t)|. \tag{4.11}$$

Take a solution $(u_1(t), u_2(t))$ of (4.10) with $u_1(0) > -1$ and $u_2(0) > -1$. Since the system (4.1) is permanent, we get $u_1(t) > -1$ and $u_2(t) > -1$ for all $t \geq 0$. Define a Lyapunov function $V(t)$ by

$$V(t) = u_1(t) - \ln(1 + u_1(t)) + u_2(t) - \ln(1 + u_2(t)).$$

Note that $V(t) > 0$, except for the zero solution $u_1(t) \equiv 0 \equiv u_2(t)$ in which $V(t)$ vanishes. Calculating the derivation of $V(t)$ along with (4.10), we have

$$\begin{aligned} \dot{V}(t) = \frac{\dot{u}_1(t)u_1(t)}{1 + u_1(t)} + \frac{\dot{u}_2(t)u_2(t)}{1 + u_2(t)} &= -b_{11}(t)u_1^2(t) - (b_{12}(t) \\ &+ b_{21}(t))u_1(t)u_2(t) - b_{22}(t)u_2^2(t). \end{aligned}$$

By the same calculation as Theorem 5.2 in [26], we deduce that

$$\dot{V}(t) \leq \lambda(t)\big(1 - e^{-(u_1(t)+u_2(t))}(1 + u_1(t))(1 + u_2(t))\big) = \lambda(t)(1 - e^{-V(t)}), \tag{4.12}$$

where

$$\lambda(t) = \max\left\{ - b_{22}(t) + \frac{(b_{12}(t) + b_{21}(t))^2}{4b_{11}(t)}, -b_{11}(t) + \frac{(b_{12}(t) + b_{21}(t))^2}{4b_{22}(t)} \right\}.$$

Integrating (4.12) from 0 to t and taking the periodic of $\lambda(t)$ into account, we obtain

$$\int_{V(0)}^{V(t)} \frac{e^v}{e^v - 1} dv \leq \int_0^t \lambda(s)ds = \frac{t}{\omega}\int_0^\omega \lambda(s)ds + q(t).$$

Since $q(t)$ is ω-periodic and $\int_0^\omega \lambda(t)dt < 0$, then

$$\lim_{t\to+\infty} \int_{V(0)}^{V(t)} \frac{e^v}{e^v - 1} dv = -\infty,$$

Table 5 Values of parameters for pulsed radiotherapy

Parameters	Values for Th.4.1	Values for Th.4.2	Values for Th.4.3	Data sources
α_1	0.156	0.01	0.31	[3]
α_2	0.14	0.162	0.38	[3, 21]
K_1	1	1	1	[3, 9]
K_2	1	1	1	[3, 9]
β_1	0.2	0.02	0.32	[3]
β_2	0.13	0.12	0.27	[3]
γ	0.2∼14	0.2∼14	0.2∼14	[3, 9]
ε	0.3	0.3	0.3	Assumption
ω	33.6	33.6	33.6	Estimation
L	0.5	0.5	0.5	Estimation

which implies that $V(t) \to 0$ as $t \to +\infty$. Hence, statement (4.11) is true. This completes the proof. □

Remark 4.1 Theorem 4.4 involves radiation dose γ in the conditions that guarantee the global stability of the positive periodic solution. This is an improvement compared with conditions of Theorem 4.3. But a clear disadvantage is that they are difficult to verify. Hence, in the following, we only numerically illustrate Theorem 4.3.

4.3 Numerical validation for pulsed radiotherapy

In this subsection, we will verify the existence and global stability of ω-periodic solution numerically for cancer eradiation periodic solution (Theorem 4.1), cancer win periodic solution (Theorem 4.2) and coexistent periodic solution (Theorem 4.3), respectively. Futher, we will discuss the effect of variation of radiation dose γ on these periodic solutions. Values of parameters for Theorems 4.1, 4.2 and 4.3 are given in Table 5. But note that they do not come from any real cell populations.

Usually, cancer radiotherapy is treated 6 weeks, 5 times a week, 30 times totally as a full course of treatment, and at a time lasts no more than 30 min. Hence, we can regard $\omega = 6 \times 7 \times 24/30 = 33.6$ hours as one treatment period, and consider $L = 0.5$ hours as one radiation time. Throughout Figures 4.1−4.3, we always choose the initial values $x_1(0) = 0.8$ and $x_2(0) = 0.5$.

It is easy to verify that values for Theorems 4.1, 4.2 and 4.3 in Table 5 satisfy all conditions of the corresponding Theorem. Conditions of Theorem 4.1 require that the radiation dose γ must satisfies $\alpha_2\omega/L < \gamma < \alpha_1\omega/(\varepsilon L)$, i.e., $9.4080 < \gamma < 34.9440$. Figure 6 illustrates the existence and globally stability of cancer eradiation 33.6-periodic solution under three different radiation doses γ, i.e., γ equals 10, 12 and 14 respectively. It can be seen from Fig. 6A1–A3 and B1–B3 that as the increase of γ, the cancer eradiation periodic solution will move down and the amplitude will increase. This inversely proves that the lower the dose, the better, if the cancer can be eradicated. Theorem 4.2 provides restrictions of radiation dose γ under which the

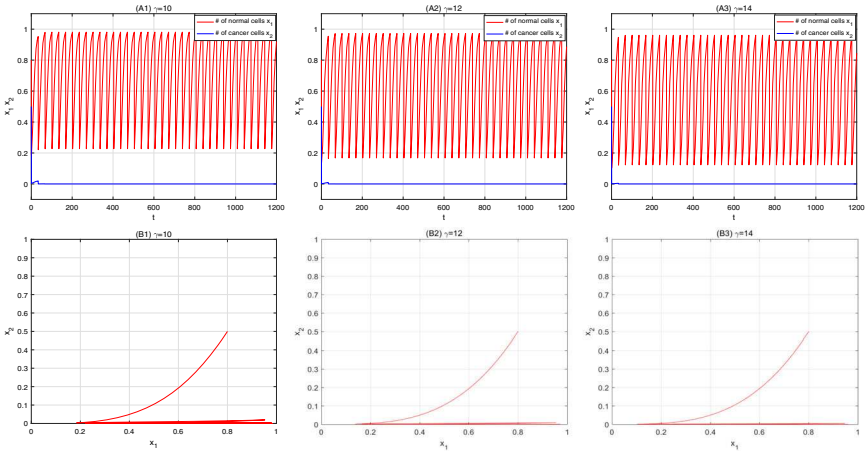

Fig. 6 The time series **A1**–**A3** and the phases **B1**–**B3** of system (4.1) under three different γ values ($\gamma = 10, 12, 14$). Obviously, system (4.1) has a globally stable cancer eradiation 33.6-periodic solution

cancer win periodic solution exists and is globally stable. Figure 7 demonstrates three different cancer win periodic solutions under different radiation dose γ, which satisfies the conditions of Theorem 4.2, i.e, $2.24 = \alpha_1\omega/(\varepsilon L) < \gamma < \alpha_2\omega/L = 10.8864$. Obviously, the cancer win periodic solution will move down as the increase of γ, but it does not disappear within the restriction of the dose. Figure 8 shows the existence and global stability of the coexistent periodic solutions under conditions of Theorem 4.3, in which the restriction of γ is $1.2396 < \gamma < 10.0066$. It is interesting to observe that as the increase of the radiation dose γ, the concentration of the normal cells will increase and the concentration of the cancer cells will decrease. But we cannot eradicate the cancer cells no matter how to choose the γ under the constraint of $1.2396 < \gamma < 10.0066$.

It follows from A4 and B4 in Fig. 7 and A7 and B7 in Fig. 8 that the same radiation dose γ ($\gamma = 3$) leads to different periodic solutions and stabilities. These mainly caused by the different selections to the proliferation and competition coefficients on the normal and tumor cells. From Table 5, comparing the values of α_1, α_2, β_1 and β_2 that taken in Theorems 4.2 and 4.3, we find that $(\alpha_1, \alpha_2, \beta_1, \beta_2)_{Th.4.2}/(\alpha_1, \alpha_2, \beta_1, \beta_2)_{Th.4.3} = (31, 2.35, 16, 2.25)$, which means that a larger proliferation and competition coefficients of healthy cells will be beneficial to the fight between healthy and tumor cells and then be beneficial to the transition from cancer win periodic solution to the coexistent periodic solution. This phenomenon is consistent with the real facts.

5 Conclusion and discussion

In this paper, we took advantage of a pair of ordinary differential equations to model the dynamics between the normal cells and cancer cells for the cancer treatment by radiotherapy. We firstly presented a continuous radiotherapy cancer treatment model.

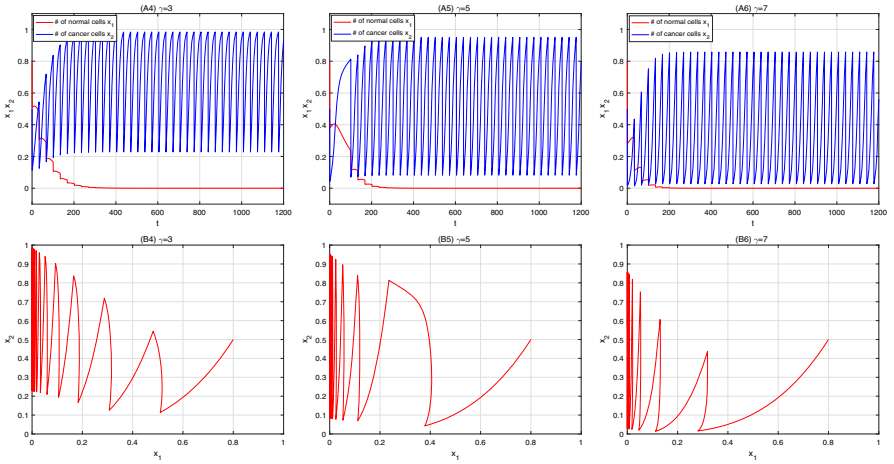

Fig. 7 The time series **A4**–**A6** and the phases **B4**–**B6** of system (4.1) under three different γ values ($\gamma = 3, 5, 7$). Obviously, system (4.1) has a globally stable cancer win 33.6-periodic solution

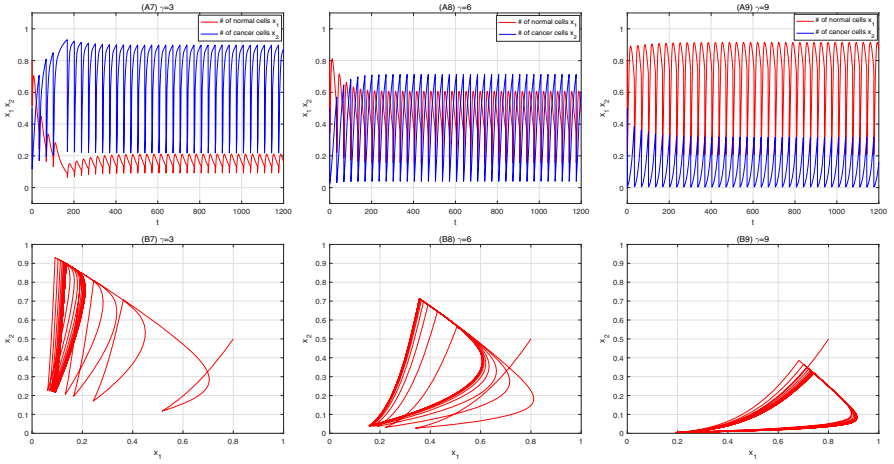

Fig. 8 The time series **A7**–**A9** and the phases **B7**–**B9** of system (4.1) under three different γ values ($\gamma = 3, 6, 9$). It is observed that system (4.1) has a globally stable coexistent 33.6-periodic solution

We figured out all the equilibrium points of the model and make a comprehensive analysis on the stabilities of these four equilibrium points. The results of the analysis demonstrated the quantitative relationship between radiation dose and cancer's cure or spread when the other parameters of the model are assumed to be unchanged. Then, we reconsidered the pulsed radiotherapy cancer treatment model presented in [12] and investigated the existence and stability of boundary periodic solutions and positive periodic solution by applying new methods that are different with the methods in [12]. Moreover, we performed numerical simulations to discuss in depth the effect of radiation dose on the cure or spread of the cancer, which are different from the

simulations in [12] that focus on the effect of the treatment time on the cancer's cure or spread.

The cancer treatment model discussed in this paper is only based on one treatment measure, radiotherapy. Recently, immunotherapy has been studied extensively and pre-clinical data and phased clinical studies have emphasized that immunotherapy can enhance the efficacy of radiotherapy [27]. It may be more effective to treat cancer by combining radiotherapy with immunotherapy. This must be an interesting problem and deserve to carry out in the further work.

Funding This research was supported by the National Science Foundation (DMS-1853562), the National Natural Science Foundation of China (12271068), Chongqing Municipal Education Commission (KJQN201900707), Joint Training Base Construction Project for Graduate Students in Chongqing (JDLHPYJD2021016), Group Building Scientific Innovation Project for universities in Chongqing (CXQT21021) and Guangxi Natural Science Foundation (2018GXNSFBA281185).

Declarations

Conflict of interest The authors declare that they have no conflict of interest.

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