African Journal of Mathematics and Computer Science Research Vol. 3(6), pp. 101-106, June 2010
Available online at http://www.academicjournals.org/AJMCSR
ISSN 2006-9731© 2010 Academic Journals

Full Length Research Paper

A mathematical model of radioimmunotherapy for tumor treatment

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Accepted 21 April, 2010

There is rapidly growing interest in the potential for synergistic, clinically relevant therapeutic responses by combining radiation therapy with immune response. A new mathematical model of radioimmunotherapy for tumor treatment was introduced. In this work, the linear and exponential spatial dependence of tumor parameters was used. The dose distributions model of radiotherapy with immune response for tumor treatment was formulated. A discussion, on the effect of immune response with radiotherapy for the treatment of tumor is explained in details.

Key words: Solid tumor, mathematical model, radioimmunotherapy, immune response.

INTRODUCTION

Radiation therapy is a certain type of energy to kill cancer cells and shrink tumors. Radiotherapy destroys cells in the area being treated by damaging their genetic material. The radiation damages both kinds of cells, cancer cells and normal cells. The goal of radiation therapy is to damage as many cancer cells as possible, while limiting harm to nearby healthy tissue. The body's immune system work to defend itself against disease and infection. Typically, when a cancer cell arises in the body, the body's immune system recognizes it as abnormal and destroys it before it starts spreading. Immunotherapy is the manipulation of the immune system in order to prevent or treat a disease. One of the most well known examples of immunotherapy is the use of vaccines to prevent infectious disease. However, in case of tumor, immunotherapy is being investigated to treat the cancer. Unlike traditional therapies for tumor, which act directly on the tumor cells, immunotherapy is designed to help a patient's immune system, which also works against the tumor cells. Immunotherapy is an experimental treatment strategy for tumor. Small et al. (2000) worked on immunotherapy of hormone-refractory prostate cancer with antigen-loaded dendritic cells. Brame and Agren (1987) introduced a model on optimal dose distribution for eradication of heterogeneous tumors. Ebert et al. (1996) also introduced a model on the characteristics of tumor control probability for heterogeneous tumor. More recent work in this area is given by Plonik et al. (2004) who introduced a model on optimization of tumor control probability for heterogeneous tumors in fractioned radiotherapy treatment protocols. In this work they optimized that the dose distribution yields a higher tumor cure probability than a typical clinical dose distribution. Hu et al. (1988) discussed the effects of radiotherapy on the immune system of patients with nasopharyngeal carcinoma. In this work, they reported on 123 patients with nasopharyngeal carcinoma whose immune status was measured at the time of diagnosis, the day radiotherapy was completed, then 2 - 3 months and finally 6 -8 months after completion of radiotherapy. There were higher incidences of recurrence and metastases in the patients with high levels of circulating immune complexes and low numbers of lymphocytes in the peripheral blood after radiotherapy. Several new approaches to radiation therapy are being evaluated to determine their effectiveness in treatment of cancer.

Radioimmunotherapy is an experimental, internal radiation treatment in which radioactive isotopes attached to antibodies from the tumor cells are injected into the body. The bloodstream carries the antibodies to the tumor where the isotopes attack and kill malignant cells. The division of radiation oncology is investigating a new

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type of radiation therapy that targets radiation to the tumor using monoclonal antibodies. This form of therapy is called radioimmunotherapy. The more recent work in this line is given by Andrew (2005) presented radio-immunotherapy of prostate cancer: does tumor size matter? This work based on the combination of monoclonal antibodies with other therapies, including chemotherapy and other biologics, and using monoclonal antibodies to deliver toxins and radioisotopes to tumor sites, have also emerged as mechanisms of increasing response rates and duration of response. The selection of suitable antigens on the surface of cancer cells for targeting with monoclonal antibodies and the biology of cellular function related to cognate antigens, remain critical factors in the success of this type of therapy, as well as in identifying new strategies for antibody-based treatment. In the presence of immune response, we are taking a heterogeneous tumor volume having a radiation response that is characterized and repopulation rate may change with time. Recently, research has begun on the design of optimal schedules for the treatment of solid tumors using modern mathematical (optimization) method. The approach to utilize optimal control theory has several advantages over the previous work on scheduling radiotherapy. In this work the dose distribution that optimizes tumor cure probability in homogeneous tumors for radiotherapy in the presence of immune response was studied. The purpose of this study is to assess the potential for optimizing the biological effect of radioimmunotherapy by matching the dose distribution with tumor structure through the selection of appropriate antibodies.

MATHEMATICAL MODEL

This model is based on the research work of Plonik et al. (2004). Since the model is for radioimmunotherapy, a term for immune response was included. A model for the special case of radiotherapy scenario in the presence of immune response is designed. In this model, the linear quadratic model was used retaining only the linear term science for tumor control while neglecting the quadratic term. In the presence of immune response, we formulate the dose distributions of radiotherapy, which optimize tumor cure probability (TCP) in tumor. The dose distribution rate is assumed to be high enough so that the dose distribution is delivered instantaneously.

Tumor cell density at time t

We represent $p(\vec{r})$ as tumor cell density at time t, and p_0 is the initial tumor cell density.

Dose distribution: The dose distribution is represented by $x(\vec{r})$ Tumor cure probability (TCP): The tumor cure probability after dose distribution has been delivered.
Immune response: The internal body immune response is represented by $e(\vec{r})$.

The given evolution of tumor cell density is

$$p = p_0 \exp\left[-\alpha x + \gamma t - ke\right] \quad (1)$$

The α is the rate of cell killed due to radiosensitivity, γ is the rate of tumor cell division and the k is the rate of cell killed due to immune response.

$$TCP = \exp\left[-\int p d^3 r\right] = \exp\left[\int p_0 e^{(-\alpha x+\gamma t-ke)} d^3 r\right] \quad (2)$$

Here the aim is to obtain the dose distribution $x(\vec{r})$ that maximizes TCP while keeping invariant, therefore

$$\langle x \rangle = \frac{\int W x d^3 r}{\int W d^3 r} \quad (3)$$

Where $\langle x \rangle$ representing the generalized average tumor dose distribution and the term $W(\vec{r})$ shows a weighting function.

We keep $W(\vec{r}) = 1$ then, we get

$$\langle x \rangle = \frac{\int x d^3 r}{V} = D \quad (4)$$

Where D represents average tumor dose distribution and V is the tumor volume. Now considering the following functions.

Linear spatial dependence

We supposed spherical symmetry of tumor as well as the functions $\alpha, \gamma \& k$ depend on radius of the tumor. We are taking the following functions for $\alpha, \gamma \& k$. The functions for $\alpha, \gamma \& k$ were taken on the basis of available research work of Plotnik et al. (2004).

$$\alpha = \alpha_0 \left(1 - \frac{r}{R}\right) + \frac{\alpha_1 r}{R} \quad (5)$$

$$\gamma = \gamma_0 \left(1 - \frac{r}{R}\right) + \frac{\gamma_1 r}{R} \quad (6)$$

$$k = k_0 \left(1 - \frac{r}{R}\right) + \frac{k_1 r}{R} \quad (7)$$

The above equations (5), (6) and (7) show linear increase/decrease in $\alpha, \gamma \& k$ form $\alpha_0, \gamma_0 \& k_0$ at $r = 0$ to $\alpha_1, \gamma_1 \& k_1$ at $r = R$. The Figure 1(a) represents the killing rate of tumor cell due to radiotherapy drug with respect to radius of tumor. The initial value (that is α_0) is 0.25/ Gy, at the centre of tumor because the tumor cell density is maximum at the centre of the tumor, while the

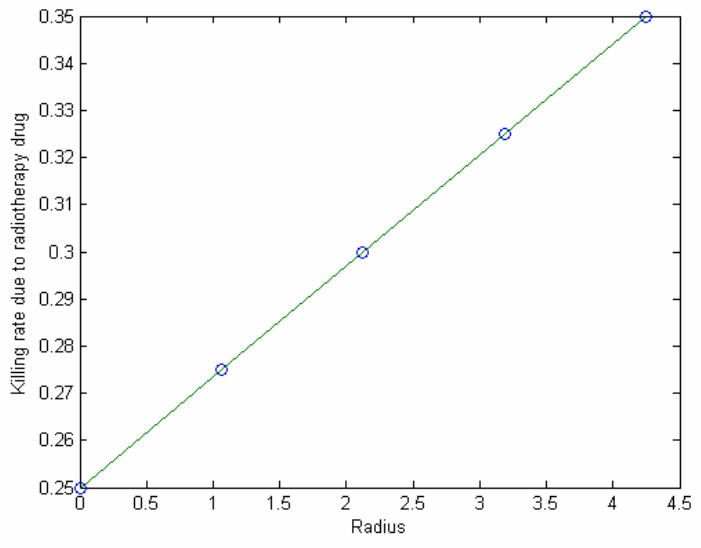

Figure 1a. Solution of equation 5 for the parameter values R = 4.25cm. $\alpha_0 = 0.25/Gy$ and $\alpha_1 = 0.25/Gy$.

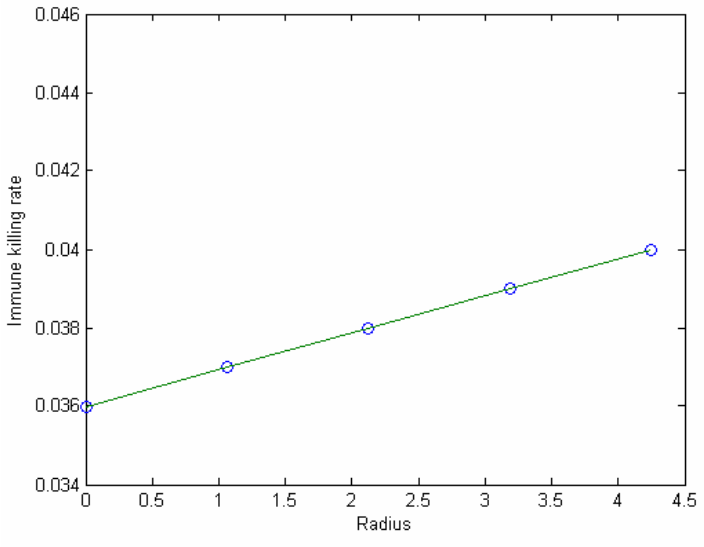

Figure 1c. solution of equation 7 for the parameter values R=4.25cm. k_0=0.036 cm^3/ng.day and k_1= 0.040 cm^3/ng.day.

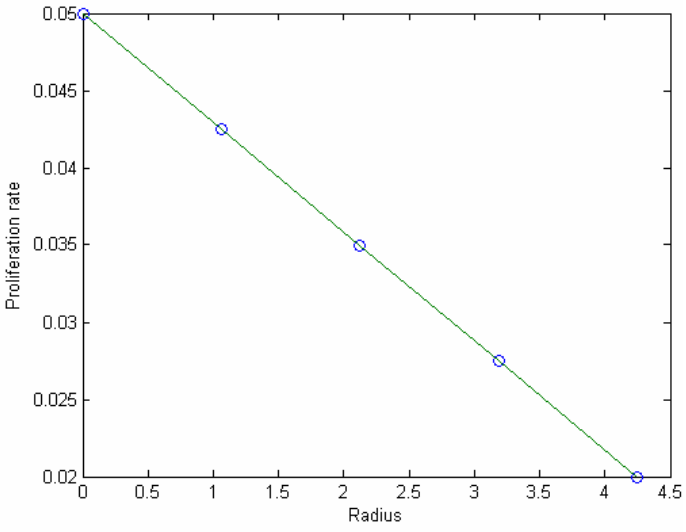

Figure 1b. solution of equation 6 for the parameter values R=4.25cm. $\gamma_0 = 0.05/day$ and $\gamma_1 = 0.02/Gy$.

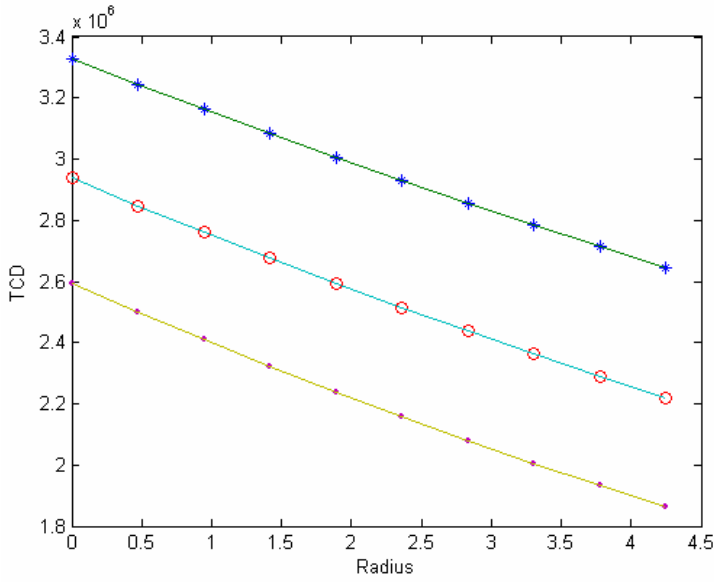

Figure 2a. plot of tumor cell density and three different values of radiotherapies dose distributions with immune response.

value at boundary of tumor (that is α_1) is 0.35/ Gy, because the tumor cell density is minimum at the boundary of the tumor. Figure 1(b) represents the proliferation rate of tumor cell with respect to radius of tumor. The initial value (that is γ_0) is 0.05/ day, at the centre of tumor because the tumor cell density is maximum at the centre of the tumor, while the value at boundary of tumor (that is γ_1) is 0.02/ day, because the tumor cell density is minimum at the boundary of the tumor. The figure suggests that the proliferation rate is maximum at the centre of the tumor and minimum at the boundary of tumor. Figure 1c represents the killing rate of tumor cell due to immune response with respect to radius of tumor. The initial value of killing rate of tumor cell due to immune response k_0 is 0.036 cm^3/ng.day, at the center of tumor because the tumor cell density is maximum at the center of the tumor, and the value of killing rate of tumor cell due to immune response at boundary of tumor k_1 is 0.040 cm^3/ng.day because the TCD is minimum at the boundary of the tumor. The immune response is maximum at the boundary of tumor.

Figure 2a represents tumor cell density at different dose distribution of radiotherapy drug. If the value of dose distribution is D =1 which shows through (*) in figure. Here the tumor cell density at the centre of tumor is 3 × 10^6 cell which is maximum while at

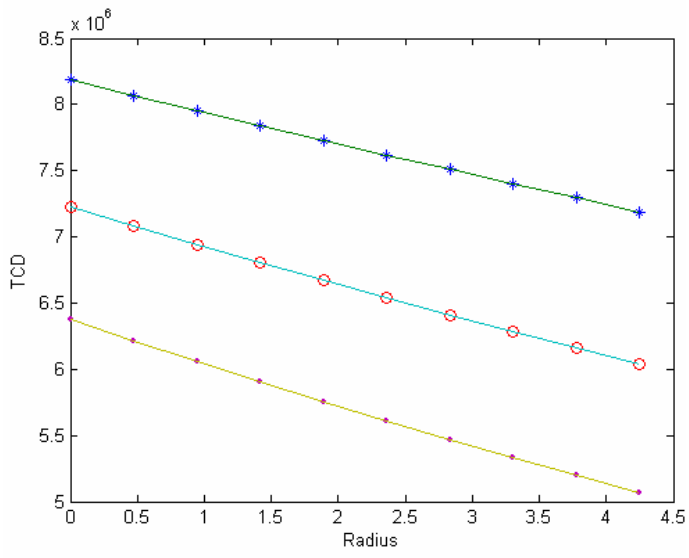

Figure 2b. plot of tumor cell density and three different values of radiotherapies dose distributions without immune response.

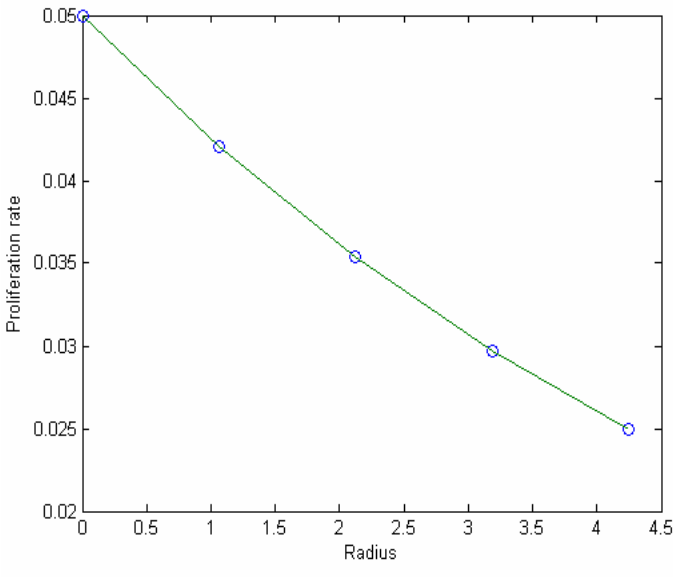

Figure 3 b. Behavior of equation 9 for the parameter values $\gamma_0 = 0.05/day$ and c = 6.13 am.

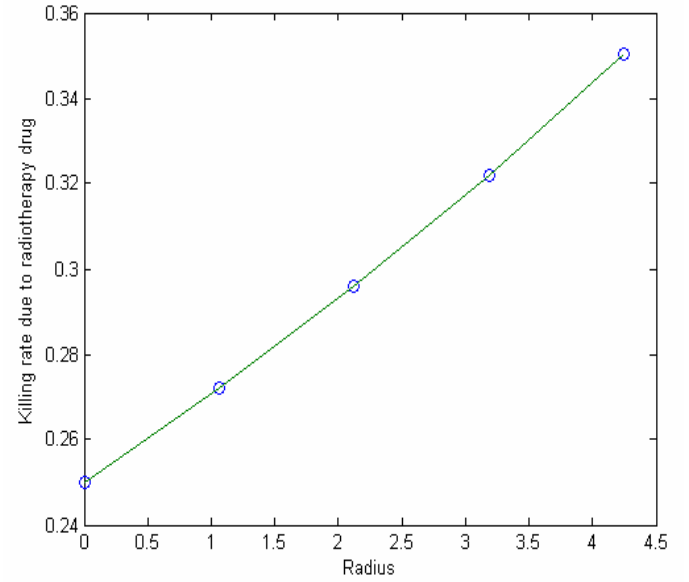

Figure 3a. behavior of equation 8 for the parameter values $\alpha_0 = 0.25$ */G and* d=12.6 cm.

the boundary of tumor 2.8 × 10^6 cell is minimum. If the value of dose distribution is D=1.5 which shows through (o) in figure. Here the tumor cell density at the centre of tumor is 2.9 × 10^6 cells which are maximum, and at the boundary of tumor 2.3 × 10^6 cells is minimum. The distribution is D = 2 which represented by (.) in figure. Here the tumor cell density at the centre of tumor is 2.6 × 10^6 cells which is maximum and at the boundary of tumor 1.9 × 10^6 cells. Figure 2b shows that tumor cell density at different dose different dose distribution of radiotherapy drug when immune response is not working. If the dose distribution (D) is 1 which shows through (*) in figure, then the tumor cell density at the centre of tumor is 8.2 × 10^6 cells which is maximum while at the boundary of tumor 7.4 × 10^6 cells is minimum. If the dose distribution is D =1.5 which represented by (o) in figure, the tumor cell density at the centre of tumor is 7.2 × 10^6 cells which is maximum and at the boundary of tumor 6.4 × 10^6 cells is minimum. If the dose distribution is D = 2 which shows through (.) in figure, the tumor cell density at the centre of tumor is 6.4 × 10^6 cells which is maximum and at the boundary of tumor 5.1 × 10^6 cells which is minimum.

Exponential spatial dependence

Another functional form for α, γ and k, given by Plotnik et al. (2004).

$$\alpha = \alpha_0 \exp[r/d] \quad (8)$$

$$\gamma = \gamma_0 \exp[-r/c] \quad (9)$$

$$k = k_0 \exp[r/f] \quad (10)$$

Figure 3a represents the killing rate of tumor cell due to radiotherapy drug with respect to radius of tumor. The initial value (that is, α_0) is 0.25/Gy, at the centre of tumor because the tumor cell density is maximum at the centre of the tumor, while the value at boundary of tumor (that is, α) is 0.35/ Gy, because the tumor cell density is minimum at the boundary of the tumor. Figure 3(b) represents the proliferation rate of tumor cell with respect to radius of the tumor. The initial value (that is γ_0) is 0.05/ day, at the centre

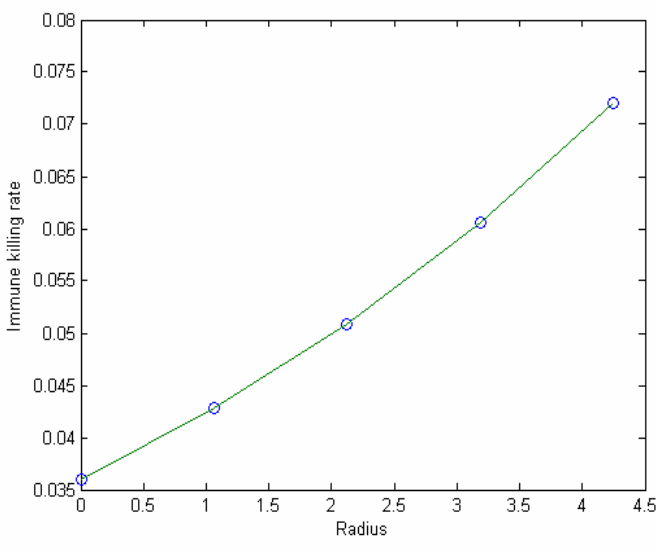

Figure 3c. behavior of equation 10 for the parameter values k_0=0.036 cm^3/ng.day and f = 6.13 cm.

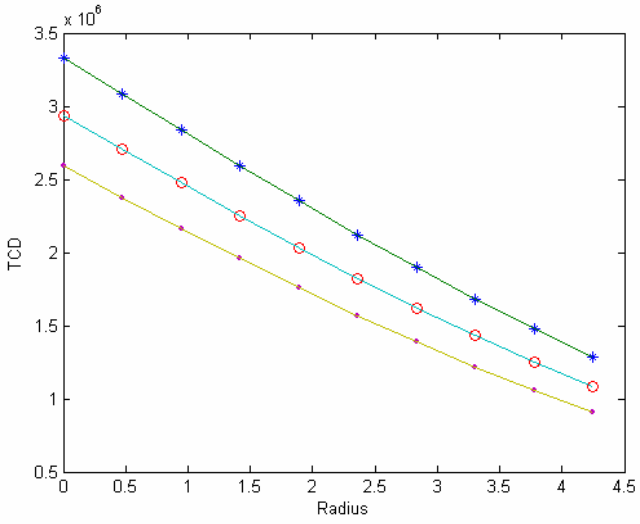

Figure 4a. Plot of tumor cell density and three different values of radiotherapies dose distributions with immune response.

of the tumor because its cell density is maximum at the centre of the tumor, while the value at boundary of tumor (that is γ) is 0.025/ day, because the tumor cell density is minimum at the boundary of the tumor. The figure suggests that the proliferation rate is maximum at the centre of the tumor and minimum at the boundary of tumor. Figure 3(c) represents the killing rate of tumor cell due to immune response with respect to radius of tumor. The initial value of killing rate of tumor cell due to immune response k_0 is 0.036 cm^3/ng.day, at the center of tumor because the tumor cell density is maximum at the center of the tumor, and the value of killing rate of tumor cell due to immune response at boundary of tumor k is 0.070 cm^3/ng.day because the TCD is min. at the boundary of the tumor. The immune response is maximum at the boundary of tumor.

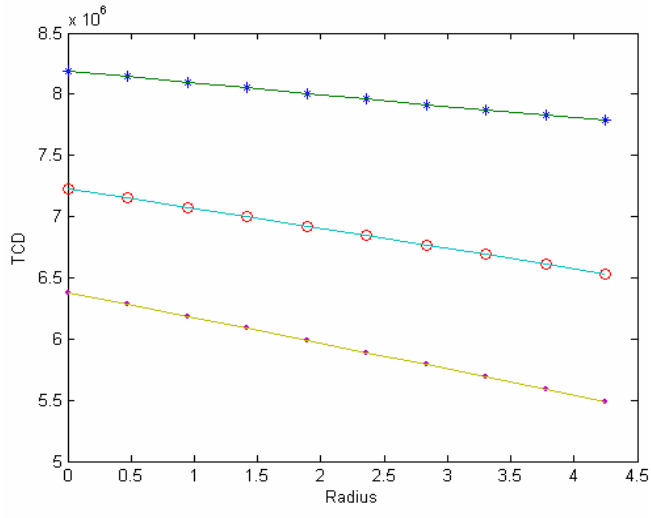

Figure 4b. Plot of tumor cell density and three different values of radiotherapies dose distributions without immune response.

Figure 4a represents that tumor cell density at different dose distribution of radiotherapy drug. If the value of dose distribution is D =1 which shows through (*) in figure. Here the tumor cell density at the centre of tumor is 3.4 × 10^6 cell which is maximum while at the boundary of tumor 1.5 × 10^6 cell is minimum. If the dose distribution is D =1.5 which shows through (o) in figure. Here the tumor cell density at the centre of tumor is 1.4 × 10^6 cell which is maximum, and at the boundary of tumor 2.3 × 10^6 cell is minimum. The distribution is D = 2 which is represented by (.) in figure. Here the tumor cell density at the centre of tumor is 2.6 × 10^6 cell which is maximum, while at the boundary of tumor 1.0 × 10^6 cell is minimum. Figure 4b shows that tumor cell density at different dose distribution of radiotherapy drug when immune response is not working. If the dose distribution (D) is 1 which shows through (*) in figure, then the tumor cell density at the centre of tumor is 8.2 × 10^6 cells which is maximum while at the boundary of tumor 7.9 × 10^6 cells is minimum. If the dose distribution is D=1.5 which represented by (o) in figure, the tumor cell density at the centre of tumor is 7.2 × 10^6 cells which is maximum and at the boundary of tumor 6.6 × 10^6 cells is minimum. If the dose distribution is D = 2 which shows through (.) in figure, the tumor cell density at the centre of tumor is 6.4 × 10^6 cells which is maximum and at the boundary of tumor 5.5 × 10^6 cells which is minimum. The numerical result of different functional forms of tumor parameters shows that α and γ works in the opposite directions. If the tumor cells in the center of tumor are hypoxic, then they are less radiosensitive, therefore require more dose at the center of tumor. The results of the exponential spatial dependency for α, γ and k are almost similar to the linear spatial dependency form. The numerical results show that tumor cell density and dose distribution are not very much sensitive to the different functional forms of the tumor parameters. This mathematical study of tumor parameters is helpful to understand the behavior with respect to radius of tumor.

DISCUSSION

The radioimmunotherapy program is a multidisciplinary effort involving basic and clinical scientists. Within the next few years, radioimmunotherapy will soon become

part of the standard therapies offered to patients. Investigators are actively evaluating the use of radioimmunotherapy in patients undergoing bone marrow transplantation, to determine whether this form of radiation can complement and/or replace traditional forms of radiation in these patients. The biological effect of radioimmunotherapy is most commonly assessed in terms of absorbed radiation dose. In tumor, conventional dosimetry methods assume a uniform radionuclide and calculate a mean dose throughout the tumor. However, the vasculature of solid tumors tends to be highly irregular and the systemic delivery of antibodies is therefore heterogeneous.

Here, the tumor treatment by radiotherapy in the presence of immune response was studied. A more detailed knowledge of tumor parameters will also be helpful to assess the relative benefits of delivering dose distribution in tumor treatment. Comparison of the tumor cell density with different dose distribution of radiotherapy in the presence and absence of immune response was made. The results of the comparison represent a lot of difference, thus this study postulates that immune response is more helpful for the treatment of tumor. These trials are evaluating strategies to further improve the therapeutic index of this treatment.

Conclusion

This study will be helpful for radiotherapy treatment of tumor because radioactive rays kill tumor cells as well as normal cells also. Then radioimmunotherapy will be very much helpful to save the normal cells because immune system will work with radiotherapy for tumor treatment. The dose distribution can be optimized in tumor by selecting the appropriate immune response and radionuclide. The recent development of strategies to reduce the renal accretion of antibody fragments and peptides enables the use of such smaller molecules for therapy, especially those also labeled with radiometals and other forms of intracellularly retained radionuclide. The most likely pattern of use for this field in the next 5 years will probably involve combination or sequential regimens incorporating both radioimmunotherapy and more conventional chemotherapy or external radiotherapy.

ACKNOWLEDGEMENT

The authors wish to thank Dr. Rashmi Sharma, Department of Pharmacy, and Dr. B. R. Ambedkar University for helpful and insightful discussion concerning this work.

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