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Optimization of Cancer Therapy: Development of a Cell Kinetic Model for Tumor Radiotherapy

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Abstract

A mathematical model for tumor growth and its perturbation by radiation has been formulated on the basis of our present understanding of cell kinetics. The tumor cell population comprises proliferating and non-proliferating cells. The non-proliferating cells are further subdivided into quiescent, hypoxic and non-viable compartments. The intercompartmental cell transfers are described by a set of differential equations containing linear and nonlinear terms. In the absence of any perturbation, the model is analytically solvable and leads to the well known Gompertzian equation of growth. The effects of iradiation are simulated by computed programmes incorporating the radiation induced processes of cell-death, cell loss rate, cellular repair and repopulation of the tumor. The parameters used in the description of these processes are experimentally determinable.

The model has been tested with the help of experimental data available on Sarcoma-180 tumor grown in the hind leg of mice. It is seen that the model is capable of reproducing and predicting the trends of the experimental data quite satisfactorily. The model has been subsequently used to analyse the mode of action of 2-deoxy-D- glucose as an adjuvant to improve tumor radiotherapy.

Key words -

Cancer therapy,
Cell kinetic model,
Tumor radiotherapy

Present day regiments used in tumor radiotherapy are largely empirical. To improve the therapeutic efficacy, treatment regiments should be selected on a rational basis, which takes into consideration the physical and biological characteristics of the tumor and the host. An evaluation of the relative significance of various factors affecting the tumor radiation response is necessary for this purpose. This is a difficult task considering the complexity and heterogeneity of the biological system. Mathematical modelling and computer aided calculations could however, prove to be important tools for achieving this objective. The models may be used to examine consequences of certain assumptions on the behaviour of the biological systems and this may help in the interpretation and design of experimental studies. The knowledge gained in this process will be useful in identifying the most important factors influencing the therapeutic response. This approach may thus facilitate designing optimal treatment strategies.

In continuation of our studies on optimization of cancer therapy [1], [2], [3], [4], we analyzed therefore, the radiation induced changes in the tumor volume with the help of a simple mathematical model based on the present understanding of cell kinetics and repair of damage after radiation injury. In this paper, a model for undisturbed tumor growth is developed first, which is extended subsequently to include the effects of radiation. The model makes use of the experimental data to determine the values of a few parameters, characteristic of the system under investigation and then proceeds to predict the behaviour of the system under a variety of experimental conditions with minimum number of free parameters. The data available on Sarcoma-180 tumor in mice have been employed for testing the model. Subsequently, the model has been used for interpreting our experimental data concerning the effects of the glucose antimetabolite, 2-deoxy-D-glucose (2-DG), on the radiation response of the tumor.

Model for the Undisturbed Growth of the Tumor

Growth of tissues can be described in terms of kinetics of the cell populations comprising the tissues. In a rapidly proliferating tumor, the following cellular compartments may be identified [5]:

(i) P-Compartment:

At any instant of time some cells within the population would either undergo mitosis or get prepared for undergoing mitotic division. These cells, known as the proliferating cells, constitute the P-compartment.

The non-proliferating cells may be further subdivided into different compartments depending on the nature of the tumor and the type of studies one desires to carry out. For investigating the effect of irradiation on a rapidly growing tumor, the following compartmentalization is convenient.

(ii) Q-Compartment:

These are potentially proliferating cells but by some homeostatic mechanisms, are excluded from entering into the mitotic division. These are known as quiescent cells and constitute the Q-compartment.

(iii) H-Compartment:

The rate of growth of the blood-vasculature may not match with the rate of cell-proliferation in a tumor thereby forcing some cells to be quite away from the blood capillaries. These cells, which are deprived from adequate supply of oxygen, are known as the hypoxic cells and constitute the H-compartment. It has been assumed here that the cells with an oxygen tension less than 10 mm of Hg, are hypoxic cells.

(iv) N-Compartment:

This compartment consists of cells which have completely lost the capacity for proliferation like dead cells, necrotic cells, differentiated cells etc.

Thus the total number of cells in a tumor NT (t) at any given moment of time t is comprised of cells in the P, Q, H and N compartments so that-

$$NT(t) = NP(t) + NQ(t) + NH(t) + NN(t) \quad (1)$$

Hereafter we shall omit the label of time in the parenthesis, with an implicit understanding that the cell numbers are always functions of time.

The inter-compartmental cell transfers are shown in Fig. 1. Kp represents the rate of proliferation of the P-cells. This is related to the cell-cycle time tc as kp=In 2/tc. Rate of transfer of cells from P, Q and

H compartments to N compartment are denoted by kPN, kQN, kHN respectively. Similarly the loss-rate of the cells from different compartments are denoted by terms like kPL, kQL etc. All the transfer rates denoted by symbol 'k' are linear-rate constants and have dimensions per cell per unit time. The non-linear processes are taken into account through functions 'f'. Thus fPH and fQH are the number of cells transferred per unit time to H-compartment form P and Q respectively; fPQ is the number of cells transferred per unit of time from P to Q. Similarly fQP is the number of cells transferred per unit time from Q to P. fHP denotes the process of recruitment from H to P, which occurs only when the tumor is perturbed. Further, for the unperturbed growth of the tumor, following simplifying assumptions are made:

Schematic diagram for the cell-kinetic model of a tumor. For details see text

(a) All hypoxic cells are assumed to be equivalent, gradient of hypotoxicity is not taken into account.

b) Entry to H compartment from P and Q is assumed to be directly proportional to the instantaneous population.

c) Since for undisturbed tumor only the average cell-loss-rate is measurable, we assume that

$$kPL = kQL = kHL = kNL = kL$$

where kL= average cell-loss rate for undisturbed tumor.

d) The tumor volume is assumed to be proportional to the number of cells, i.e., it is assumed that the density of the tumor is invariant with respect to different compartments and age of the tumor.

With the help of these assumptions and using the model shown in Fig. 1, the following set of differential equation can be written

$$NP=kPNP-kPNNP-k^{-}LNP-fPH-fPQ+fQP+fHP \quad (2a),$$
$$NQ=kQNNQ-k^{-}LNQ-fQH+fPQ-fQP \quad (2b),$$
$$NH= - kHNNH-k^{-}LNH+fPH+fQH-fHP \quad (2c),$$
$$NN=kPNNP+kQNNQ+kHNNH \quad (2d),$$

Adding the equations 2a - 2d and using eq. (1) we get

$$NT=kPNP-k^{-}LNT \quad (3a),$$

If we define the growth fraction[6] G(t) as

$$G(t)=NP/NT$$

equation (3a) may be rewritten as

$$NT=[kPG(t)-k^{-}L]NT \quad (3b)$$

In general, G(t) may be approximated[7,8] by the equation

$$G(t)=G\infty+(GO-G\infty)e^{-at} \quad (4)$$

where

$G\infty$= Growth fraction at large time ($t \rightarrow \infty$)

GO= Growth fraction at time t = 0

a = a parameter, characteristic of the tumor.

Hence, at large values of time ($t \rightarrow \infty$), we get

$$NT=[kPG\infty - k^{-}L]NT$$

t has been observed that at sufficiently large values of time, an undisturbed tumor reaches a saturation v $\rightarrow \infty$, NT $\rightarrow$ O thereby necessitating the constraint that

$$kPG\infty = k^{-}L$$

which shows that for aged tumors, the rate of cell loss is equal to the rate of cell birth.

Using eq. (5), (4) and (3b) we get,

$$NT = ke^{-at}NT \quad (6)$$

where $k = kP(GO - G\infty)$ (6a)

Integrating eq. (6)

$$NT = NO \text{ Exp } [(k/a) (1 - e^{-at})] \quad (7)$$

Where NO = number of tumor cells at time t = o,

Assuming that the tumor volume at any time t is directly proportional to the total number of cells NT, equation (7) can be written as

$$V(t) = VO \text{ Exp } [(k/a) (1 - e^{-at})] \quad (8)$$

This is the well known Gompertzian equation of growth for the tumors [9].

For a detailed analysis, information about the cell populations in the various compartments postulated in the model is also needed. The effect of perturbation depends on a detailed knowledge of the population in various cell-compartments, at the time of perturbation. The population in the P-compartment, as already discussed, is dictated by the growth fraction G(t). The number of hypoxic cells NH can be estimated in the following manner.

It has been shown both theoretically [10] and experimentally [11] that the hypoxic cells start getting generated when the cells are beyond a certain critical distance from the blood capillaries (so that the oxygen tension falls below 10 mm of Hg). The number of hypoxic cells increases with the distance from the blood capillaries in almost sigmoid manner. This phenomenon can be equivalently [12] described in terms of tumor volume instead of "distance from the blood capillaries". The hypoxic fraction varies with the volume of the tumor also in an almost sigmoid nature. Empirically one can determine the hypoxic fraction H(V) at any volume V of the tumor with the help of the following relation.

$$H(V) = 1 + (1 - H\infty) (V / V\infty)^{\alpha - 1} \quad (9)$$

where $H\infty$, $V\infty$ and α are characteristic parameters of the tumor. $H\infty$ and α are constants and dimensions and $V\infty$ has the unit of volume and α is much less than one. [Equation (9) is derivable from the assumption that the volume of tumor having adequate blood-vasculature also grows in a Gompertzian fashion like the total tumor volume as given by equation (6) except that it grows with a much lower rate, i.e., k is replaced by (α k)]. Once H(V) is known, the number of hypoxic cells is also determined because

$$NH = H(V)NT \quad (10)$$

It may also be noted that for young tumors, the N-compartment is not large, therefore, one may write

$$NQ = [1 - G(t)] NT - NH \quad (11)$$

Thus the cell-population in different compartments can be estimated.

Perturbation in the Tumor Growth Following Irradiation

On exposing living systems to ionizing radiations, a number of physico-chemical and biological processes take place, which extend over all levels of organization and cover an enormous time scale

[13]. For the purpose of the present study, we shall continue our attention to important processes occurring at the cellular and tissue levels only.

Radiation Induced Cell Killing and Repair of Potentially Lethal Damage

Considering reproductive capacity as the end-point of interest, the response of viable cells (A) to radiation are represented schematically [14] in Fig. 2. Radiation can cause either a potentially lethal (B) or lethal damage (C). Potentially lethal damage (PLD) can be repaired either without error or some error can be introduced (misrepair) which might lead to a non-viable cell (N). Lethal damage (LD) is irrepairable and invariably leads to cell death. If NA(O) and NA(D) are the number of cells in state A, before and after radiation respectively, the surviving fraction is defined as-

Schematic diagram to show the cellular response to irradiation. For details, see text

$$S = NA(D) / NA(O)$$

The empirical radiation dose-response relationship for cell survival is usually [15] described by the equation-

$$S = [1-(1-e^{-D/Do})^{n}]$$

$$= [1-(1-e^{-\lambda D})^{n}] \quad (12)$$

where DO is the mean lethal dose i.e., the absorbed dose required to reduce S by the factor 1/e, the inverse of DO is the inactivation constant (; n, known as the extrapolation number, is a measure of change in radiation sensitivity at low values of D.

At high values of D or for n=1, one may write equation 12 as-

$$S = e^{-D/D}O = e^{-\lambda D} \quad (13)$$

If ηAB and ηAC represent the number of repairable and irrepairable lesions produced per unit of absorbed dose of radiation, it can be shown [14] that-

$$S = e^{-(\eta AB + \eta AC).D} \quad (14)$$

which is of the same form as eqn. 13.

Thus we find that ηAC and ηAB jointly determine the radiation sensitivity. After irradiation, there is a depletion in the number of cells in state A, the depleted cells being transferred to states B and C. The cells from B can return to A provided repair processes which are time dependent can be successfully completed. In principle, all the cells in state B, given sufficient time, can eventually return to State A, if there is no misrepair. In such a case, at large time, the surviving fraction would be given by

$$S = e^{-\eta AC \cdot D} \quad (15)$$

If, however, the repair processes are inactive, S would be given by eq. 14. Thus the net result of repair is to reduce the value of the inactivation constant or to increase the value of Do so that eq. (13) can be rewritten as

$$S = e^{-D/D}O^{*} \quad (16)$$

where $DO^{*} = DO + \Delta DO$

Thus the gross effect of cellular repair of potentially lethal lesions can be incorporated in the programme by an increase Δ Do in the mean lethal dose Do.

Cell-Loss-Rate

The rate of cell-loss from the tumor depends upon the type and architecture of the tumor and also on the number of dead cells. After irradiation, the rate of tumor cell-loss has been observed to increase in proportion to the absorbed dose D. Denoting such increase in cell-loss-rate by Δ kL, the following relation has been observed [12] to satisfy empirically.

$$\Delta kL = \sigma (1 - e^{-\gamma D}) \quad (17)$$

where σ and γ are two parameters dependent on the radiation sensitivity and type of tumor. However post-irradiation and experiments [16] reveal two generalised features. Firstly, there is a shoulder in the cell-loss-rate vs time curve, which shows that the enhancement of cell-loss-rate is not immediate after irradiation but rather starts after a time-delay. Such an effect may be taken into account by introducing [17] delay compartment or a transit time-delay in the model. However, there is unique model for this phenomenon and in the present paper we have neglected the shoulder effect. Secondly, the cell-loss-rate after certain time (of the order of 100 hrs) reverts back to its pre-irradiation value. Empirically [16] this feature can be accounted by the relation

$$kL(t) = kL(t)r + \Delta kL\, e^{-b(t-tr)} \quad (18)$$

where kL(t)=Cell-loss-rate at any time t such that t > tr
kL(tr)=pre-irradiation cell-loss-rate
tr=time of irradiation
and b is a characteristic parameter.

Cell Proliferation

Radiation may affect the cell proliferation kinetics in many ways. It is known to inhibit the cell progression in the cell-cycle and delay the cell division. The mitotic or division delay is proportional to the absorbed dose of radiation [5].

The cells which received LD or could not successfully repair the PLD may die during the subsequent cell divisions. Since the P-cells are most radiation sensitive, the growth fraction falls to a very low value immediately compensate for the cell death and cell loss in two ways
(a) by reducing the cell-cycle time and
(b) by increasing the growth fraction through recruitment of Q and H cells into the P-compartment.

Very little information about the kinetics and molecular mechanisms underlying these processes, is at present available [18] and hence it is very difficult to adopt any unique model to account for this process. However, we have incorporated the phenomenon of recruitment in this model in the following way.

Recruitment to P-compartment from H and Q compartment is accomplished through the following algorithm. The growth fraction G(t) i.e., the fraction of the P-cells at any time t, as defined beforehand, would no longer satisfy the equation (4) after irradiation because of sudden massive cell-killing. We therefore define a post-irradiation growth fraction G*(t) as distinguished from G(t). If G(t) is the growth-fraction at the time of irradiation (tr), then we assume for the sake of simplicity that the

recruitment process would remain operative until the growth fraction attains the pre-irradiation value i.e., the number of cells recruited per unit of time would be given by-

$$fQP = \beta [G(tr) - G^{*} (tr + \Delta t)] [NQ] \quad (19)$$

where β is a proportionally constant and (t is the time after irradiation.

Recruitment of hypoxic cells in this model is done through re-oxygenation only which we have assumed to be proportional to the tumor volume shrinkage. Thus whenever there is a depletion of total number of tumor cells after irradiation, the recruitment of H to P per unit of time, i.e., fHP would be proportional to this depletion i.e.

$$fHP=\mu [NT(tr-NT(tr+ \Delta t)] \quad (20)$$

whereμ is a proportionality constant and becomes zero in the absence of volume shrinkage.

Results

To test the usefulness of the model, its ability to reproduce experimental data on tumor growth kinetics after irradiation should be examined. For this purpose, published data on Sarcoma-180 tumor grown in the hind leg of mice was employed. All the computations were performed in DEC-10 computer at IISc, Bangalore.

Estimation of relevant parameters for S-180 tumor

The values of the parameters G0, G∞ and 'a' were determined from the experimental measurements of growth fraction during unperturbed tumor growth [7], [8]. These values are G0 = 0.9; G∞ = 0.1 and a = 0.3/per day. The value of 'a' was further confirmed from three different sets of data by three different groups [2], [12], [19]. The duration of cell-cycle time (tc) for S-180 cells is known [20] to be 14 hours which gives kp=1.888/day. The varlue of k comes through equation (6a) as 0.95/day. The average cell-loss-rate before 0.95/day. The average cell-loss-rate before irradiation [2], i.e., kL = 0.12/cell/day. The hypoxic fraction is calculated by fitting the equation (9) with experimental values [12], so that the parameters are H∞ = 0.8, α = 0.1 and V∞ = 270 mm [3]. With the help of these values and eq. 7, the undisturbed tumor growth can be computed for any value of N0 which is a free parameter. Variation of tumor volume and relative rate of growth (V/V) are shown in Fig. 3a and are compared with experimental results [19]. In Fig. 3b the changes in the relative population of various cellular compartments as functions of the tumor volume are shown.

A typical undisturbed tumor growth kinetics generated by the model. The parameters (Go = 0.9, G∞ = 0.1 and a = 0.3/day) are obtainable from the experimental [19] ***control curve by fitting with equation (7). The parameters, controlling the hypoxic-fraction, (α = 0.1, Hinfin = 0.8 and Vinfin = 2700mm^3) are taken in consistency with Gewehr's model*** [12]***. In (a) the comparision between the theoretical (solid curve) and experimental*** [19] ***(closed circles and open triangles) results are shown for tumor volume (V) and relative rate of growth (V/V) of the tumor as a function of time. In (b) the number of cells in P, Q and H compartments expressed as fractions of total number of cells are shown as functions of tumor volume***

In order to incorporate the effects of irradiation, the values of the mean lethal dose D0 and extrapolation number n for different cell-compartments are to be estimated. The average values of D0 and n for mammalian cells in mitotic phase can be estimated [21], [22] nearly as 1.6 Gy and 2

respectively. The relative values of D0 in different phases of the cell-cycle can now be calculated according to the ratio [23].

G1:S:G2:M::1.3:1.75:1:1,

where we have taken an average of early and late 5 phases.

Percentage of proliferating cells in each of these phase may be calculated from the relative durations of these phases in the cell-cycle. For exponentially growing Sarcoma-180 this is given by [20]

G1:S:G2:M::0.2:0.58:0.184:0.036.

Thus the weighted average value of D0 for the proliferating cells is estimated to be 2.4 Gy. The value of D0 of Q-cells will be higher than the P-cells but lower than the S-phase cells. So we take it 2.6 Gy. The value of Go for H cells may be taken as 2.5 times that of the P-cells.

Mitotic delay was assumed to be 1/10th of the cell-cycle per Gy [5]. Radiation induced enhancement of cell-loss rate was taken into account through equations (17) and (18). The parameters as fixed from experiment [12], [16] are $\gamma = 0.171\ Gy^{-1}$, b = 0.1/day, σ euoxic = 0.38 and σ hypoxic = 0.27. Post-irradiation recruitment of cells to P-compartment from Q-compartment is accomplished by taking β equal to unity in equation (19). The percentage of hypoxic cells recruited is controlled by the parameterμ in equation (20). The number of cells to be recruited are computed in the algorithm after every 1/10th of the cell-cycle.

Radiation response of S-180 tumor

Having thus fixed all the parameters, computations for relative tumor volume were done with variation of radiation doses and the volume on the day of irradiation.

Comparison of calculated and experimental [12] results on the effects of gamma irradiation over the tumor volume are presented in Figs. 4 and 5. The Fig. 4 shows the effect of variation of the volume at the time of irradiation under identical dose of irradiation. The figures demonstrate that the model is capable of predicting the main trends of the experimental data quite satisfactorily.

- ***Effects of different doses of gamma irradiation on the tumor growth. Curves are obtained from the model. The experimental points*** [12] ***are shown by closed circles. The volume on the day of irradiation was about 700 mm^3***
- ***Radiation response of the tumor at the different volumes on the day of irradiation. Curves are obtained from the model, which are matched with experimental*** [12] ***points (D = 20 Gy). The volumes indicated in the figure are the corresponding volumes on the day of irradiation***

To evaluate the influence of various factors affecting the tumor radiation response, the values of the parameters of interest were systematically varied within certain limits while the rest of parameters were kept constant. Results of these calculations are presented in the Fig. 6.

- ***Variation of radiation response of the tumor with the changes in various parameters, as indicated by subheadings. Only one parameter is changed at a time. Relative values of the parameters X/X* are indicated, where X* represents the new value and X represents the reference values in Figs. 3-5, viz., cell-loss-rate = 0,12/cell/day, cell-cycle time = 14 hrs, Do = 6 Gy and percentage of recrutiment of hypoxic cells = 100***

The effects of variation of post-irradiation cell loss-rate and cell-cycle time are shown in Figs. 6(a) and 6(b). The figures show that the cell loss rate is an important parameter for tumor regression whereas the rate of regrowth of the tumor is greatly influenced by changes in the cell cycle time. The effects of

hypoxic cell sensitizers are shown in Fig. 6(c). It is seen that a reduction in Do leads to a greater regression of the tumor but the rate of regrowth is not affected. Finally Fig. 6(d) demonstrates that inhibiting the recruitment of hypoxic cells also has a profound influence on the tumor radiation response.

Effects of 2-DG+irradiation

2-DG has been shown to inhibit repair of radiation damage in the absence of respiratory metabolism and in cells with high rates of glycolysis [1], [24], [25], [26], [27]. When given before or immediately after gamma-irradiation, 2-DG has been shown to increase radiation induced tumor regression, tumor cell loss rate and animal survival in S-180 tumor bearing mice [2]. Experimental evidence suggesting that 2-DG could inhibit the entry of G0 cells in the cell-cycle has been presented [28].

It is therefore, of interest to seek the help of the present model in interpreting the data on the effects of the combined treatment of 2-DG plus irradiation on tumor bearing animals.

Fig. 7 shows a comparison of the experimental data [2], [27] with the theoretical calculations made under the assumptions that the administration of 2-DG leads to inhibition of repair of PLD and recruitment of hypoxic cells. The enhancement of cell-loss-rate due to 2-DG is taken into accordance with the experimental values [2]. The comparison has been made for two different sets of experimental data using the same values of the parameters. It can be seen that a reasonably satisfactory agreement between theory and experiment is obtained under the assumption that 2-Dg is able to inhibit repair and recruitment of hypoxic cells in the tumor. It was not possible to satisfactorily fit the data on the basis of inhibition of repair of PLD alone. Possibly, therefore, 2-DG is able to inhibit the recruitment process in the tumor system examined.

The effect of 2-deoxy-D-glucose (2-DG) on the radiation response of tumor Sarcoma-180. Reasonable agreements between theory (curves) and experiments [2]***,*** [27] ***(open circles) for both 10 Gy and Gy are obtained by assuming that 2DG simultaneously inhibit the repair (Do of H cells = 420 Gy) and also inhibit the recruitment of hypoxic cells (upto an extent of 50 per cent) to the P-compartment. For details, see text***

Thus, in this paper, the radiation induced changes in the tumor volume have been analysed with the help of a simple mathematical model. It is to be noted that though the model essentially does not contain any free parameters, it is capable of predicting the major trends of experimental results quite reasonably. However, while developing the model we had to make simplifying assumptions. Some of these assumptions may not be quite correct and justifiable. For example, the number of tumor cell is assumed to be proportional to the tumor volume and this proportionality constant (density function) is assumed to be independent of the nature of the compartment or the age of the tumor. Secondly, migration of cells from outside to the inside of tumor has been neglected. The present results, however, demonstrate that despite these simplifications the model could be useful in analysing the experimental data and to study the action of modifiers of the radiation response on tumor therapy.

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