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Mathematical Model for Studying the effect of one-Step Individual Multiple Fractions in Cancer Treatments Optimization

نموذج رياضي لدراسة تأثير الشعاع متعدد الضربات المنفصلة ذات الخطوة الواحدة في تحسين علاج السرطان

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Abstract.

As connection with our previous publication, we have reported the application of a mathematical model for one–step with multiple fractions in cancer treatment optimization [1, 2]. In addition to the correction and extending for some previously calculated, we studied the important role of the initial tumor cell density on optimization results. We found similar behavior with different values but not equivalent. In this paper we present more physically reasonable new cases of (1-step) radiation profiles during the two fractions, three fractions, … , i fractions. By examining cases and expansion on the results by using the partial differential equation models which solved by using computational methods (MATLAB, we have obtained a great results. Finally we have compared different cases of one-Step i.e. with individual multiple fractions in mathematical models of cancer treatments optimization .

Keywords: Mathematical, Models, Glioblastomas , Radiation, Equation, Optimization

نموذج رياضي لدراسة تأثير الشعاع متعدد الضربات المنفصلة ذات الخطوة الواحدة في تحسين علاج السرطان

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ملخص البحث :

استمرارا لعملنا المنشور سابقا، نحن قدمنا في هذا البحث تطبيق نموذج رياضي لدراسة تأثير الشعاع متعدد الضربات المنفصلة ذات الخطوة الواحدة في تحسين علاج السرطان كما هو مشار في المرجع [2] . اضافةً لتوسيع بعض الاعمال السابقة نحن درسنا الدور الهام لكثافة خلايا الورم الاولية على نتائج التحسين. نحن توصلنا لسلوك مشابهة مع قيم مختلفة ولكن غير متساوية. في هذا البحث نحن ايضا قدمنا حالات جديدة لوضع الشعاع خلال ضربتين ، ثلاث ضربات، ...، ن من الضربات. بواسطة تتبع الحالات و توسيع النتائج باستخدام نماذج المعادلات التفاضلية التي تم حلها باستخدام برنامج الماتلاب نحن حصلنا على نتائج قيّمة. واخيرا قمنا بمقارنة النتائج..

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Introduction:

Cancer tumors are very dangers diseases that killed many patients in short time. The reasons of creation of cancer tumors are many and uncontrollable mostly. The number of cancer victims are increasing annually. One of the famous therapy method that used in cancer treatments is called radiation therapy. The most advantage of this method is the accuracy in covering whole cancer cells by radiations dose. However, the radiation treatment has many disadvantage points such as side effect and non-accurate intensity value that required for the specific tumor and specific patient. The mathematical models are introducing the solutions to overcome the disadvantage points of radiation therapy. It control and produce the exact optimize values of intensity, radius and all other variables in radiation therapy.

Glioblastomas are a type of malignant tumor that is well-known. They've been labeled as one of the most dangerous types of primary brain tumors. Glioblastomas are recognized for their highly aggressive development and invasion patterns. Another concern of this type of cancer is that it can kill a patient in less than a year, even after major surgery, radiotherapy, and chemotherapy. [2-4].

Radiation therapy is a viable therapeutic option for this form of cancer. This is owing to the accuracy with which radiation therapy is administered. It completely encircles the tumor, allowing radiation to be targeted directly at cancer cells. [5-7].

Many researchers show that, the mathematical models can be used for a precise modeling, simulation and predication of optimization results in cancer treatment using Beam Radiation Therapy (XRT). It utilizes both analytical and computational mathematical methods as well as data from MRI imaging. [1, 3, 8-11].

In addition, a mathematical model can be applied for developing an analytical method to describe the response to radiotherapy (RT). Model Ribba [12] developed an ODE model of the response of low-grade glioma to different therapies with a number of undetermined parameters that can be fit to describe the individual patient's response with a good qualitative agreement [13-16].

We have successfully studied the capability of the mathematical model in optimization brain tumor radiation treatment(one–step) [2]. We have corrected some previously calculated values and extended the range of calculations up to 10 value. In addition, we studied the dependency of results on the initial tumor cell density and found that the behavior is similar but not equivalent. The current efforts focus on using the radiation therapy treatments because of the precision with which it targets of the tumor region which leading to longer survival times.

In this paper we present more physically reasonable new cases of one-step radiation profiles during the two fractions, three fractions,…, i fractions. By

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examining cases and expansion on the results by using the partial differential equation models which solved by using computational methods (MATLAB). Finally we have compared different cases of one-Step i.e. with individual multiple fractions in mathematical models of cancer Treatments Optimization.

Theoretical Background

According to the model which introduced by Meaney [1], and which depend on applying the Beam Radiation Therapy (XRT) to the tumor that evolved according to the equation

$$\frac{\partial n(x,t)}{\partial t} = D_n \nabla^2 n(x,t) + \rho n(x,t)\left(1 - \frac{a n(x,t)}{n_{max}}\right) \qquad (1)$$

Where $n(\vec{x},\ t)$ is the tumour cell density at position $\vec{x}$, $\nabla^2 = \sum_{\alpha=1}^{d} \frac{\partial^2}{\partial x_\alpha^2}$ is the Laplace operator, D_n is the tumor cell diffusivity, ρ is the tumor cell proliferation rate, and d is the dimensional. That was accomplished by including the term $-\gamma f(\vec{x},t)\, n(1 - \frac{nb}{n_{max}})$ on the right side of equation (1) as a result of therapeutic procedures that eliminate a part of cells. By assuming that there is no cell development at the time of the radiation therapy, the model is reduced to

$$\frac{\partial n(\vec{x},t)}{\partial t} \cong -\gamma f(\vec{x},t)\, n(\vec{x},t)\left(1 - \frac{b\, n(\vec{x},t)}{n_{max}}\right) \qquad (2)$$

which has a solution

$$n(\vec{x}, t_0 + \Delta t) = \begin{cases} n(\vec{x},t_0) e^{-\gamma f(\vec{x},t_0)\Delta t}, & for\ b = 0 \text{ (Exponential growth)} \\ \dfrac{n_{max}}{1 - \left(\dfrac{n(\vec{x},t_0) - n_{max}}{n(\vec{x},t_0)}\right) e^{-\gamma f(\vec{x},t_0)\Delta t}}, & for\ b = 1 \text{ (logistic growth)} \end{cases} \qquad (3)$$

Constraints are also imposed on $f(\vec{x},t)$ such as ,

$$0 \le f(\vec{x},t) \le C \text{ for some } C \qquad (4)$$

As an upper limitation for $f(\vec{x},t)$ that follows patient safety standards and

$$\gamma \int d^d x\, dt \quad f(\vec{x},t) \le F \qquad (5)$$

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As limits the total dose received by the patient. In his model, we have been minimized the tumor cells after the final fraction, N(T), where

$$N(T) = \int d^d x \;\; n(\vec{x}, t) \tag{6}$$

Subject to equation (5), to produce,

$$f(\vec{x}, t_0) = \ln\left(\frac{n(\vec{x}, t_0)}{\lambda}\right) \tag{7}$$

But this value for $f(\vec{x}, t_0)$ does not fit the other constrain for some cases. So, it was overtaken by considering the simplest case of a Gaussian profile and reach to the cell density profile application of XRT will attain a flat-top, as

$$n(r, t_0 + \Delta t) = \begin{cases} n_0 \; e^{-f_m} & If \;\; r \le r_m \\ n(r, t_0) & If \;\; r \ge r_m \end{cases}$$

Meaney examined the physically reasonable cases of $1-$step and $2-$step radiation profile during the first and second XRT fractions for some values of treatment parameters, [1], while Al-Masuodi et al. corrected some calculated values and extended the range of calculations up to 10 values. In addition, we showed the relation between final tumor cell density with tumor size and initial number of tumor cells, [2].

For the one-step radial profile with one-fraction, the one fraction will apply within the circular range with the radius r_1 as

$$f(r, t_0) = \begin{cases} f_1 \;\; , & 0 \le r \le r_1 \\ 0 \;\; , & otherwise \end{cases}$$

The optimal profile of radiation and killed cells can be found with the help of $r_1$which satisfies the following equation, [1]

$$0 = e^{-\frac{\gamma F' \Delta t}{r_1^2}} \left[1 + \left(\frac{r_1^4}{2F'\gamma \Delta t s^2} - 1\right) e^{-\frac{r_1^2}{2s^2}}\right] - \frac{r_1^4}{2F'\gamma \Delta t s^2} e^{-\frac{r_1^2}{2s^2}}.$$

Where F'=$r_1^2 f_1$, and

$$\widetilde{N} = 2\pi \, n_0 s^2 \left[\; e^{-\gamma f_1 \Delta t}\left(1 - e^{-\frac{r_1^2}{2s^2}}\right) + e^{-\frac{r_1^2}{2s^2}} - e^{-\frac{R^2}{2s^2}} \right]$$

$$- \lambda(f_1 r_1^2 - F') \tag{8}$$

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Values of r_1 and f_1 that satisfy the above equations, specify optimal of killed cells, $N(r_1, f_1)$.

We can easily note that at t_0 , i.e. $\Delta t = 0$, Equation (8) becomes

$$N = 2\pi\, n_0 s^2$$

which shows the relation between initial number of tumor cells N_0 and cell density n_0 at center.

In this paper mathematical models for the cases of 1 −step radiation profile during the second, third and n XRT individual fractions are be introduced, such that first fraction radial started from 0 to r_1 while second fraction started from 0 to r_2 where r_2 larger than r_1.

The Improved Model

In our model we have worked on the fact that, the amount of applied radiation in treatment should be used in higher intensity over the central of tumor cells more than outer tumor cells even in more distribution of radial profile. We have started with introducing the one-step, two fractions model. In this model the two radiation profile used in one step simultaneously. First fraction radial started from 0 to r_1 while second fraction started from 0 to r_2 where r_2 larger than r_1. Therefore, the second fraction is againg covering first area that coverd by first fraction and increased the exposer area beyond r_1. The resulting the first area $0 - r_1$ which represent the central area of tumor will be under exposure to the radiation more than that of outer limit of tumor, this will reduce the tumor cells rabidly. We have extended our model to one-step with individual *two* fractions, *three* fractions, … , *n* fractions (see Figure 1).

1- Optimization the radiation profile of 1 –step with Individual *two* fractions model

We have studied the application of two-fractions of radiation with one- step. As shown previously, to describe the one fraction we need to introduce two variables r_1,f_1 with respect to $f(r,t)$, but in describing two fractions we need four variables r_1,f_1 ,r_2, & f_2. Therefore, we can write $f(r,t)$ during separate fractions as

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$$f(r,t_0^*) = \begin{cases} f_1\,, & 0 \le r \le r_1 \\ 0\,, & otherwise \end{cases} \quad \text{and} \quad f(r,t_1^*) = \begin{cases} f_2\,, & 0 \le r \le r_2 \\ 0\,, & r_2 \le r \le R \end{cases}$$

Where $t_0^* \in [t_0^*, t_0^* + \Delta t]$ and $t_1^* \in [t_0^* + \Delta t + \tau, t_0^* + 2\Delta t + \tau$ and τ indicate the interval between the two fractions.

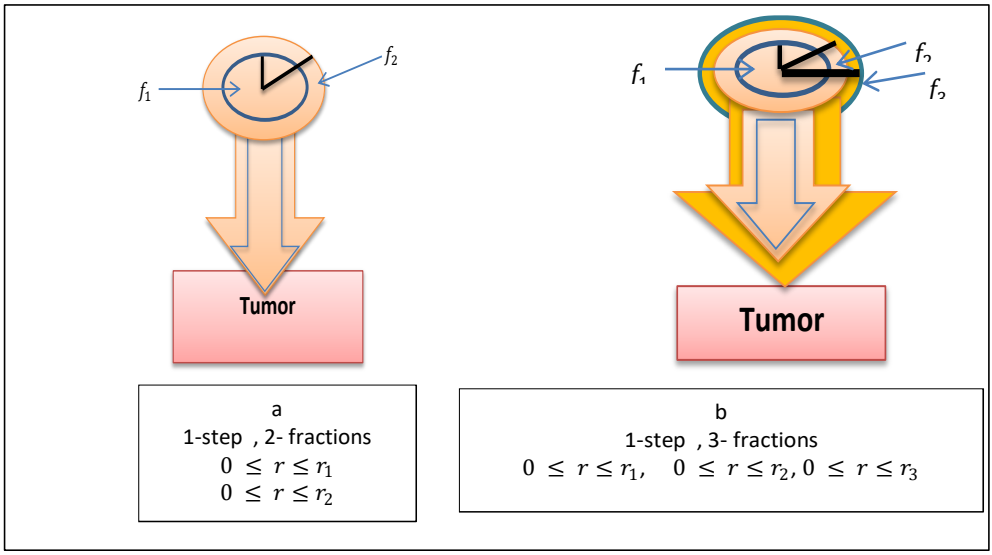

Fig. 1 The Improved Model

The goal is to minimize $N(t_0 + \Delta t) = 2\pi \int r, (n(r, t_0 + \Delta t)\, dr$, Where the fractions constrained individually, such that $F' = r_1^2 f_1$ and $F' = r_2^2 f_2$. Where $f(r, t_0^*)$ is the value associated with $f(r, t_0^*)$ remain unchanged. We believe that τ is small enough that spatial migrations represented by the diffusion term may be ignored. As a result, the density profile simply grows exponentially by a factor of $e^{\rho\tau}$.

$$n_1(r, t_0 + \Delta t + \tau) = \begin{cases} n(x,t_0)\, e^{\rho\tau}\, e^{-f_1\gamma\Delta t} & 0 \le r \le r_1 \\ n(x,t_0)\, e^{\rho\tau} & r_1 \le r \le R \end{cases}$$

Where $n(x,t_0) = n_0 e^{-\frac{r^2}{2s^2}}$, Thus

$$n_1(\mathrm{r}, t_0 + \Delta t + \tau) = \begin{cases} n_0 e^{-\frac{r^2}{2s^2}} e^{\rho\tau}\, e^{-f_1\gamma\Delta t} & 0 \le r \le r_1 \\ n_0 e^{-\frac{r^2}{2s^2}} e^{\rho\tau} & r_1 \le r \le R \end{cases}$$

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but after application of the second fraction is given by:

$$n_2(\mathrm{r}, t_0 + 2dt + \tau) = \begin{cases} n_1(\mathrm{r}, t_0 + \Delta t + \tau)\, e^{-f_2\gamma\Delta t} & 0 \le r \le r_2 \\ n_1(\mathrm{r}, t_0 + \Delta t + \tau) & r_2 < r \le R \end{cases}$$

The factor of $e^{-f_1\gamma\Delta t}$ is specifying the effect of one-step with 1-fraction that is before second fraction immediately. It is only have effect on the range $0 \le r \le r_1$. So during the second fraction we should multiply its effect, $e^{-f_2\gamma\Delta t}$ by the effect of first fraction as following:

$$n_2 = \begin{cases} n_1 e^{-\frac{r^2}{2s^2}} e^{\rho\tau}\, e^{-f_1\gamma\Delta t}\ e^{-f_2\gamma\Delta t} & 0 \le r \le r_2 \\ n_1 e^{-\frac{r^2}{2s^2}} e^{\rho\tau} & r_2 < r \le R \end{cases}$$

Which leads to

$$n_2 = \begin{cases} n_1 e^{-\frac{r^2}{2s^2}} e^{\rho\tau}\ e^{-\gamma[f_1+f_2]\Delta t} & 0 \le r \le r_2 \\ n_1 e^{-\frac{r^2}{2s^2}} e^{\rho\tau} & r_2 < r \le R \end{cases}$$

integrating this result gives total number of cells as:

$$N(t_0 + \Delta t) = \iint n(r, t_0 + \Delta t)\, dA$$

$$= 2\pi \left[e^{\rho\tau}\ e^{-\gamma[f_1+f_2]\Delta t}\, n_0 \int_0^{r_2} r\, e^{-\frac{r^2}{2s^2}} dr + n_0 \int_{r_2}^{R} r\, e^{-\frac{r^2}{2s^2}} dr \right]$$

$$= 2\pi\, n_0 s^2 e^{\rho\tau} \left[e^{-\gamma[f_1+f_2]\Delta t} \left(1 - e^{-\frac{r_2^2}{2s^2}}\right) + e^{-\frac{r_2^2}{2s^2}} - e^{-\frac{R^2}{2s^2}} \right]$$

Where τ is very small, it can be neglected $(e^{\rho\tau} = 1)$ then

$$N(t_0 + \Delta t) = 2\pi\, n_0 s^2 \left[e^{-\gamma[f_1+f_2]\Delta t} \left(1 - e^{-\frac{r_2^2}{2s^2}}\right) + e^{-\frac{r_2^2}{2s^2}} - e^{-\frac{R^2}{2s^2}} \right]$$

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A Lagrange multiplier λ can be used to impose a restriction on the total beam flux, resulting in an augmented N as

$$\widetilde{N} = 2\pi\, n_0 s^2 \left[e^{-\gamma[f_1+f_2]\Delta t}\left(1 - e^{-\frac{r_2^2}{2s^2}}\right) + e^{-\frac{r_2^2}{2s^2}} - e^{-\frac{R^2}{2s^2}} \right] - \lambda(f_2 r_2^2 - F')$$

Extremizing with respect to r_2, f_2 and λ, we get

$$0 = 2\pi\, n_0 s^2 r_2 \left[e^{-\gamma[f_1+f_2]\Delta t}\left(1 - e^{-\frac{r_2^2}{2s^2}}\right) + e^{-\frac{r_2^2}{2s^2}} \right] - 2\lambda(f_2 r_2)$$

$$0 = 2\pi\, n_0 s^2 \gamma \Delta t\; e^{-\gamma[f_1+f_2]\Delta t}\left[e^{-\frac{r_2^2}{2s^2}} - 1 \right] - 2\lambda(r_2^2)$$

$$0 = f_2 r_2^2 - F'$$

By eliminating f_2 and λ, from the above equations we arrive at the following expression for r_2 :

$$0 = e^{-\frac{\gamma[r_2^2 f_1 + F']\,\Delta t}{r_2^2}} \left[1 + \left(\frac{r_2^4}{2F'\gamma\Delta t s^2} - 1\right) e^{-\frac{r_2^2}{2s^2}} \right] - \frac{r_2^4}{2F'\gamma\Delta t s^2} e^{-\frac{r_2^2}{2s^2}}$$

2- Optimization the radiation profile of 1 –step with Individual *three* fractions model

We consider that one-step case of XTR with the three fractions individually consist a beam of radius r_1,r_2 and r_3 and strength are f_1, f_2 and f_3. The radiation profiles are: separate fractions as

$$f(r, t_0^*) = \begin{cases} f_1\,, & 0 \le r \le r_1 \\ 0\,, & otherwise \end{cases}$$

$$f(r, t_1^*) = \begin{cases} f_2\,, & 0 \le r \le r_2 \\ 0\,, & r_2 \le r \le R \end{cases}$$

$$f(r, t_2^*) = \begin{cases} f_3\,, & 0 \le r \le r_3 \\ 0\,, & r_3 \le r \le R \end{cases}$$

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By continuing and extending the case of two fractions and by similar procedures, the optimal radiation profile and killed cells can be found by help r_3 that satisfy the following equation

$$0 = e^{-\frac{\gamma[r_3^2[f_1+f_2]+F']\,\Delta t}{r_3^2}}\left[1+\left(\frac{r_3^4}{2F'\gamma\Delta t s^2}-1\right)e^{-\frac{r_3^2}{2s^2}}\right]-\frac{r_3^4}{2F'\gamma\Delta t s^2}e^{-\frac{r_3^2}{2s^2}}.$$

Where $F'=r_3^2 f_3$ and

$$\widetilde{N} = 2\pi\, n_0 s^2\left[\, e^{-\gamma[f_1+f_2+f_3]\Delta t}(1-e^{-\frac{r_3^2}{2s^2}})+e^{-\frac{r_3^2}{2s^2}}-e^{-\frac{R^2}{2s^2}}\right]$$
$$-\lambda(f_3 r_3^2 - F')$$

3- The Generalization case, optimization the radiation profile of 1 –step with Individual i fractions model

In the section for applying i fractions, describing i fractions requires introducing i new variables to parameterize $f\,(r,t)$ and i new variables to parameterize r, we can write the $f\,(r,t)$ of $i's$ separate fractions as.

$$f(r,t_0^*) = \begin{cases} f_1\,, & 0 \le r \le r_1 \\ 0\,, & otherwise \end{cases}$$
$$f(r,t_1^*) = \begin{cases} f_2\,, & 0 \le r \le r_2 \\ 0\,, & r_2 \le r \le R \end{cases}$$
$$\vdots$$
$$f(r,t_{i-1}^*) = \begin{cases} f_i\,, & 0 \le r \le r_i \\ 0\,, & r_i \le r \le R \end{cases}$$

By continuing and extending the case of $i-1$ fractions and by similar procedures to case two and three fractions, the optimal radiation profile and killed cells can be found by help r_i that satisfy the following equation

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$$0 = e^{-\frac{\gamma[r_i^2[f_1+f_2+\cdots+f_{i-1})]+F']\,\Delta t}{r_i^2}}\left[1+\left(\frac{r_i^4}{2F'\gamma\Delta t s^2}-1\right)e^{-\frac{r_i^2}{2s^2}}\right]$$

$$-\frac{r_i^4}{2F'\gamma\Delta t s^2}e^{-\frac{r_i^2}{2s^2}}.$$

Where $F'=r_i^2 f_i$ and

$$\widetilde{N} = 2\pi\, n_0 s^2\left[\, e^{-\gamma[\sum_{k=1}^{i} f_i]\Delta t}(1-e^{-\frac{r_i^2}{2s^2}})+e^{-\frac{r_i^2}{2s^2}}-e^{-\frac{R^2}{2s^2}}\right]-\lambda(f_i r_i^2-F')$$

Numerical discussion

One-Step with Individual two-Fractions: In the Table-1 we have calculated values of $N(t+dt)$ in two cases: 1) one-step, one-fraction N_1; 2) one-step, two-fractions, N_2, where $N(t+dt)$ are the final tumor cell number at the end of radiation, s is the tumor size while r_1, r_2, f_1 and f_2 are the two radii and strengths of the (one-step, two-fractions), respectively.

s	n_0	r_1	f_1	r_2	f_2	$N_1 \times 10^6$	$N_2 \times 10^6$
1	1591549	2.140695	5.455447	3.113118	2.579578	1.9204	0.4182
2	397887.4	3.0274	2.727724	5.339606	0.876842	5.3490	2.4214
3	176838.8	3.707793	1.818482	7.945889	0.395963	7.1475	4.1267
4	99471.84	4.28139	1.363862	10.85839	0.212036	8.0985	5.2804
5	63661.98	4.78674	1.091089	13.96681	0.128158	8.6486	6.0735
6	44209.71	5.243611	0.909241	17.20539	0.084452	8.9924	6.6438
7	32480.6	5.663747	0.77935	20.53785	0.059269	9.2207	7.0714
8	24867.96	6.0548	0.681931	23.94278	0.04361	9.3798	7.4031
9	19648.76	6.422085	0.606161	27.40649	0.033284	9.4948	7.6676
10	15915.49	6.769472	0.545545	30.91958	0.02615	9.5806	7.8833

***Table-1**: optimization values in (one-step with ,two- fractions)*

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The listed values in Table-1 conform the validity and superiority of our model. The last columns that contain the total number of remaining tumor cell N_1 and N_2 show clearly the effective reducing in total number of tumor cells when second fraction applied with first fraction in the same time. Other parameters show logical sequence which comfortable with all results. For example, the model suppose that r_1 larger than $r_1$which is clearly verified in columns 3 &5. Similar logic for relation between r_1 with f_1 and r_2 with f_2 values. However, there is another interesting results about the decreasing steps of N_1 and N_2 with size of tumor (s). The table shows the very slow effect of radiation with increases of tumor size (s). In fact, this behavior is due to the constraints condition for limiting the total dose received by patient which is reported in equation (5)

The comparison between the final tumor cell density in (one –step ,with one-fraction) and (one-step, with two-fractions) :

Figure-2 shows the plotted comparison between $N(t+dt)$ in the cases one-step with one-fraction and one-step with two-fractions. The curves has been plotted for N_1 with r_1, $f_1$and s. similar plotting is done for N_2 with r_2, f_2 and s The curves in all graphs in Figure-2 shown clearly the advantage for using our proposed model. The valuable rate of difference between N_1 and N_2 conforms our model in tumor treatment optimization.

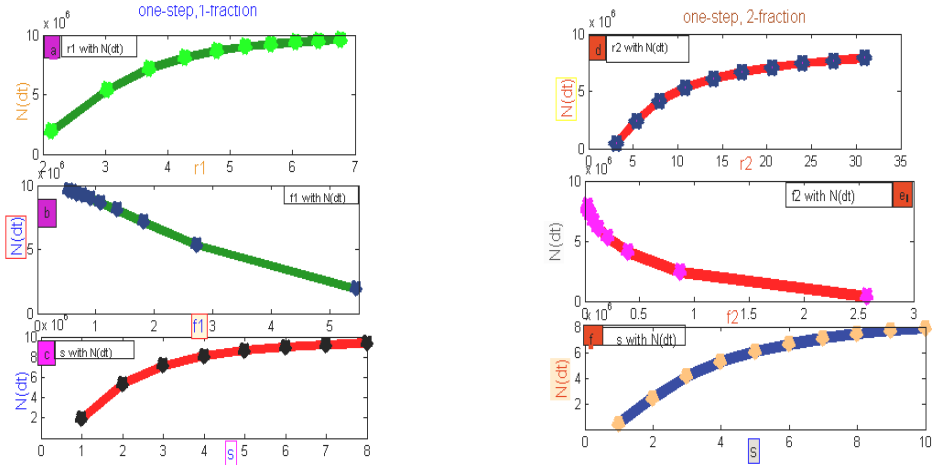

***Figure-2**: comparison between the final tumor cell density in (one –step with one-fraction and one-step with two-fraction)*

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Optimization the radiation profile for one-step profile with 3 fractions:

In the Table 2, we have calculated values of $N(t+dt)$ in the case one-step with three fractions, where $N(t+dt)$ are the final tumor cell number at the end of radiation. And s is the tumor size. r_1, r_2, r_3, f_1, f_2 and f_3 are the three radii and strengths of the one-step three fractions. Also in the Table-2 we presented the $N(t+dt)$ in the case one-step one fraction, one-step with two fractions and one-step with three fractions for the explain that in the case one-step with three fractions response to radiation therapy is better than cases of (one-step, one fraction & one-step, two fractions).

s	n_0	r_1	f_1	r_2	f_2	r_3	f_3	$N_1 \times 10$	$N_2 \times 10$	$N_3 \times 10$
1	1591549	2.140695	5.455447	3.113118	2.579578	3.521225	2.016288	1.9204	0.4182	0.16676
2	397887.4	3.0274	2.727724	5.339606	0.876842	5.866417	0.726431	5.3490	2.4214	1.7353
3	176838.8	3.707793	1.818482	7.945889	0.395963	8.464817	0.348903	7.1475	4.1267	3.5306
4	99471.84	4.28139	1.363862	10.85839	0.212036	11.32512	0.194919	8.0985	5.2804	**4.8486**
5	63661.98	4.78674	1.091089	13.96681	0.128158	14.38081	0.120885	8.6486	6.0735	**5.7646**
6	44209.71	5.243611	0.909241	17.20539	0.084452	17.57601	0.080928	8.9924	6.6438	6.4175
7	32480.6	5.663747	0.77935	20.53785	0.059269	20.87415	0.057375	9.2207	7.0714	6.9006
8	24867.96	6.0548	0.681931	23.94278	0.04361	24.25184	0.042506	9.3798	7.4031	7.2706
9	19648.76	6.422085	0.606161	27.40649	0.033284	27.69362	0.032597	9.4948	7.6676	7.5624
10	15915.49	6.769472	0.545545	30.91958	0.02615	31.18873	0.025701	9.5806	7.8833	7.7981

***Table-2**: optimization values in (one-step one fraction, one-step with two fractions and one-step with three fractions)*

In similar logic, the listed values in Table-2 again conform the validity and superiority of our model. The last three columns that contain the total number of remaining tumor cell N_1, N_2 and N_3 show more clearly the effective reducing in total number of tumor cells specially after second and third fraction applied with first fraction in the same time. Also, in similar result to previous model. Other parameters show logical sequence that comfortable with all remaining results. For example, the model suppose that r_3 larger than r_2 which is larger than r_1, that is clearly verified in columns 3, 5 &7. The similar logic for relation between r_1 with f_1 and r_2 with f_2 and r_3 with f_3 values. However, the most interesting results is about the decreasing steps of N_2 and N_3 with size of tumor (s). The table shows that at high values of S, the values of N_2, almost become very close to N_3 values. This is another result controlled by the constraints condition for limiting the total dose received by patient which is reported in equation (5)

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The comparison between the final tumor cell density in the cases (one –step with one fraction, one-step with two-fractions and one-step with three fractions):

Figure 3 shows the plotted comparison between of $N(t+dt)$ in the cases (one-step with one fraction, one-step with two fractions and one-step with three fractions) this leading to the one-step with three fractions is most effect of XRT.

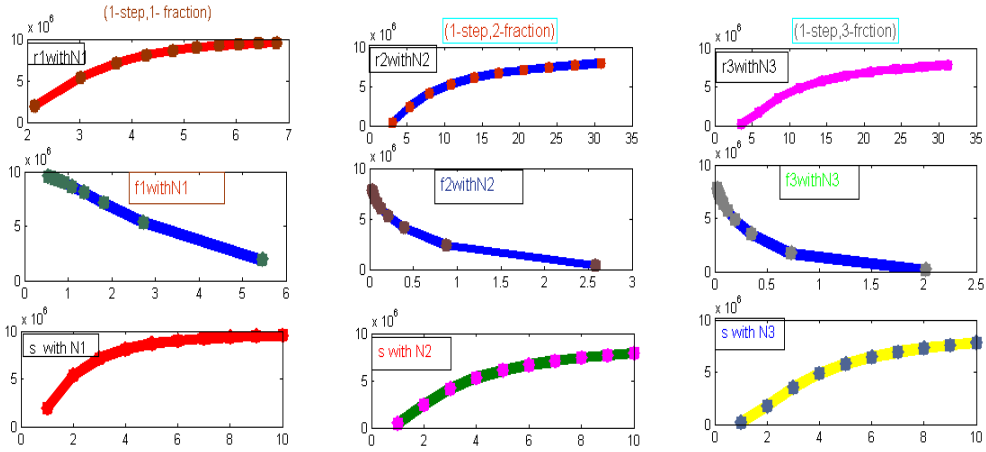

Figure-3 *The comparison between the final tumor cell density in the cases (one–step with one fraction, one-step with two fractions and one-step with three fractions).*

Conclusions:

We have successfully studied the capability of the mathematical model in optimization brain tumor radiation treatment. We have corrected some previously calculated values and extended the range of calculations up to 10 values. In addition, we studied the dependency of results on the initial tumor cell density and found that the behavior is similar but not equivalent. We have successively introduced a new effective mathematical model for tumor treatment optimization. The obtained results of the total number of remaining tumor cell N1, N2 and N3 show more clearly the effective reducing in total number of tumor cells specially after second and third fraction applied with first.

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