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RESEARCH ARTICLE

A Mathematical Model for Treatment of Differentiated Thyroid Cancer using Radioactive Iodine

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Abstract

Objectives: This study describes a mathematical model with radioactive iodine therapy for differentiated thyroid cancer using a system of non-linear ordinary differential equations. **Methods**: The four non-linear ordinary differential equations in the proposed model are concentration of thyroglobulin, interleukin concentration, the number of cancer cells, and concentration of radioactive iodine. **Findings**: This model displays two equilibria, including a drug-free steady state and a drug steady state. This study has created a standard for the radioactive iodine threshold level that the system must reach in order to lower the number of cancer cells. Using parameters obtained from experimental data, numerical simulations are used to support the analytic results. **Novelty:** The model makes it simple to investigate the effects of radioactive iodine deletion on disease-specific morbidity and recurrence rate. The costs of drug discovery and development can be offset with the use of mathematical modelling and simulations of modifying treatments, which can also promote the creation of new treatments.

Keywords: Mathematical Modelling; Thyroid Cancer; NonLinear System of ordinary Differential Equations; Stability Analysis; Asymptotically Stable

1 Introduction

Whole or nearly total thyroidectomy (surgical removal of the thyroid) is the major therapeutic option for differentiated thyroid cancer. Thyroid hormone therapy and radioactive iodine therapy are then employed as additional treatments, primarily with thyroxine. Recurrence locally and isolated metastases both are part of the thyroid carcinoma's metastatic illness or tumor spread. Patients with differentiated thyroid cancer (DTC) have a worse prognosis due to metastatic disease. Located metastases should, if possible, be removed by a skilled surgeon as the primary form of treatment. Iodine-131 therapy is a recognized treatment option for inoperable metastases that can accumulate radioiodine [(1)].

Thyroglobulin is the protein produced in the thyroid gland, that secretes the hormones thyroxine and triiodothyronine, and radioiodine is commonly propagated by differentiated thyroid cancer. Only thyroid cells can develop thyroglobulin. Any thyroglobulin later found in a patient with the DTC is assumed to be the result of

recurring malignancy, if both healthy and cancerous thyroid tissue has been effectively eradicated. As a result, the two primary techniques for identifying metastatic disease of DTC are the assessment of blood thyroglobulin levels and radioiodine diagnostic whole-body scanning. Undetectable thyroglobulin levels and radioiodine whole-body scan, negative results reflect complete remission, but detectable or increased thyroglobulin levels are correlated with the existence of radioiodine uptake in neighboring or distant metastases [2].

Immunotherapies and targeted monoclonal antibodies are two relatively new and promising cancer treatments that take advantage of the capabilities of the immune system. Simulation and modeling are effective techniques that give an analytical framework for examining the advantages of the immune system. A thorough understanding of the pharmacokinetics of the immune response to therapy is necessary when designing treatment strategies including dose, timing, and predicting the response to a certain medicine [3].

Despite the fact, radioiodine treatment has been around for more than 70 years, most of the data come from limited, retrospective research that did not randomly compare various methods. Many problems are not (completely) obvious because treatment approaches vary widely. The decrease in iodide absorption and metabolism is a factor aided by increased TSH. The hypothesis that high-dose radioiodine therapy given after surgery can improve disease-specific survival and disease-free survival in high-risk patients is backed by substantial evidence. The unstimulated thyroglobulin level may still be detectable in roughly 50% of patients with a full response on imaging. Thyroglobulin levels are frequently low, steady, or even declining without further therapy [4]. The majority of facilities use a fixed dose of radioiodine treatments. Typically, a 3.7–7.4 GBq empiric dosage of 131I is used in situations of widespread distant metastases. The lack of studies that directly compare 3.7, 5.5, and 7.4 GBq as the initial radioiodine therapy in metastatic DTC. It stands to reason, though, that the intended biological effect will be more pronounced the higher the dose delivered to the metastatic deposit [5]

In the tumor microenvironment, inflammatory substances can either encourage or hinder tumor growth. Interleukin is a subset of these that mostly comes from CD3+ and CD4+ T cells and is essential for intercellular communication. Numerous studies have shown a connection between interleukins and thyroid cancer. In addition to being able to discriminate between benign and malignant thyroid diseases, predict the possibility of carcinogenesis, evaluate the prognosis, and monitor thyroid cancer recurrence, interleukins also regulate the proliferation and migration of thyroid cancer cells. Additionally, some research using cells and animals has demonstrated the value of interleukins in the treatment of thyroid cancer [6].

So many models involving immune cells and tumor cells were developed for thyroid cancer [7]. And Also models involving tumor cells and therapy like immunotherapy, chemotherapy, radiotherapy are constructed, which provide a deep explanation and the mechanisms involved in the process [8,9]. In that way, this model was constructed for Differentiated thyroid cancer with Radioactive iodine treatment. This nonlinear system of ordinary differential equations, involves four variables that are the concentration of Radioactive iodine, the number of cancer cells, the concentration of thyroglobulin, and the concentration of Interleukins.

2 Methodology

2.1 Construction of the model

We consider the model with radioactive iodine (RAI) treatment. Let A(t) represents the concentration of RAI, N(t) depicts the number of cancer cells, I(t) be the concentration of interleukins. T_g denotes the concentration of thyroglobulin. The proposed model is,

$$\begin{aligned}
\frac{dA}{dt} &= D-\mu A \\
\frac{dN}{dt} &= rN\left(1-\frac{N}{K}\right)-\alpha IN-\rho\left(1-e^{-A}\right)N \\
\frac{dI}{dt} &= \gamma+\frac{c_1 N}{\delta+N}+b\left(1-e^{-A}\right)I-mI \\
\frac{dT_g}{dt} &= \varepsilon+pN-\beta T_g
\end{aligned} \tag{1}$$

With $A(0)$, $N(0)$, $I(0)$, $T_g(0) > 0$

Where A is the recommended daily dose of RAI and μ is the elimination rate of drug. After a total thyroidectomy, there is just one administration required to remove the residual thyroid tissue. Function K represents the carrying capacity of cancer cells

and $\rho\left(1-e^{-A}\right)N$ is the efficiency rate of iodine in cancer cells. The constants γ refer to the natural production of Interleukin. The term $\frac{c_1 N}{\delta+N}$ represents the interleukin production by tumor mass, the δ is the number of cancer cells by which the interleukin production rate is half its maximum. The term b represents the increase of interleukin due to RAI treatment and $m$is the natural elimination of Interleukin. The term ε represents the natural production of T_g and p is the Production rate of thyroglobulin by tumor cells and β is the elimination rate of thyroglobulin.

Table 1. Parameters and used values in the model's numerical simulations

Parameters	Values	Units
μ	5.5	days
r	7.52 x 10^{-1}	Cells x t^{-1}
α	4 x 10^{-2}	(GBq x t)$^{-1}$
K	10^{10}	Cells
ρ	4.07 x 10^{-2}	(GBq x t)$^{-1}$
γ	5 x 10^{-2}	Pg x (mL x t x GBq)$^{-1}$
c_1	5 x 10^{-1}	Pg x (mL x t x GBq)$^{-1}$
δ	10^{9}	Cells
b	2 x 10^{-2}	Pg x (mL x t x GBq)$^{-1}$
m	2.39 x 10^{-2}	t^{-1}
p	3.86 x 10^{-9}	μg x (L x t)$^{-1}$
β	3.18 x 10^{-1}	t^{-1}

Theorem 2.1:
Using the initial conditions given in Equation (1), the solutions $A(t)$, $N(t)$, $I(t)$, $T_g(t)$ are non-negative for all time $t > 0$
Proof:
From the first equation of Equation (1)

$$\frac{dA}{dt} \geq -\mu A$$

Both sides multiply by $e^{\mu t}$

$$e^{\mu t}\frac{dA}{dt} \geq -\mu A(t)e^{\mu t}$$

$$e^{\mu t}\frac{dA}{dt} + \mu A(t)e^{\mu t} \geq 0$$

$$\int_0^t \frac{d}{ds}(e^{\mu s}.A(s))ds \geq 0$$

$$A(t) \geq A(0)$$

$$A(t) > 0$$

If $N(t_0) \neq 0$ for all $t_0 \geq 0$ from the second equation of Equation (1)

$$N(t) = N(0) * exp\left\{\int_0^t \left[r\left(1-\frac{N(s)}{K}\right) - \alpha I(s) - \rho H(s)\right]ds\right\}$$

$$\geq 0$$

For all $t \geq 0$, Hence $N(t) \geq 0$ for any non-negative initial values.

From the third equation of Equation (1)

$$\frac{dI}{dt} \geq -mI$$

Both sides multiply by e^{mt}

$$e^{mt}\frac{dI(t)}{dt} \geq -mI(t)e^{mt}$$

$$e^{mt}\frac{dI(t)}{dt} + mI(t)e^{mt} \geq 0$$

$$\frac{d}{dt}(e^{mt}.I(t)) \geq 0$$

$$\int_0^t \frac{d}{ds}(e^{ms}.I(s))ds \geq 0$$

$$I(t) \geq I(0)$$

$$I(t) > 0$$

From the fourth equation of Equation (1)

$$\frac{dT_g}{dt} \geq -\beta T_g(t)$$

Both sides multiply by $e^{\beta t}$

$$e^{\beta t}\frac{dT_g(t)}{dt} \geq -\beta T_g(t)e^{\beta t}$$

$$e^{\beta t}\frac{dT_g(t)}{dt} + \beta T_g(t)e^{\beta t} \geq 0$$

$$\frac{d}{dt}(e^{\beta t}.T_g(t)) \geq 0$$

$$\int_0^t \frac{d}{ds}(e^{\beta s}.T_g(s))ds \geq 0$$

$$T_g(t) > 0$$

Hence all are non-negative.

2.2 Equilibrium and stability analysis

To better understand the dynamic of the system, we first analyse the system without any drug input (A(t)=0 for all t). System of Ordinary differential equations reconstructed as

$$\begin{aligned}\frac{dN}{dt} &= rN\left(1-\frac{N}{K}\right)-\alpha IN\\ \frac{dI}{dt} &= \gamma+\frac{c_1N}{\delta+N}-mI\\ \frac{dT_g}{dt} &= \varepsilon+pN-\beta T_g\end{aligned} \tag{2}$$

The model Equation (2) has two non-negative equilibrium point namely $\bar{E}(0,\bar{I},\bar{T})$ and $E^*(N^*,I^*,T^*)$. These are obtained from solving the equations

$$rN\left(1-\frac{N}{K}\right)-\alpha IN=0$$

$$\gamma+\frac{c_1N}{\delta+N}-mI=0$$

$\varepsilon+pN-\beta T_g=0$ From above equations, we obtain

$N=0$ or $N=K\left(1-\frac{\alpha I}{r}\right)$

From these value we get two equilibria corresponding to each N as shows following

2.2.1 Existence of $\bar{\mathrm{E}}\,(0,\,\bar{\mathrm{I}},\,\bar{\mathrm{T}})$

For $\bar{E}\,(0,\,\bar{I},\,\bar{T})$, the equilibrium values are

$$\bar{I}=\frac{\gamma}{m}$$

$$\bar{T}=\frac{\varepsilon}{\beta}$$

2.2.2 Existence of $E^*(N^*,\,I^*,\,T^*)$

For $E^*(N^*,\,I^*,\,T^*)$, the value of

$$rmN^2+N(rm\delta-Krm+K\alpha\gamma+\alpha cK)-Krm\delta+K\alpha\gamma\delta=0$$

$$I^*=\frac{1}{m}\left(\gamma+\frac{cN}{\delta+N}\right)$$

$T^*=\frac{\varepsilon+pN}{\beta}$ The values of $\mathrm{I}^\star$ and T^* are depends on the value of N. The value of N is positive.

Then $\mathrm{I}^\star$ and T^* are positive.

$\frac{dN}{d\alpha}<0$ These conditions show that the number of cancer cells decrease with its interaction with Interleukin.

$$N^*=\frac{-(rm\delta-Krm+K\alpha\gamma+\alpha cK)+\sqrt{(rm\delta-Krm+K\alpha\gamma+\alpha cK)^2-4\gamma m(K\alpha\gamma\delta-Krm\delta)}}{2rmN^2}$$

$$= \frac{-\left(\frac{rm\delta}{\alpha} - \frac{Krm}{\alpha} + K\alpha\gamma + \alpha cK\right) + \sqrt{\left(\frac{rm\delta}{\alpha} - \frac{Krm}{\alpha} + K\alpha\gamma + \alpha cK\right)^2 - 4\gamma m\left(\frac{K\gamma\delta}{\alpha} - \frac{Krm\delta}{\alpha^2}\right)}}{2rmN^2}$$

Then we get

$$\lim_{\alpha\to\infty} N^* = 0$$

Theorem 2.2: The equilibrium $\bar{E}$ is asymptotically stable only if the following condition holds

$$r < \frac{\alpha\gamma}{m}$$

Proof:

The Jacobian matrix of the model about $\bar{E}$ is$J = \begin{vmatrix} r - \frac{\alpha\gamma}{m} - \lambda & 0 & 0 \\ \frac{c}{\delta} & -m - \lambda & 0 \\ p & 0 & -\beta - \lambda \end{vmatrix}$

The values are

$$\lambda_1 = r - \frac{\alpha\gamma}{m}$$

$$\lambda_2 = -m < 0$$

$$\lambda_3 = -\beta < 0$$

$\bar{E}$ is Asymptotically Stable when $r < \frac{\alpha\gamma}{m}$

Theorem 2.3 . The equilibrium E^* is asymptotically stable with the condition $r > f(N)$

Proof:

The Jacobian matrix of the model about E^* is$J = \begin{vmatrix} r - \frac{2rN*}{K} - \alpha I^* - \lambda & -\alpha N^* & 0 \\ \frac{\delta c}{(\delta + N^*)^2} & -m - \lambda & 0 \\ p & 0 & -\beta - \lambda \end{vmatrix}$

The values are

$$\lambda_1 = r - \frac{2rN*}{K} - \alpha I^*$$

$$\lambda_2 = -m < 0$$

$$\lambda_3 = -\beta < 0$$

By substituting the equilibrium values the first eigen value becomes

$$-r + f(N) < 0$$

Therefore,E^* is asymptotically Stable only when $r > f(N)$.

Otherwise, it is unstable.

Equilibrium and Stability Analysis for Equation (1)

The model has only one equilibrium point namely $\widetilde{E}(\widetilde{A},\widetilde{N},\widetilde{I},\widetilde{T})$. Its obtained by solving the below equations.

$$D-\mu A=0$$

$$rN\left(1-\frac{N}{K}\right)-\alpha IN-\rho\left(1-e^{-A}\right)N=0$$

$$\gamma+\frac{c_1N}{\delta+N}+b\left(1-e^{-A}\right)I-mI=0$$

$$\varepsilon+pN-\beta T_g=0$$

Theorem 2.4:

The equilibrium $\widetilde{E}$ is locally asymptotically stable with certain condition.

Proof:

Solving by Lyapunov, Consider a positive definite function

$$V=\frac{1}{2}\left[k_1A_1^2+k_2N_1^2+k_3I_1^2+k_4T_{g1}^2\right]$$

Differentiating with respect to 't' we get

$$\frac{dV}{dt}=k_1A_1\frac{dA_1}{dt}+k_2N_1\frac{dN_1}{dt}+k_3I_1\frac{dI_1}{dt}+k_4T_{g1}\frac{dT_{g1}}{dt}$$

$$\frac{dV}{dt}=-\delta k_1A_1^2-p\theta\widetilde{N}A_1k_2N_1-\left(r\frac{\widetilde{N}}{K}+\alpha\widetilde{I}+p(1-\theta)\right)k_2N_1^2-\alpha\widetilde{N}I_1k_2N_1+A_1\theta k_3I_1+\frac{\delta c}{(\delta+N^*)^2}N_1k_3I_1+(b(1-\theta)-m)k_3I_1^2-pN_1k_3I_1^2-pN_1k_4T_{g1}-k_4\beta T_{g1}^2$$

$\frac{dV}{dt}$ will be negative definite under the following conditions

$$\left[\frac{\delta c}{\left(\delta+\widetilde{N}\right)^2}k_3-\alpha\widetilde{N}k_2\right]^2<k_2k_3\left[r\frac{\widetilde{N}}{K}+\alpha\widetilde{I}+p(1-\theta)\right](b(1-\theta)-m]$$

$$k_2\left(p\theta\widetilde{N}\right)^2<\delta k_1\left[r\frac{\widetilde{N}}{K}+\alpha\widetilde{I}+p(1-\theta)\right]$$

$$k_3(\theta)^2<\delta k_1[b(1-\theta)-m]$$

$$k_4(p)^2<k_2\left[r\frac{\widetilde{N}}{K}+\alpha\widetilde{I}+p(1-\theta)\right]\beta$$

Now choosing

$$k_1=1,\ k_4=1,k_2=\delta\left[\frac{r\frac{\widetilde{N}}{K}+\alpha\widetilde{I}+p(1-\theta)}{\left(p\theta\widetilde{N}\right)^2}\right],k_3=\delta\left[\frac{b(1-\theta)-m}{(\theta)^2}\right]$$

$\frac{dV}{dt}$ will be negative definite provided the above conditions are satisfied.

Hence its asymptotically stable.

3 Results and Discussion

For numerical simulation, we consider the data on thyroglobulin concentration which presented by Haugen, were the precise amounts of thyroglobulin that separate cancerous tissue from normal residual tissue are unknown, while rising Tg values over time may be an indicator of cancer persistence. Low serum Tg levels, Tg < 1 μg/L, and the absence of interfering antibodies are required for patients receiving thyroidectomy and RAI treatment to be considered disease-free. Therefore, in numerical simulations, the initial condition for Tg, is taken to be 10 μg/L.

Barbolosi [10] took into account that patients with metastases and those who had undergone thyroid surgery typically had $N_0 = 1.12 \times 10^9$ malignant cells. Da Salva considered three numbers of cancer cells first after thyroidectomy and before RAI for papillary thyroid cancer. Here we considered the initial number of cancer cells for DTC patient as $N_0 = 6 \times 10^8$ malignant cells.

Barbolosi [10] considered the radioactive iodine dosage as A =3.7 GBq and 5.55 GBq for the treatment of papillary thyroid cancer patient, which expose the mechanism of drug. That led to the simulation of a treatment scenario with a dosage adjustment. Although it is uncommon in clinical practice, this alternation could be included in treatment plans in the future. The RAI activity assumed in simulations, the doses A =3.7 GBq, 5.55 GBq, 7.4 GBq are considered.

In the past, various models were developed for thyroid cancer, but the current model focuses specifically on differentiated thyroid cancer. Unlike previous model, this proposed model take into account the significant role of interleukins in thyroid cancer. By incorporating the role of interleukins, the model yields improved results compared to others that neglect this factor.

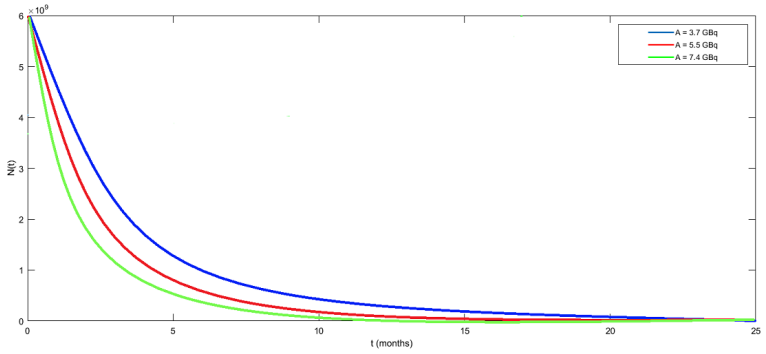

Fig 1. Evolution of number of cancer cells according to RAI activity used over time, t $\geq$ 0

The parameters used are given in Table 1. The values used in the initial conditions are given by A= 3.7,5.55, 7.4 GBq, N=6 X 10^8 and I = 7.92 pg/mL. In some cases, a patient's ability to respond well to a treatment varies on the RAI activity that is given to them, despite the same initial conditions N(0).

4 Conclusion

The mathematical model has been constructed for DTC Patients with RAI therapy. The model was the non-linear system of ordinary differential equations, which consist of four variables and twelve parameters. Using the mathematical model based on the RAI treatment to DTC patients, the parameters of RAI activity, Interleukin, and the number of cancer cells were calculated to determine the effectiveness of treatment. In addition, the stability of the model was analyzed. We performed RAI simulations to simulate several treatment scenarios for DTC using the above model. According to Barbolosi et al. [10], the low values attributed to the parameter may be coupled with the tumor going through a sequence of molecular alterations or with a lack of response to treatment. Typically, patients in such conditions are resistant to RAI therapy because of a decline in NIS, necessitating the use of additional therapeutic modalities that are not reliant on iodine incorporation. More research and clinical trials are required to employ this model in clinical practice. The model makes it simple to investigate the effects of iodine-131 deletion on disease-specific morbidity and recurrence rate. Additionally, we found that mathematical modeling is a useful tool in clinical investigations of cancer since it can help to determine the best treatment protocols for DTC and, as a result, prevent undesirable side effects or ineffective treatments.

5 Declaration

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