

A Mathematical Model on Vorinostat (Histone Deacetylase Inhibitor) in Combination with Radiotherapy

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Abstract

There are four main and most types of cancer treatments, which are surgery, chemotherapy, radiotherapy, and immunotherapy. In this paper, we consider cancer treatment by radiotherapy. Radiation therapy is a treatment procedure that uses radiation to kill tumor cells. The Histone deacetylases inhibitor (HDAC) Vorinostat (suberoylanilide hydroxamic acid or SAHA) combination with radiotherapy blocks cancer cell proliferation. In this study we developed and analyse Mathematical model for tumor growth and histone deacetylase inhibitor, in combination with radiotherapy then we analyse the stability of equilibria. And fitting Patient 1 data to numerical simulation for locally weighted smoothing linear regression.

Keywords- Histone Deacetylase Inhibitors, Radiation Therapy, Mathematical Model

I. INTRODUCTION

Cancer treatment includes many physical therapeutic agents, all having the same basic shrinkage of tumor: to directly kill tumor cells or prevent their proliferation. Radiation may be used to cure or shrink early-stage cancer, stop cancer from coming back, or to treat symptoms when cancer has spread. Radiation therapy uses high-energy particles or waves, such as x-rays, gamma rays, electron beams, or protons, to destroy or damage cancer cells. But Radiation therapy is not a common way to treat colon cancer, though it may be used in certain circumstances.

In advanced stages of colon cancer, radiation therapy is often given instead of surgery when an operation cannot be performed depending on patient's age that means above Septuagenarian. Radiation may be used in combination with surgery as definitive therapy, or may be used to shrink tumor, or providing relief from the symptoms of colorectal cancer such as pain, bleeding, or blockage. Radiation therapy is sometimes given prior to surgery to improve outcomes in selected patients with rectal cancer. Radiation may be used to shrink a tumor before surgery or destroy any remaining cancer cells after removal.

Cells are normally proliferating and divide in to form new cells. But cancer cells grow and divide faster than most normal cells. Radiation helps by making small breaks in the DNA inside cells. These breaks keep cancer cells from proliferating and dividing and cause them to die.

II. MODEL FORMULATION

Consider the Logistic growth model describes tumor growth and the treatment doses

$$\frac{dT}{dt} = \lambda T \left(1 - \frac{T}{K}\right) - \xi VT - \tau R(t)T \quad (1)$$

$$\frac{dV}{dt} = g(t) - \delta V \quad (2)$$

Where

λ - Tumor growth rate, negative growth rate indicates that the tumor population is decreasing

K - Carrying capacity

$0 \leq \xi \leq 1$ -HDAC induces a continuous tumor cell kill with the degree of intensity $0 \leq \xi \leq 1$

$g(t)$ - Concentration of the drug.

δ - Natural death of HDAC cells.

Where

$$g(t) = \int_0^t a(t') e^{(-\alpha(t-t'))} dt' \quad (3)$$

$a(t')$ -the rate of given of HDAC concentration at time t' . α - Substance is completely removed per unit time.

$$R(t) = \begin{cases} \gamma, & n\omega \leq t \leq n\omega + I \\ 0, & n\omega + I \leq t \leq (n+1)\omega \end{cases} \quad (4)$$

Where $n = 0, 1, 2, 3, 4$. ω is the recurring at intervals of time.
 $0 < I < \omega$ is the radiation therapy time.

A. Analyse the Stability of Equilibrium

Let us establish some properties of our model. We assume positive values for all parameters. That is we assume $T(t) = T_0 \geq 0$ at $t=0$, and $V(t)=V_0 \geq 0$ at $t=0$. $T=0$ is a solution of the first equation.

Since $\frac{dV}{dt} = g(t) - \delta V$, no solution $V(t)$ of second equation with $V(t) > 0$ can become zero.

$$\frac{dT}{dt} \leq \lambda T \left(1 - \frac{T}{K}\right)$$

$$\lim_{t \rightarrow \infty} \sup T(t) \leq K$$

Similarly we have $\frac{dV}{dt} \leq g(t) - \delta V$ giving

$$\lim_{t \rightarrow \infty} \sup V(t) \leq \delta^{-1} g(t).$$

Consider the region $R = \{(T, V) \in R^2 / 0 \leq T \leq K, 0 \leq V \leq \delta^{-1} g(t)\}$ and analyse the stability of equilibria. The equilibria are found by solving the first two equations.

We get $T_E = 1 - V - R(t)$ and $V_E = \frac{g(t)}{\delta}$. The Jacobian matrix J is given by

$$J = \begin{pmatrix} 0 & 1 - \frac{g(t)}{\delta} - R(t) \\ 0 & -\delta \end{pmatrix}$$

The Eigen values are $0, -\delta$ where $\delta > 0$. Therefore the system is unstable.

B. HDAC Inhibitors

Histone deacetylase inhibitors (HDAC) use in psychiatry and neurology as mood stabilizers and anti-epileptics, for example, valproic acid. In more recent times, HDAC are being studied as a mitigator or treatment for neurodegenerative diseases [12][10]. In recent years HDAC used for cancer therapy [7][6].

In colorectal cancer, the curable stage is depending on patient's age and GTV. Histone deacetylase inhibitors are currently being admitted as single therapy or combination with either chemotherapy or with other agents. However, patients with colorectal cancer need to be recruited in randomized clinical trials for evaluate the maximum response achievable from dosed agents.

Histone deacetylase inhibitors (HDAC) are a heterogeneous group of epigenetic therapeutics. Epigenetic therapy offers a potential way to influence those pathways directly. Anticancer effect's in both pre-clinical and clinical settings, in most the effect of radiosensitisation when given in combination with radiotherapy. Histone deacetylase inhibitors (HDAC) are epigenetic drugs that can alter histone modifications, and could potentially be used as anticancer therapy, either as a single-agent or in combination with other therapies [12].

Histone deacetylase to adjust a mechanism for accurate and proper functioning the acetylation of a variety of histone and nonhistone proteins, conscious restraint and regulation of impulses and suppression of instincts and affects the transcription and regulation of genes involved in proliferation, cell cycle control, survival, DNA repair and differentiation.

Vorinostat is also being studied as a single agent in other lymphomas, multiple myeloma and solid tumor malignancies including: colon, non-small-cell lung, breast, mesothelioma, glioblastoma multiforme, prostate, head and neck, renal cell, neuroendocrine, ovarian and cervical [11]. Vorinostat blocks growth promoting signal transduction pathways and the proliferation of a broad spectrum of cultured cancer cells [5].

Early Phase trial of daily oral administration of Vorinostat 400 mg, 300 mg, 200 mg and in 5 patients for their respective toxicities. Because single-agent Vorinostat is known to be distress at 400 mg daily for regular dosing, with the most common side effects being lack of energy and gastrointestinal toxicities [4]. Consider maximum limit of drug according to the patient's toxicities.

C. Radiation Therapy

For certain cancers that can be cured either by radiation or by surgery, radiation may be the more desired treatment. This is because radiation can produces less damage and the organ may be work likewise the way it should after treatment. In 2002, the Cancer Services Collaborative suggested that radiotherapy alone is responsible for 78% of non-surgical cancer cures. Between 30 and 40% of the people will develop cancer, and at least half require radiation treatment at some time in their illness.

Patients having radiotherapy, about 60% are treated with curative intent, frequently in combination with surgery and chemotherapy. In this study for each of the 5 patients, data on gross tumor volume(GTV), internal radiation target, relative volumes of small bowel receiving radiation doses between 6 Gy and 30 Gy at 6-Gy intervals (V6-V30). The gross tumour volume (GTV) is the visible/demonstrable extent and location of the malignant growth. Due to the high density of the cancer cells in the GTV, an adequate dose must be delivered to the whole GTV to obtain local tumour control in radical treatments.

In this study we consider 5 patients with different GTV. Numbered the patients depend on their GTV volume in descending order. Patient 1 had GTV 285 cubic centimetre receiving radiation dose per 6Gy in 5 fractions with Vorinostat 300 mg. This stage is not a curable stage but temporarily relive from the pain. Similarly remaining 4 patients were receiving radiation dose

and Vorinostat for respective GTVs and toxicities of drug. The data fitted to our model and find the evolution of the tumor for each patient as shown in the following figures.

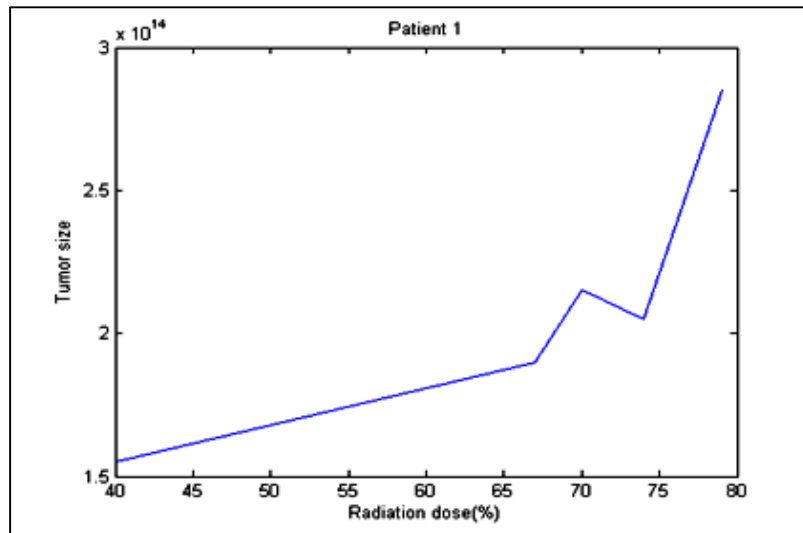


Fig. 1: Patient 1

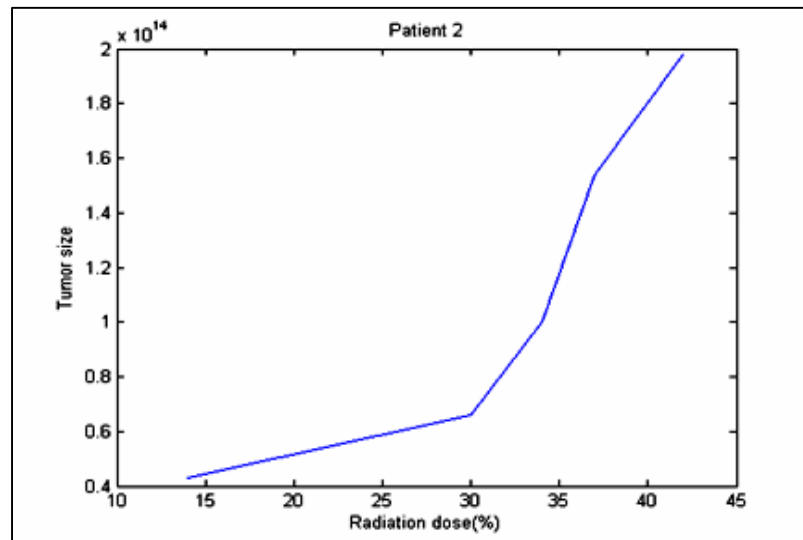


Fig. 2: Patient 2

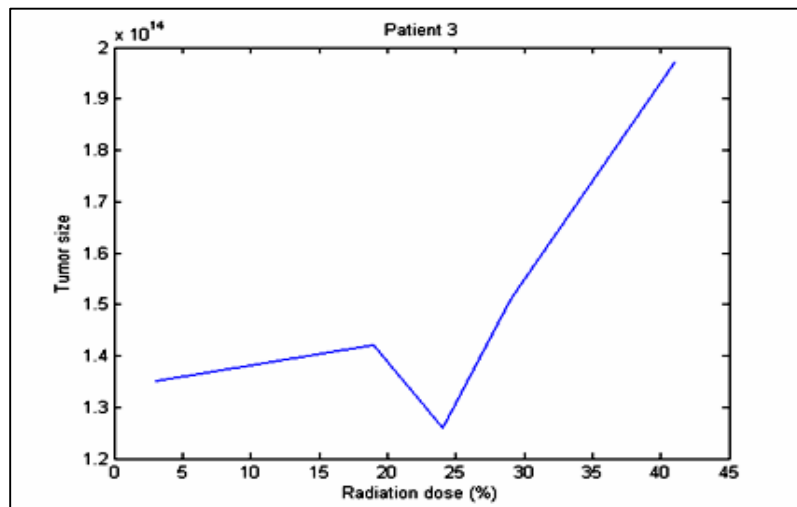


Fig. 3: Patient 3

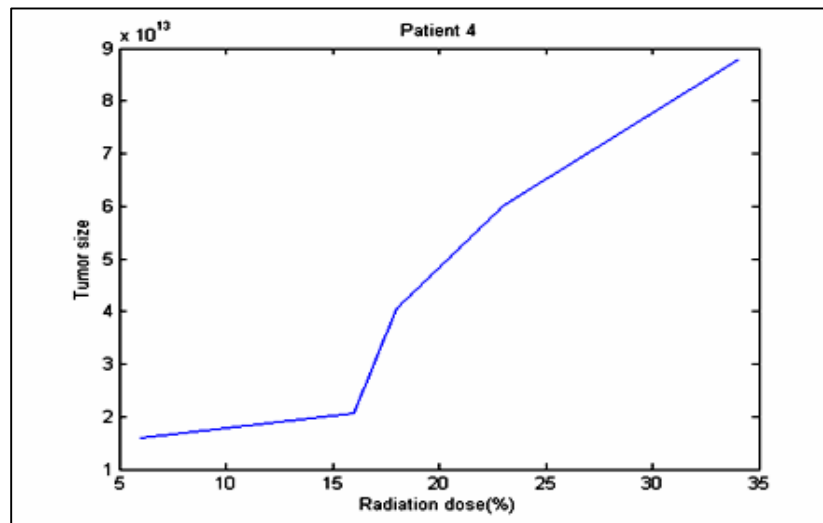


Fig. 4: Patient 4

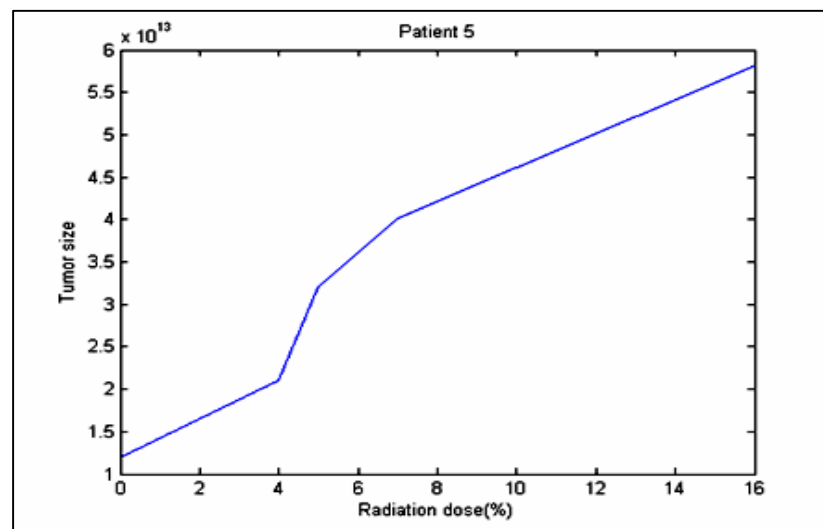
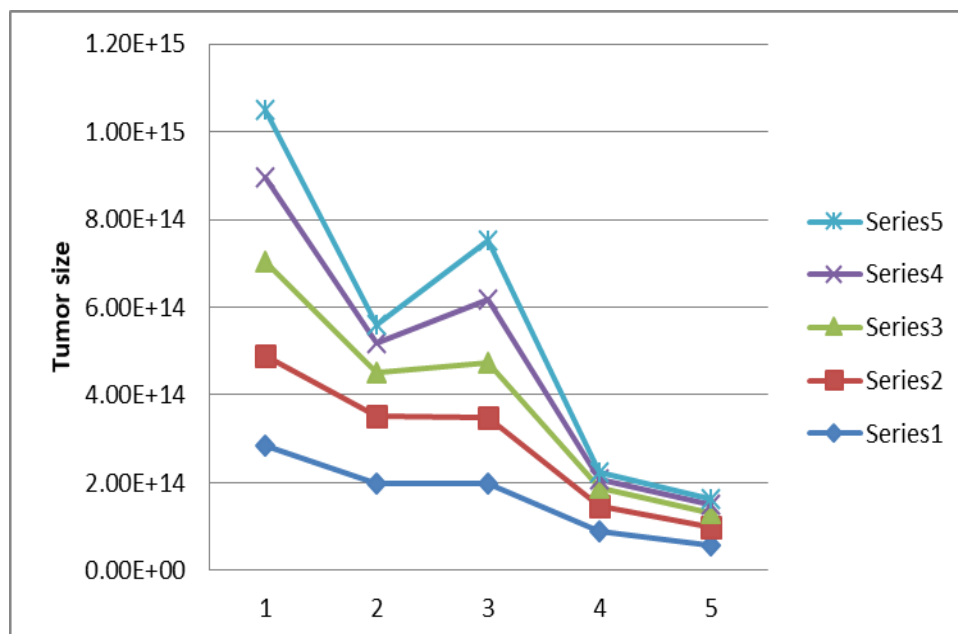


Fig. 5: Patient 5



Graph 1: Tumor evolution of each patient

III. NUMERICAL SIMULATION

Consider locally weighted smoothing linear regression model to fit the data for Patient 1 where the Radiation dose is normalized by mean 66 and standard deviation 15.22 and where day is normalized by mean 30.2 and standard deviation 23.4. Adjusted R square is 0.7324

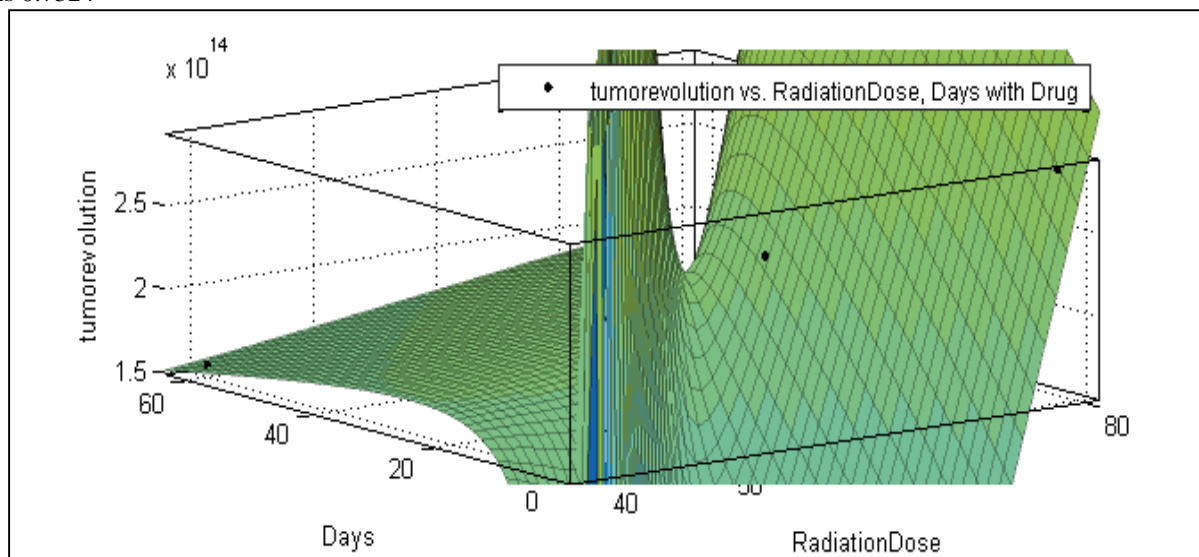


Fig. 6: Locally weighted smoothing linear regression fitting model

IV. CONCLUSIONS

Dose to increase in intensity up to 30 Gy in 5 fractions is able to be done with radiotherapy for recurrent colon cancer. Higher radiotherapy doses were associated with significantly higher loco regional rates. Large tumor volume required higher radiotherapy doses and relevant dosage of HDAC to achieve optimal response rates compared with smaller tumor volume. Smaller GTV with young and middle aged patients take additional therapy to recover the health. In future we analyse cancer by using various combinations of drugs and treatments.

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