COMPUTATIONAL MODELING OF THE BREAST CANCER TREATMENT BY IMMUNOTHERAPY, RADIATION AND ESTROGEN INHIBITION.

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Abstract. A mathematical study has been conducted in this article combining immunotherapy, radiation therapy, and estrogen inhibition to treat breast cancer. In this regard, a computational model has been developed consisting of eight nonlinear reaction-diffusion equations which have been solved numerically by perturbed functional iterations. The interactions between the immune system, estrogen-inhibitor, antioxidant, localized radiation therapy and progress of cancer have been considered in the reaction part of the equations. The diffusion part shows the flux of cancer cells toward distant organs followed by various leukocytes and medications which try to destroy cancer cells and inhibit any metastasis. Computational results have strong agreement with some of the findings recorded in the literature on this topic.

Introduction.

Because of earlier diagnosis and better treatment, the number of long-term survivors of breast cancer is increasing every year. Tamoxifen, which is a synthetic, non-steroidal anti-estrogen in breast tissue is now being used quite successfully to stop proliferation of cells in the breast tissues by estrogen, yet every year over two million women in the United States are plagued with breast cancer [1]. Most of these treatments resulted from in vitro experiments in laboratories, or in vivo statistical findings with radiation and/or chemotherapies. Together with these studies, some mathematical modeling could be very helpful. In order to do this, we need to analyze the dynamics of our defense mechanism. Cancer cells try to proliferate indefinitely, overpower the dynamic defense mechanism of the body and disperse through blood and lymph to distant organs of the body to metastasize. They form specific antigen. Due to chemotaxis, a process which leukocytes maintain moving from more dense area to less dense area, all cancer sites attract leukocytes. Some leukocytes, consisting of neutrophiles, macrophages, eosinophils and natural killer cells (NK cells) form our first line of defense. They attack all pathogens regardless what antigen is presented on the outside surface of these invading molecules. This is the innate immune response of our body. The cognate immune response is, however, very antigen-specific. It consists of lymphocytes which are the T-cells and B-cells. These fighter cells are programmed to attack a foreign microorganism bearing a specific antigen. T-cells are trained in the thymus, a lymphoid organ which lies on the upper part of the chest, right above the heart. Dendritic cells and macrophages are antigen-presenting cells. They bring in helper-T cells trained to release cytokines for the specific antigen of the attacker attracting thereby B-cells and cytotoxic T-cells to launch humeral and cell-mediated immune responses respectively for the cytolysis of the invader. For humeral response, B-cells differentiate into plasma cells which secrete only one particular antibody such as an immunoglobin for the destruction of the

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specific antigen. The macrophages secrete a cytokine—Interleukin 1 (IL-1)—in response to which helper T-cells, specific for the antigen is activated. Then these helper T-cells release interluekin2 (IL-2) so that all different kinds of T-cells may proliferate and as that process starts helper T-cells release another cytokine which is interferon gamma to enhance the ability of the cytotoxic T-cells, NK cells and macrophages to destroy the antigen, which could be a cancer. This direct fight is the cell-mediated immune response. In general, B and T cells win. The battle ends. Then the suppressor T-cells terminate the immune response and phagocytic leukocytes ingest the debris. Under the state of relaxation and youthful vigor, the immune response is stimulated. Aging and a state of stress could suppress the immune response [2]. Antioxidants like vitamin C could encapsulate a tumor inhibiting its growth thereby [11]. Local radiation could be conducted to destroy more cancer cells and less lymphocytes and other healthy cells of the body. These biological facts have been incorporated in this computational model.

The human body is a three dimensional configuration. Thus any in vivo model requires a three dimensional geometry. Cells forming malignant tumors, lymphocytes and drugs for treatment of cancer have been considered as biochemicals and the unit to measure their concentration is the same (like micro mole per micro liter).

Mathematical Model

Let us consider a control volume V enclosed by a surface area S. Let q be the concentration of a biochemical in V. Let $\vec{n}$ be the unit outward normal vector to S.

Then, the rate of change of q in V = Growth of q in V-Decay of q in V + accumulation of q in V due to transport.

Thus,

$$\frac{\partial}{\partial t}\iiint\limits_V q\,dV = \iiint\limits_V f(q)dV - \iiint\limits_V g(q)dV - \iint\limits_S \vec{J}\cdot\vec{n}\,dS \tag{1}$$

where $\vec{J}$ = Flux of q, $f(q)$ = Growth function of q in V, $g(q)$ = Decay function of q in V. By the divergence theorem,

$$\iint\limits_S \vec{J}\cdot\vec{n}\;dS = \iiint\limits_V \vec{\bigtriangledown}\cdot\vec{J}\;dV \tag{2}$$

Fick's Law for flux of biochemicals is given by

$$\vec{J} = -\nu\,\vec{\bigtriangledown}\,q, \tag{3}$$

ν = coefficient of dispersion. This basically means, biochemicals are moving from "more" concentration to "less" concentration [13]. Biochemical species like bacteria, virus, cancer cells, follow chemotaxis. Chemotactic flux is an attraction, which is a negative diffusion, in the sense that leukocytes move toward the bacterial/viral infection or the sites of cancer.

In the model $f(q)$, the growth function of a species consists of progeny and growth due to chemotaxis. Combining (1), (2), and (3) we get,

$$\frac{\partial}{\partial t}\iiint\limits_V q\,dV = \iiint\limits_V f(q)dV - \iiint\limits_V g(q)dV + \nu\iiint\limits_V \bigtriangledown^2 q dV$$

Assuming q, $f(q)$ and $g(q)$ to be sufficiently smooth on V, we get,

$$\frac{\partial q}{\partial t} = f(q) - g(q) + \nu\bigtriangledown^2 q \tag{4}$$

The dimension of ν, the diffusion coefficient is $(\text{length})^2/\text{time}$. For hemoglobin molecules, $\nu = 10^{-7}$ cm^2/sec., for oxygen molecules $\nu = 10^{-5}$ cm^2/sec. [13].

Concentrations in micro moles per micro liter of the following biochemicals are considered to model breast cancer. (ag) = cancerous cells, (ct) = cytotoxic T-cells, (dm) = dendrific cells and macrophages, (b) = B-lymphocytes, (nk) = natural killer cells. The following chemicals are also considered (ei) = estrogen inhibitor, (rd) = localized radiation and (vc) = antioxidants.

In general, when the immune system of the body is strong, cancer cells cannot survive. Sometimes they stay latent inside an adipose tissue or a scar tissue for years. With the decline of the strength of the body's defense mechanism, and with the support of helping agents like carcinogens, they proliferate. Working very closely with a number of cancer patients over two years, consulting with oncologists, surgeons and radiologists, the author is convinced that at the site of the primary tumor, the ratio

$$(ag)/\{(ct)+(dm)+(b)+(nk)\} >> 1.$$

and each cancer cell attempts to maintain this ratio as it proliferates. Thus in two ways these malignant cells grow: First, they grow naturally which may be noticed in an in vitro experiment. Secondly, they accelerate their growth when they experience the presence of the immune response of the body. Considering these, the equation for (ag), the aggressor becomes (following (4)),

$$\begin{aligned}\frac{\partial(ag)}{\partial t} &= r_1\cdot(ag) - r_{11}\cdot(ag) - r_{12}\cdot(ag)\cdot(vc) + r_{13}\cdot\theta\cdot(ag) \\ &- r_{14}\cdot(ag)\cdot(ct) - r_{15}\cdot(ag)\cdot(b) - r_{16}\cdot(ag)\cdot(nk) \\ &- r_{17}\cdot(ag)\cdot(ei) - r_{18}\cdot(ag)\cdot(rd) - r_{19}\cdot(ag)\cdot(dm) \\ &+ \nu_1 \bigtriangledown^2 (ag)\end{aligned} \tag{5}$$

where,

$$\theta = \frac{(ag)}{(ct)+(dm)+(b)+(nk)} >> 1 \tag{6}$$

r_1 = percent of growth of (ag) due to progeny per unit time. ($r_1 = 1$ means there is a 100% proliferation of cancer cells).
r_{11} = percent of natural death of (ag), which occurs inside the core of a tumor
r_{12} = percent of (ag) destroyed by each unit of antioxidant (like vitamin C) per unit of time.
r_{13} = percent of θ used by each unit of (ag) for progeny.
r_{14} = percent of (ag) killed by each unit of (ct) per unit time,
r_{15} = percent of (ag) killed by each unit of (b) per unit time,
r_{16} = percent of (ag) destroyed by each unit of (nk) per unit time,
r_{17} = percent of (ag) destroyed by each unit of (ei) per unit time,
r_{18} = percent of (ag) destroyed by each unit of (rd) per unit time,
r_{19} = percent of (ag) destroyed by each unit of macrophages per unit time,
ν_1 = coefficient of dispersion of (ag).
In three dimension,

$$\bigtriangledown^2(ag) = \frac{\partial^2(ag)}{\partial x^2} + \frac{\partial^2(ag)}{\partial y^2} + \frac{\partial^2(ag)}{\partial z^2}.$$

As the cancer cells (ag) activate a fight, the immune dynamics sends the inhibitors—the leukocytes—to fight back. The most vehement fighters are the lymphocytes which target the specific antigen of (ag).

The equation representing the defense mechanism of (ct), cytotoxic T-cells is

$$\begin{aligned}\frac{\partial(ct)}{\partial t} &= r_2\cdot(ag) - r_{21}\cdot(ct) - r_{22}\cdot(ct)\cdot(ag) + r_{23}\cdot(ct)\cdot(vc) \\ &\quad -r_{24}\cdot(ct)\cdot(rd) + r_{25}\cdot(ct)\cdot(dm) + (\mathrm{ISN})\cdot(ct)\cdot(ag) \\ &\quad +\nu_2\,\nabla^2\,(ct)\end{aligned} \tag{7}$$

where, $r_2\cdot(ag)$ = Growth of (ct) which is equivalent to r_2 percent of (ag), induced by (ag) through chemotaxis and/or other biological process, r_{21} = percent of (ct) which dies due to natural biological process. Other rate constants are defined similar to those defined for the equation (5).

ISN is the Immuno Stimulation or Immuno Suppression Number. Regular exercise, relaxation techniques and immunotherapy can stimulate our immune system. If ISN = 1, it means 100% of (ct) will grow for each unit of (ag) per unit time. Stress hormones (like cortisols [2,5]), lack of exercise, insomnia and certain medications could weaken our defense mechanisms. If ISN $= -1$, it means 100% of (ct) will die for each unit of (ag) per unit time. Human psychology plays a very significant role, strengthening or weakening the immune system. In the term $(\mathrm{ISN})\cdot(ct)\cdot(ag)$ it has been assumed that

$$-1 \le \mathrm{ISN} \le 1 \tag{8}$$

With stress, thymus atrophies, lymphocytes die and their rate of proliferation declines. Thus under stress ISN < 0. With immunostimulation due to immunotherapy lymphocytes gain strength and proliferate which makes ISN > 0.

The second equation for inhibitors represents the functions of dendritic cells and macrophages:

$$\begin{aligned}\frac{\partial(dm)}{\partial t} &= r_3\cdot(ag) - r_{31}\cdot(dm) - r_{32}\cdot(dm)\cdot(ag) + r_{33}\cdot(dm)\cdot(vc) \\ &\quad -r_{34}\cdot(dm)\cdot(rd) + (\mathrm{ISN})\cdot(dm)\cdot(ag) \\ &\quad +\nu_3\,\nabla^2\,(dm).\end{aligned} \tag{9}$$

For B-cells and the Natural Killer cells the equations are respectively,

$$\begin{aligned}\frac{\partial(b)}{\partial t} &= r_4\cdot(ag) - r_{41}\cdot(b) - r_{42}\cdot(b)\cdot(ag) + r_{43}\cdot(b)\cdot(vc) \\ &\quad -r_{44}\cdot(b)\cdot(rd) + r_{45}\cdot(b)\cdot(dm) + (\mathrm{ISN})\cdot(b)\cdot(ag) \\ &\quad +\nu_4\,\nabla^2\,(b).\end{aligned} \tag{10}$$

$$\begin{aligned}\frac{\partial(nk)}{\partial t} &= r_5\cdot(ag) - r_{51}\cdot(nk) - r_{52}\cdot(nk)\cdot(ag) - r_{53}\cdot(nk)\cdot(rd) \\ &\quad +r_{54}\cdot(nk)\cdot(vc) + r_{55}\cdot(nk)\cdot(dm) \\ &\quad +(\mathrm{ISN})\cdot(nk)\cdot(ag) + \nu_5\,\nabla^2\,(nk)\end{aligned} \tag{11}$$

When breast cancer strikes, estrogen inhibitors [8,9,11] like tamoxifen or raloxifen are commonly used. Recently aromatase [1] is also used which blocks the action of an enzyme that women need to produce estrogen. For estrogen inhibition, use of antioxidants and localized radiation therapy (which should kill less lymphocytes and more malignant cells), the equations are respectively:

$$\frac{\partial(ei)}{\partial t} = r_6 \cdot (ag) - r_{61} \cdot (ei) - r_{62} \cdot (ei) \cdot (ag) - r_{63} \cdot (ei) \cdot (rd) + \nu_6 \bigtriangledown^2 (ei) \tag{12}$$

$$\begin{aligned}\frac{\partial(vc)}{\partial t} = {} & r_7 \cdot (ag) - r_{71} \cdot (vc) - r_{72} \cdot (vc) \cdot (ag) - r_{73} \cdot (vc) \cdot (ct) \\ & - r_{74} \cdot (vc) \cdot (dm) - r_{75} \cdot (vc) \cdot (b) - r_{76} \cdot (vc) \cdot (nk) \\ & - r_{77} \cdot (vc) \cdot (rd) + \nu_7 \bigtriangledown^2 (vc)\end{aligned} \tag{13}$$

$$\begin{aligned}\frac{\partial(rd)}{\partial t} = {} & r_8 \cdot (ag) - r_{81} \cdot (rd) - r_{82} \cdot (rd) \cdot (ag) - r_{83} \cdot (rd) \cdot (ct + dm + b + nk) \\ & - r_{84} \cdot (rd) \cdot (ei) - r_{85} \cdot (rd) \cdot (vc) + \nu_8 \bigtriangledown^2 (rd)\end{aligned} \tag{14}$$

The eight equations (5), (7), (9), (10), (11), (12), (13) and (14) form the model. Not all equations are coupled with one another. It has been assumed that (ei) does not significantly affect the performance of lymphocytes. Thus (12) is not coupled with (7), (9), (10), and (11). The dosages of (ei), (vc) and (rd) are conducted by doctors. Thus the values of r_6, r_7 and r_8 are obtained from biochemists and oncologists. Obviously, the values of the rate constants are not fixed. For each patient they could vary. They are inputs for the code, solving this model.

Rate Constants and Diffusion Coefficients.

With extensive consultation with doctors and biochemists [15,16,17] the following values of rate constants and diffusion coefficients have been chosen.

$r_1 = 1$, $r_{11} = 0.0001$, $r_{12} = 0.001$, $r_{13} = 1$, $r_{14} = r_{15} = r_{16} = r_{17} = 0.001$, $r_{18} = 0.025$, $r_{19} = 0.0005$, $\nu_1 = 10^{-7}$

$r_2 = 2$, $r_{21} = 0.0001$, $r_{22} = 0.002$, $r_{23} = 0.00005$, $r_{24} = 0.025$, $r_{25} = 0.001$, $\nu_2 = 10^{-7}$.

$r_3 = 2$, $r_{31} = 0.0001$, $r_{32} = 0.002$, $r_{33} = 0.00005$, $r_{34} = 0.025$, $\nu_3 = 10^{-7}$.

$r_4 = 2$, $r_{41} = 0.0001$, $r_{42} = 0.002$, $r_{43} = 0.00005$, $r_{44} = 0.025$, $r_{45} = 0.001$, $\nu_4 = 10^{-7}$.

$r_5 = 2$, $r_{51} = 0.0001$, $r_{52} = 0.002$, $r_{53} = 0.025$, $r_{54} = 0.00005$, $r_{56} = 0.001$, $\nu_5 = 10^{-7}$.

$r_6 = 1.5$, $r_{61} = 0.00001$, $r_{62} = 0.005$, $r_{63} = 0.025$, $\nu_6 = 10^{-6}$.

$r_7 = 1.5$, $r_{71} = 0.001$, $r_{72} = 0.001$, $r_{73} = r_{74} = r_{75} = r_{76} = 0.00005$, $r_{77} = 0.025$, $\nu_7 = 10^{-6}$.

$r_8 = 2$, $r_{81} = 0.000001$, $r_{82} = 0.005$, $r_{83} = 0.006$, $r_{84} = r_{85} = 0.000005$, $\nu_8 = 10^{-4}$.

Initial Conditions

The first fundamental assumption is that cancer grows initially at a site where it expects the very least resistance. Thus initial conditions are assumed to contain the following information (i) at the site of the cancer there are less leukocytes in comparison with the number of cancer cells, (ii) just outside this site, cytotoxic T-cells, B-cells, Natural Killer cells, dentritic cells and macrophages are congregating to get ready for the fight, (iii) radiation therapy is confined to the cancer site and (iv) estrogen inhibitor and antioxidant are uniformly distributed over the entire computational field.

The three-dimensional computational field is given by $i = 1, 2, \ldots I$, $j = 1, 2, \ldots J$ and $k = 1, 2, \ldots K$. The site of the cancer is given by $i = 1, 2, \ldots$ ISTAR, $j = 1, 2, \ldots$ JSTAR and $k = 1, 2, \ldots$ KSTAR where ISTAR $< I$, JSTAR $< J$ and KSTAR $< K$.

The initial conditions are: for $i = 1$ to ISTAR, $j = 1$ to JSTAR and $k = 1$ to KSTAR, $ag_{ijk} = \alpha_1$, $rd_{ijk} = \alpha_2$, else $ag_{ijk} = \alpha_3$ and $rd_{ijk} = 0$. For $i =$ ISTAR to I, $j =$ JSTAR to J and $k =$ KSTAR to K, $ct_{ijk} = \alpha_4$, $dm_{ijk} = \alpha_5$, $b_{ijk} = \alpha_6$, $nk_{ijk} = \alpha_7$, else $ct_{ijk} = \alpha_8$, $dm_{ijk} = \alpha_9$, $b_{ijk} = \alpha_{10}$, $nk_{ijk} = \alpha_{11}$. And in the entire field, $ei_{ijk} = \alpha_{12}$, $vc_{ijk} = \alpha_{13}$.

In the code, $\alpha_1 = 100$, $\alpha_2 = \alpha_{12} = \alpha_{13} = 10$, $\alpha_3 = \alpha_8 = \alpha_{10} = \alpha_{11} = 1$, $\alpha_4 = \alpha_6 = \alpha_7 = 20$, $\alpha_5 = 50$, $\alpha_9 = 5$.

Boundary Conditions.

It has been assumed that dispersions of all biochemicals can take place at both boundaries given by $i = j = k = 0$ and $i = I + 1$, $j = J + 1$ and $k = K + 1$. If u represents a biochemical then, applying extrapolations:

$$\begin{aligned} u_{0,j,k} &= 2u_{1,j,k} - u_{2,j,k} \\ u_{i,0,k} &= 2u_{i,1,k} - u_{i,2,k} \\ u_{i,j,0} &= 2u_{i,j,1} - u_{i,j,2} \end{aligned}$$

Also,

$$\begin{aligned} u_{I+1,j,k} &= 2u_{I,j,k} - u_{I-1,j,k} \\ u_{i,J+1,k} &= 2u_{i,J,k} - u_{i,J-1,k} \\ u_{i,j,K+1} &= 2u_{i,j,k} - u_{i,j,K-1} \end{aligned}$$

The values of the terms on the left sides are updated every time, whenever the values of the terms on the right side are computed.

Numerical Experiment

For numerical solution of (4), $\dfrac{\partial q}{\partial t}$ is approximated by a two-point backward difference formula and $\dfrac{\partial^2 q}{\partial x^2}$, $\dfrac{\partial^2 q}{\partial y^2}$ and $\dfrac{\partial^2 q}{\partial z^2}$ have been approximated by central differences. The finite difference equation is:

$$\begin{aligned} q^n_{ijk} &= q^{n-1}_{ijk} + \triangle t \left(f(q^n_{ijk}) - g(q^n_{ijk}) \right) \\ &\quad + (\nu \triangle t / \triangle x^2)(q^n_{i-1jk} - 2q^n_{ijk} + q^n_{i+1jk}) \\ &\quad + (\nu \triangle t / \triangle y^2)(q^n_{ij-1k} - 2q^n_{ijk} + q^n_{ij+1k}) \\ &\quad + (\nu \triangle t / \triangle z^2)(q^n_{ijk-1} - 2q^n_{ijk} + q^n_{ijk+1}) \end{aligned}$$

This is how equations (5), (7), (8), (9), (10), (11), (12) and (13) have been approximated for solution by PFI [18].

With ISN $= -0.025$ (which means that the immune system is weakened by depression, anxieties, medications, insomnia, etc.), two graphical results have been presented showing the largest concentrations of all the variables at the site of the cancer. Fig. 1 shows in the absence of medication a rampant growth of tumor from a small value of

$$\max(ag_{ijk}) = 50 \quad \text{to} \quad \max(ag_{ijk}) = 8705.72$$

whereas all defending leukocytes $\max(ct_{ijk})$, $\max(dm_{ijk})$, $\max(b_{ijk})$ and $\max(nk_{ijk})$ attained at steady state value of 74 units. When drugs are brought in (Fig. 2), even with initial $\max(ag_{ijk}) = 100$, the tumor regresses to $\max(ag_{ijk}) = 9.95$. Since the battle is won, concentrations of cytotoxic T-cells, B-cells, NK-cells, dendritic cells and macrophages, estrogen inhibitor and antioxidants at the site of the cancer decline whereas units for radiation reaches a steady state. If just immunotherapy is administered increasing the value of ISN to 0.01 and the initial conditions as shown in Fig. 1 are restored, this boosted immune system wins the fight and cancer starts receding (Fig. 3).

In all computational models, all variables must be quantified. Quantifications conducted in this model with regard to the values of ISN has not been validated experimentally. With the advancement of therapeutic techniques, it is expected that values of ISN for various cancer patients could be found through statistical investigations. Computational results

will then be more meaningful. However, results shown here have been presented to various oncologists and immunologists [15,16] and a qualitative agreement with available medical data has been established.

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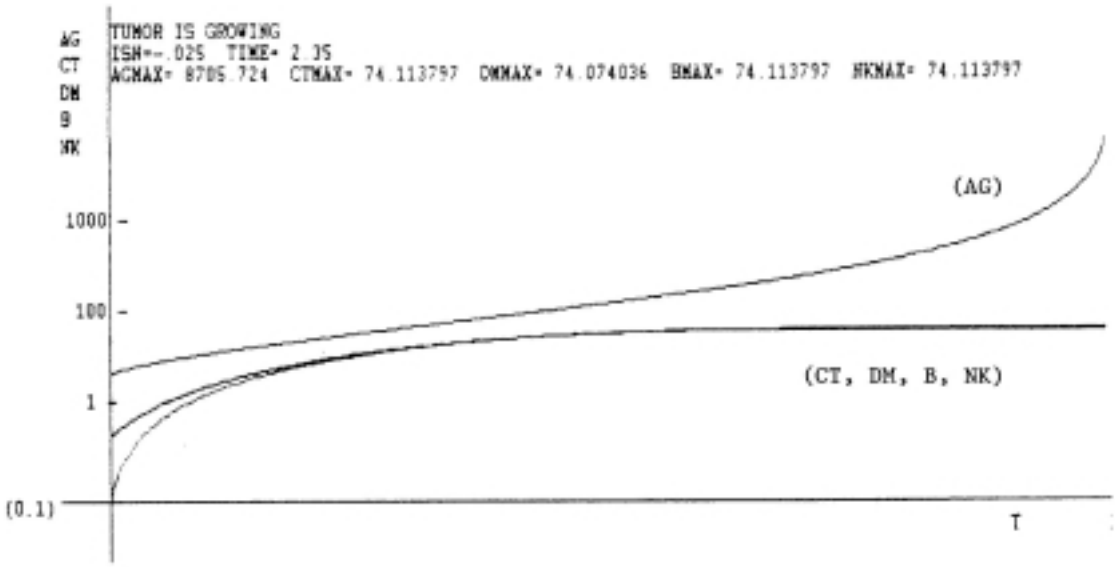

Fig: 1 Tumor is growing under immunosuppression (ISN = - 0.025). Cytotoxic T-cells (CT), B-cells and Natural Killer Cells (NK) are unable to stop the progress of cancer. No external medication has been used.

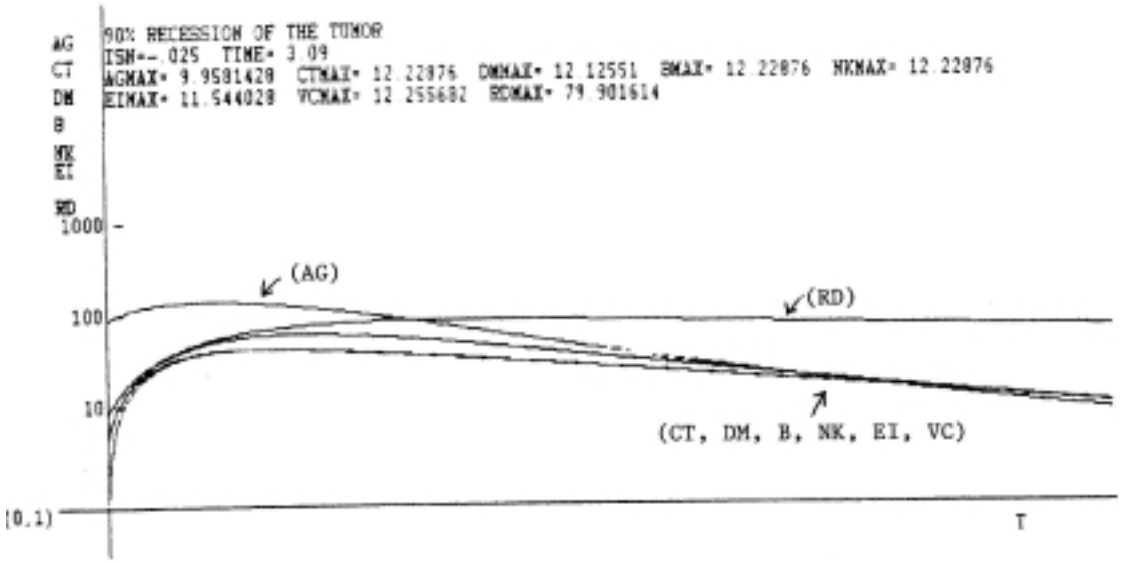

Fig: 2 With a weak immune system (ISN = -0.025), cancer is receding when medications have been applied. Dosages of localized radiation is at a steady state.

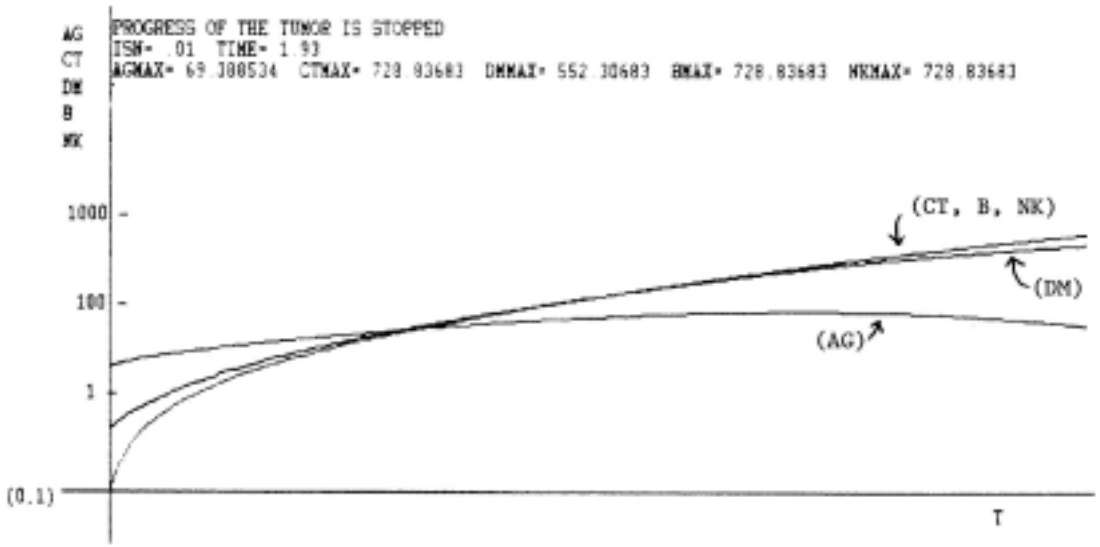

Fig: 3 Cancer (AG) is receding under immunotherapy (ISN = 0.01). The numbers of cytotoxic T-cells (CT) B-cells (B), Natural KIller cells (NK) are slowly increasing and those of dentritic cells and macrophages (DM) are coming to a steady state.