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A Mathematical Model of Cervical Cancer Treatment by Radiotherapy Followed by Chemotherapy

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Abstract

Cervical cancer is the second most common type of malignant tumor found in women aged 15-44 years worldwide. Radiotherapy is one form of treatment that uses radiation that can eliminate or kill cancer cells and one way to treat cervical cancer is quite popular. Chemotherapy is a cancer treatment using anticancer drugs designed to kill or slow the growth of cancer cells that divide rapidly in the body. The method used is to study mathematical model of cervical cancer with radiotherapy and radiotherapy treatment followed by chemotherapy. The results of this study are for the early stages of cervical cancer with radiotherapy is quite effective, while for the late stages of radiotherapy and chemotherapy is less effective. Therefore, the need for other treatments for end-stage cervical cancer in addition to radiotherapy and chemotherapy.

Keywords: Cervical cancer; radiotherapy; chemotherapy.

INTRODUCTION

Cervical cancer is still the leading cause of cancer deaths among women in developing countries including Indonesia (Hoffman, et.al, 2008 and Woodman et al., 2007). Indonesia Cancer Foundation explained, the mortality rate of cervical cancer most among other types of cancer among women. It is estimated that 52 million Indonesian women are at risk for cervical cancer, while 36 percent of all women with cancer are cervical cancer patients. There are 15,000 new cases per year with the death of 8,000 people per year (Kompas, 2008). In Southeast Asia the incidence of cervical cancer becomes number two in women after breast cancer. Nevertheless, in Globocan (2012) the mortality rate due to cervical cancer is higher than the mortality rate due to breast cancer.

Radiotherapy is one of treatments that can be done for a patient with cervical cancer. Radiotherapy is used as a therapy for cancer patients by using radiation that can eliminate and kill cancer cells, a way to treat cervical cancer which is quite popular. Treatment with radiation therapy is usually done with chemotherapy, or accompanied by other therapies and sometimes only with radiotherapy alone depending on the type of cervical cancer suffered and the level of cancer.

MODEL FORMATION

This model develops from Asih, et al. (2015) on the development of cervical cancer, Liu and Yang (2014) on general cancer treatment models with radiotherapy and Pillis et al. (2007) on general cancer treatment models with chemotherapy.

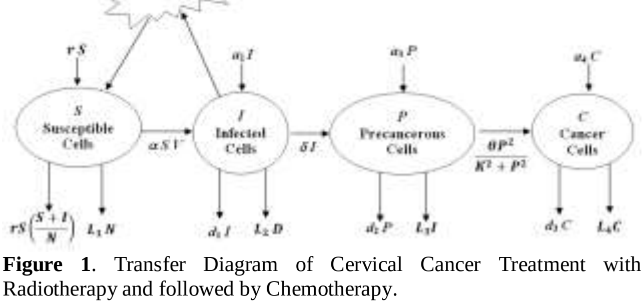

Figure 1. Transfer Diagram of Cervical Cancer Treatment with Radiotherapy and followed by Chemotherapy.

Caption Figure 1:

$$L_1\left(S\right)=k_S MS+\varepsilon_1\eta S\ ,\ \ L_2(I)=k_I MI+\varepsilon_2\eta I\ ,\ L_3(P)=k_P MP+\varepsilon_3\eta P\ ,$$

$L_4(C) = k_C MC + \varepsilon_4 C$ is a function of chemotherapy and radiotherapy.

Table 1. Subpopulations, Parameters and Units.

Symbol	Explanation	Unit
$S(t)$	Normal cells density	cells/mm^3
$I(t)$	Infected cells density	cells/mm^3
$P(t)$	Pre-cancerous cells density	cells/mm^3
$C(t)$	Cancer cells density	cells/mm^3
$V(t)$	Free virus density	virus/mm^3
$M(t)$	Concentrations of chemotherapy drugs	mg
r	Intrinsic cell growth rate is normal	1/ day
N	Homeostatic carrying capacity	cells/mm^3
α	The rate infection	1/(day x virus)
a_1	The rate of proliferation of infected cell	1/day
d_1	The rate of apoptosis of infected cell	1/day
δ	The rate of progression, from being infected to pre-cancer	1/day
a_2	The rate of proliferation of pre-cancerous cells	1/day
d_2	The rate of apoptosis of pre-cancerous cells	1/day
θ	The maximum invasion rate, from precancer to cancer	1/day
K	Half-saturation concentration	cells/mm^3
a_3	The rate of proliferation of cancer cells	1/day
d_3	The rate of apoptosis of cancer cells	1/day
n	The average number of viruses produced one infected cell	constant
d_4	The death rate of free virus	1/day
ε_1	The proportion of radiation to susceptible cells (normal cells)	constant
ε_2	The proportion of radiation to infected cells	constant
ε_3	The proportion of radiation to pre-cancerous cells	constant
η	Strategy of radiotherapy	1/day
k_S	Fractional susceptible cells killed by chemotherapy	1/day
k_I	Fractional infected cells killed by chemotherapy	1/day
k_P	Fractional pre-cancerous cells killed by chemotherapy	1/day
k_C	Fractional cancer cells killed by chemotherapy	1/day
γ	The rate of chemotherapy drug decay	1/day
v_M	The rate of chemotherapy drug enter	mg/day

The dynamics of cervical cell changes from normal cells to cancer cells are given in the following differential equation Systems (1).

$$\frac{dS}{dt} = rS\left(1-\frac{S+I}{N}\right) - \alpha SV - k_S MS - \varepsilon_1 \eta S \qquad (1a)$$

$$\frac{dI}{dt} = \alpha SV + a_1 I - d_1 I - \delta I - k_I MI - \varepsilon_2 \eta I \qquad (1b)$$

$$\frac{dP}{dt} = \delta I + a_2 P - d_2 P - \frac{\theta P^2}{K^2+P^2} - k_P MP - \varepsilon_3 \eta P \qquad (1c)$$

$$\frac{dC}{dt} = \frac{\theta P^2}{K^2+P^2} + a_3 C - d_3 C - k_C MC - \eta C \qquad (1d)$$

$$\frac{dV}{dt} = nd_1 I - d_4 V \qquad (1e)$$

$$\frac{dM}{dt} = -\gamma M + v_M \qquad (1f)$$

THE POINT OF EQUILIBRIUM

The equilibrium point with radiotherapy alone, without chemotherapy

System (1) without chemotherapy is

$$\frac{dS}{dt} = rS\left(1-\frac{S+I}{N}\right) - \alpha SV - \varepsilon_1 \eta S \qquad (2a)$$

$$\frac{dI}{dt} = \alpha SV + a_1 I - d_1 I - \delta I - \varepsilon_2 \eta I \qquad (2b)$$

$$\frac{dP}{dt} = \delta I + a_2 P - d_2 P - \frac{\theta P^2}{K^2+P^2} - \varepsilon_3 \eta P \qquad (2c)$$

$$\frac{dC}{dt} = \frac{\theta P^2}{K^2+P^2} + a_3 C - d_3 C - \eta C \qquad (2d)$$

$$\frac{dV}{dt} = nd_1 I - d_4 V. \qquad (2e)$$

The requirement to determine the equilibrium point of System (2) is $\frac{dS}{dt}=0, \frac{dI}{dt}=0, \frac{dP}{dt}=0, \frac{dC}{dt}=0, \frac{dV}{dt}=0$. So the point of equilibrium with radiotherapy in cervical cancer, without chemotherapy, is

$$\begin{aligned} EP_{1R}\left(S^*, I^*, P^*, C^*, V^*\right) &= \left(\xi_2, \xi_3, P_{1R}, \xi_{51}, \xi_4\right) \\ EP_{2R}\left(S^*, I^*, P^*, C^*, V^*\right) &= \left(\xi_2, \xi_3, P_{2R}, \xi_{52}, \xi_4\right) \qquad (3) \\ EP_{3R}\left(S^*, I^*, P^*, C^*, V^*\right) &= \left(\xi_2, \xi_3, P_{3R}, \xi_{53}, \xi_4\right), \end{aligned}$$

where

$$\xi_1 = \frac{nd_1}{d_4}, \quad \xi_2 = \frac{d_1+\delta+\varepsilon_2\eta - a_1}{\alpha \xi_1}, \quad \xi_3 = \frac{\left(r-\varepsilon_1\eta\right)N - r\xi_2}{r+\alpha\xi_1 N}, \quad \xi_4 = \xi_1 \xi_3,$$

$$A_1 = \frac{\delta\xi_3 - \theta}{a_2 - d_2 - \varepsilon_3\eta}, \quad B_1 = \frac{a_2K^2 - d_2K^2 - \varepsilon_3\eta K^2}{a_2 - d_2 - \varepsilon_3\eta}, \; C_1 = \frac{\delta\xi_3 K^2}{a_2 - d_2 - \varepsilon_3\eta}, \quad D_1 = 2A_1^3 - 9A_1B_1 + 27C_1,$$

$$E_1 = \left(2A_1^3 - 9A_1B_1 + 27C_1\right)^2 - 4\left(A_1^2 - 3B_1\right)^3,$$

$$P_{1R} = -\frac{A_1}{3} - \frac{1}{3}\sqrt[3]{\frac{1}{2}\left(D_1 + \sqrt{E_1}\right)} - \frac{1}{3}\sqrt[3]{\frac{1}{2}\left(D_1 - \sqrt{E_1}\right)},$$

$$P_{2R} = -\frac{A_1}{3} + \frac{1-i\sqrt{3}}{6}\sqrt[3]{\frac{1}{2}\left(D_1 + \sqrt{E_1}\right)} + \frac{1+i\sqrt{3}}{6}\sqrt[3]{\frac{1}{2}\left(D_1 - \sqrt{E_1}\right)},$$

$$P_{3R} = -\frac{A_1}{3} + \frac{1+i\sqrt{3}}{6}\sqrt[3]{\frac{1}{2}\left(D_1 + \sqrt{E_1}\right)} + \frac{1-i\sqrt{3}}{6}\sqrt[3]{\frac{1}{2}\left(D_1 - \sqrt{E_1}\right)},$$

$$\xi_{5i} = \frac{\theta P_i^2}{\left(K^2+P_i^2\right)\left(d_3+\eta-a_3\right)}.$$

Existence of the equilibrium points with radiotherapy alone, without chemotherapy if it satisfies

1. $d_1+\delta+\varepsilon_2\eta-a_1\geq 0$,
2. $(r-\varepsilon_1\eta)N-r\left(\frac{(d_1+\delta+\varepsilon_2\eta-a_1)d_4}{\alpha n d_1}\right)\geq 0$,
3. $P_i\geq 0,\quad i=1,2,3$ and
4. $d_3+\eta-a_3>0$.

The equilibrium points with radiotherapy and followed by chemotherapy

In this system is the same as System (1). To find the equilibrium point in a way $\frac{dS}{dt}=0$, $\frac{dI}{dt}=0$, $\frac{dP}{dt}=0$, $\frac{dC}{dt}=0$, $\frac{dV}{dt}=0$, $\frac{dM}{dt}=0$. So the equilibrium point of radiotherapy followed by chemotherapy in cervical cancer is

$$\begin{aligned}
EP_{1RC}\left(S^*,I^*,P^*,C^*,V^*,M^*\right)&=\left(\xi_7\xi_9+\xi_8,\xi_9,P_{1RC},\xi_{101RC},\xi_1\xi_9,\xi_6\right)\\
EP_{2RC}\left(S^*,I^*,P^*,C^*,V^*,M^*\right)&=\left(\xi_7\xi_9+\xi_8,\xi_9,P_{2RC},\xi_{102RC},\xi_1\xi_9,\xi_6\right)\\
EP_{3R}\left(S^*,I^*,P^*,C^*,V^*,M^*\right)&=\left(\xi_7\xi_9+\xi_8,\xi_9,P_{3RC},\xi_{103RC},\xi_1\xi_9,\xi_6\right)
\end{aligned}\tag{4}$$

where

$$\xi_6=\frac{v_M}{\gamma},\ \xi_7=-\left(1+\frac{N\alpha\xi_1}{r}\right),\qquad \xi_8=N-\frac{Nk_S\xi_6}{r}-\frac{N\varepsilon_1\eta}{r},$$

$$\xi_9=\frac{-\alpha\xi_1\xi_8-a_1+d_1+\delta+k_I\xi_6+\varepsilon_2\eta}{\alpha\xi_1\xi_7},\qquad A_2=\frac{\delta\xi_{11}-\theta}{a_2-d_2-k_P\xi_6-\varepsilon_3\eta},$$

$$B_2=\frac{(a_2-d_2-k_P\xi_6-\varepsilon_3\eta)K^2}{a_2-d_2-k_P\xi_6-\varepsilon_3\eta},\qquad C_2=\frac{\delta\xi_{11}K^2}{a_2-d_2-k_P\xi_6-\varepsilon_3\eta},$$

$$D_2=2A_2^{\ 3}-9A_2B_2+27C_2,\qquad E_2=\left(2A_2^{\ 3}-9A_2B_2+27C_2\right)^2-4\left(A_2^{\ 2}-3B_2\right)^3$$

$$P_{1RC}=-\frac{A_2}{3}-\frac{1}{3}\sqrt[3]{\frac{1}{2}\left(D_2+\sqrt{E_2}\right)}-\frac{1}{3}\sqrt[3]{\frac{1}{2}\left(D_2-\sqrt{E_2}\right)},$$

$$P_{2RC}=-\frac{A_2}{3}+\frac{1-i\sqrt{3}}{6}\sqrt[3]{\frac{1}{2}\left(D_2+\sqrt{E_2}\right)}+\frac{1+i\sqrt{3}}{6}\sqrt[3]{\frac{1}{2}\left(D_2-\sqrt{E_2}\right)},$$

$$P_{3RC}=-\frac{A_2}{3}+\frac{1+i\sqrt{3}}{6}\sqrt[3]{\frac{1}{2}\left(D_2+\sqrt{E_2}\right)}+\frac{1-i\sqrt{3}}{6}\sqrt[3]{\frac{1}{2}\left(D_2-\sqrt{E_2}\right)},$$

$$\xi_{10iRC}=-\frac{\theta P_{iRC}^{\ 2}}{\left(K^2+P_{iRC}^{\ 2}\right)\left(a_3-d_3-k_C\xi_6-\varepsilon_4\right)}.$$

Existence of the equilibrium points with radiotherapy and followed by chemotherapy, if it satisfies

1. $N-\frac{Nk_S\xi_6}{r}-\frac{N\varepsilon_1\eta}{r}-\xi_7\xi_9\geq 0$,
2. $-\alpha\xi_1\xi_8-a_1+d_1+\delta+k_I\xi_6+\varepsilon_2\eta\geq 0$ and
3. $P_{iRC}\geq 0$.

STABILITY OF THE EQUILIBRIUM POINT

Stability of the equilibrium points with radiotherapy alone, without chemotherapy

Theorem 1.

If $a_3-d_3-\eta<0$, $a_2-d_3-\frac{2\theta P_iK^2}{\left(K^2+P_i^2\right)^2}-\varepsilon_3\eta<0$, $A_i>0$, $2A_i^3-9A_iB_i+27C_i=0$, $A_i^2-3B_i=0$ where $i=3,4,5$ then the equilibrium point

$EP_{iR}\left(S^*,I^*,P^*,C^*,V^*\right)=\left(\xi_2,\xi_3,P_i,\xi_6,\xi_{5i}\right)$
asymptotically stable.

Proof.
From System (2) is obtained characteristic equation in Equation (5).

$$
\begin{gathered}
\left(a_3-d_3-\eta-\lambda\right)\left(a_2-d_3-\frac{2\theta P_1K^2}{\left(K^2+P_1^2\right)^2}-\varepsilon_3\eta-\lambda\right)\\
\left(\begin{array}{l}
\lambda^3-\left(r-\frac{2r\xi_2}{N}-\frac{r\xi_3}{N}-\alpha\xi_{51}-\varepsilon_1\eta+\left(a_1-d_1-\delta-\varepsilon_2\eta-d_4\right)\right)\lambda^2+\\
\left[\begin{array}{l}
\left(r-\frac{2r\xi_2}{N}-\frac{r\xi_3}{N}-\alpha\xi_{51}-\varepsilon_1\eta\right)\left(a_1-d_1-\delta-\varepsilon_2\eta-d_4\right)-\\
\left(\left(a_1-d_1-\delta-\varepsilon_2\eta\right)d_4+\alpha\xi_2nd_1\right)+\alpha\xi_{51}\frac{r\xi_2}{N}
\end{array}\right]\lambda+\\
\left(r-\frac{2r\xi_2}{N}-\frac{r\xi_3}{N}-\alpha\xi_{51}-\varepsilon_1\eta\right)\left(\left(a_1-d_1-\delta-\varepsilon_2\eta\right)d_4+\alpha\xi_2nd_1\right)+\\
\alpha\xi_{51}\left(\frac{r\xi_2}{N}d_4+\alpha\xi_2nd_1\right)
\end{array}\right)=0
\end{gathered}
\tag{5}
$$

Stability of the equilibrium points with radiotherapy and followed by chemotherapy

Theorem 2.
If $a_3-d_3-k_C\left(\frac{v_M}{\gamma}\right)-\varepsilon_4<0$, $a_2-d_2-\frac{2\theta P_{iRC}K^2}{\left(K^2+P_{iRC}{}^2\right)^2}-k_P\left(\frac{v_M}{\gamma}\right)-\varepsilon_3\eta<0$, where $i=3,4,5$ and $A_6>0$, $2A_6{}^3-9A_6B_6+27C_6=0$, $A_6{}^2-3B_6=0$ then the equilibrium point $EP_{iRC}\left(S^*,I^*,P^*,C^*,V^*,M^*\right)=\left(\xi_7\xi_9+\xi_8,\xi_9,P_{iRC},\xi_{10iRC},\xi_1\xi_9,\xi_6\right)$ asymptotically stable.

Proof.
From System (1) is obtained characteristic equation in Equation (6).

$$
\begin{gathered}
\left(a_3-d_3-\eta-\lambda\right)\left(a_2-d_3-\frac{2\theta P_2K^2}{\left(K^2+P_2{}^2\right)^2}-\varepsilon_3\eta-\lambda\right)\\
\left(\begin{array}{l}
\lambda^3-\left(r-\frac{2r\xi_2}{N}-\frac{r\xi_3}{N}-\alpha\xi_{52}-\varepsilon_1\eta+\left(a_1-d_1-\delta-\varepsilon_2\eta-d_4\right)\right)\lambda^2+\\
\left[\begin{array}{l}
\left(r-\frac{2r\xi_2}{N}-\frac{r\xi_3}{N}-\alpha\xi_{52}-\varepsilon_1\eta\right)\left(a_1-d_1-\delta-\varepsilon_2\eta-d_4\right)-\\
\left(\left(a_1-d_1-\delta-\varepsilon_2\eta\right)d_4+\alpha\xi_2nd_1\right)+\alpha\xi_{52}\frac{r\xi_2}{N}
\end{array}\right]\lambda+\\
\left(r-\frac{2r\xi_2}{N}-\frac{r\xi_3}{N}-\alpha\xi_{52}-\varepsilon_1\eta\right)\left(\left(a_1-d_1-\delta-\varepsilon_2\eta\right)d_4+\alpha\xi_2nd_1\right)+\\
\alpha\xi_{52}\left(\frac{r\xi_2}{N}d_4+\alpha\xi_2nd_1\right)
\end{array}\right)=0
\end{gathered}
\tag{6}
$$

SIMULATION

In this section will be discussed about the numerical simulation and medical interpretation of the mathematical model of cervical cancer in the presence of radiotherapy and chemotherapy effects are divided into 2 cases.

1. The influence of radiotherapy
2. The influence of radiotherapy and followed by chemotherapy

Simulation of radiotherapy effect

The parameter values for this case are given in the following Table 2.

Table 2. Values of parameters for cases of radiotherapy effects.

Symbol	Value	Reference
r	0.0255	Asih et al. (2015)
N	9900.99	Asih et al. (2015)
α	0.00001	Asih et al. (2015)
ε_1	0.004	Liu and Yang (2014)
η	0.05	Liu and Yang (2014)
a_1	100	Asih et al. (2015)
d_1	100.01	Asih et al. (2015)
δ	0.0082	Asih et al. (2015)
ε_2	0.03	Liu and Yang (2014)
a_2	101	Asih et al. (2015)
d_2	100	Asih et al. (2015)
θ	20.03	Asih et al. (2015)
K	2	Asih et al. (2015)
a_3	0.03	Asih et al. (2015)
d_3	101.01	Asih et al. (2015)
n	1	Asih et al. (2015)
d_4	500	Asih et al. (2015)

Figure 2 shows the first 30 days or the first month after radiotherapy is showed a decrease in the number of cells from 13 cell/mm^3 to 12.78 cell/mm^3. This means that the decrease in cell number is 0.22 cell/mm^3. At six months and one year of radiotherapy if it continues to show a successive decrease to 11.8 cell/mm^3 and 10.73 cell/mm^3. This shows the ill effects of radiotherapy because of healthy cells. For infected cells in the first and third months after radiotherapy successively from 13 cell/mm^3 to 4,156 cell/mm^3 and 0.4364 cell/mm^3. This is good for curing cancer, because the infected cells will eventually become pre-cancerous cells. While the cancer cells on the fourth day after radiotherapy immediately fell rapidly, from 13 cell/mm^3 to 0.3526 cell/mm^3. For pre-cancerous cells almost the same as cancer cells, that is down very quickly. For the virus goes down quickly, because the infected cell goes down as well. This is because the virus replicates itself from infected cells.

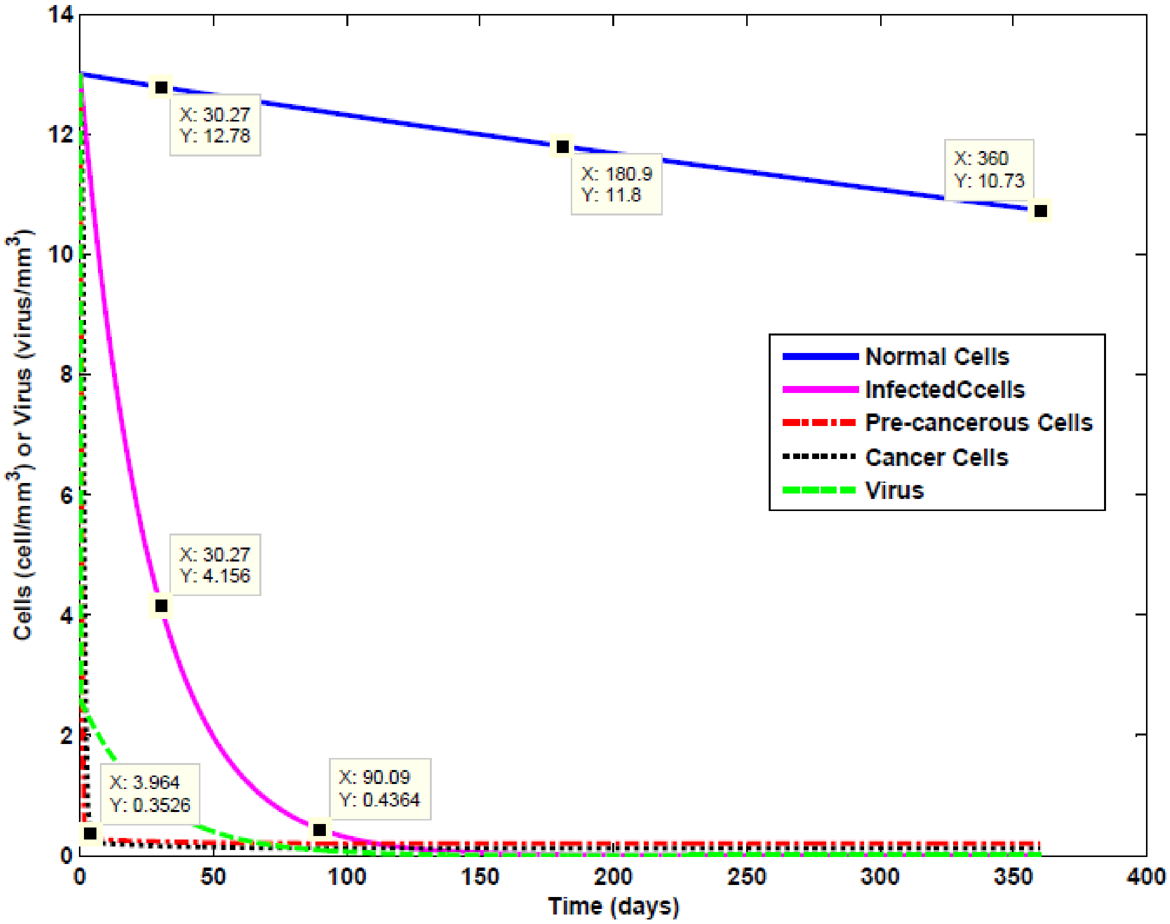

Figure 2. Trajectory diagram the influence of radiotherapy.

Simulation of the Influence of Radiotherapy and Followed by Chemotherapy

The parameter values for this case are given in the following Table 3.

Table 3. Value of case parameters the influence of radiotherapy and followed by chemotherapy.

Symbol	Value	Reference
r	0.0255	Asih et al. (2015)
N	9900.99	Asih et al. (2015)
α	0.00001	Asih et al. (2015)
ε_1	0.004	Liu and Yang (2014)
η	0.05	Liu and Yang (2014)
a_1	100	Asih et al. (2015)
d_1	100.01	Asih et al. (2015)
δ	0.0082	Asih et al. (2015)
ε_2	0.03	Liu and Yang (2014)
a_2	101	Asih et al. (2015)
d_2	100	Asih et al. (2015)
θ	20.03	Asih et al. (2015)
K	2	Asih et al. (2015)
a_3	0.03	Asih et al. (2015)
d_3	101.01	Asih et al. (2015)
n	1	Asih et al. (2015)
d_4	500	Asih et al. (2015)
k_S	0.01	Pillis et al. (2007)
k_I	0.01	Pillis et al. (2007)
k_P	0.01	Pillis et al. (2007)
k_C	0.01	Pillis et al. (2007)
γ	0.1	Pillis et al. (2007)
v_M	0.01	Pillis et al. (2007)

Figure 3 shows a trajectory with the effects of radiotherapy and followed chemotherapy, which is an advanced patient of cervical cancer. Normal cells during the first 30 days showed a rapid decline, from 13 cell/mm^3 to 3,638 cell/mm^3. This makes patients with advanced cervical cancer in this condition will get worse. Therefore, in this study advised not to use this treatment. Cancer cells also drop very rapidly, in the first 4 days of radiotherapy and chemotherapy, from 13 cell/mm^3 to 0.2061 cell/mm^3.

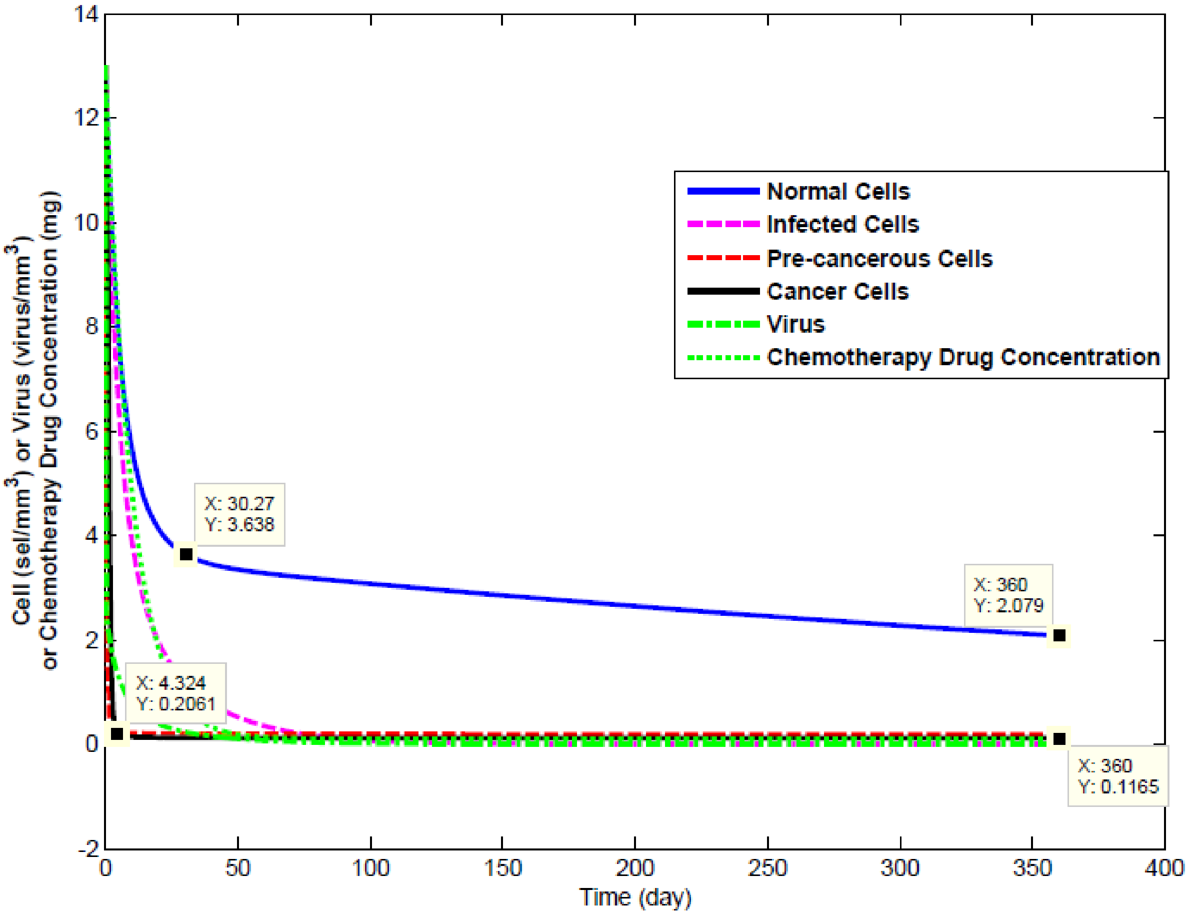

Figure 3. Trajectory diagram the influence of radiotherapy and followed by chemotherapy.

CONCLUSION

Cervical cancer is one type of cancer and second highest incidence of cancer in women compared to other cancers. Treatment of cervical cancer with radiotherapy at an early stage is quite effective. This mathematical model showed that treatment of cervical cancer at an advanced stage with radiotherapy and followed by chemotherapy is not effective. Because normal cells die very quickly, and will aggravate the patient's condition of cervical cancer. This research needs to be continued with other more effective treatments, especially for advanced stages of cervical cancer.

Conflict of Interest: The authors declare that there is no conflict of interest.

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