CLINICAL STUDY - PATIENT STUDY

Modeling the effects of resection, radiation and chemotherapy in glioblastoma

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Abstract The standard treatment for newly diagnosed glioblastoma multiforme is surgical resection followed by radiotherapy and chemotherapy. Most studies on these treatments are retrospective clinical data analysis. To integrate these studies, a mathematical model is developed. The model predicts the survival time of patients who undergo resection, radiation, and chemotherapy with different protocols.

Keywords Glioblastoma · Resection · Radiation · Chemotherapy · Mathematical modeling

Introduction

Glioblastoma multiforme, a type of glioma, is the most aggressive of brain tumors; life expectancy from the time when it is diagnosed is typically 1 year. The current treatment is surgical resection followed by radiotherapy and chemotherapy. There are only a few consistent clinical studies which compare life expectancy of patients who underwent different resections (residual or complete) and different protocols of radiotherapy and chemotherapy. Among the most consistent studies are those of Albert et al. [1], Lacroix et al. [2], and Stupp et al. [3].

A detailed study of 135 patient data by Albert et al. [1] showed that patients who underwent subtotal surgery postoperatively had 6.6 times higher risk of death in comparison to patients who underwent complete resection, and patients treated by radiotherapy had 0.26 times lower risk of death in comparison to patients who were not treated with radiation. Lacroix et al. [2] analyzed 416 patients data and showed that a significant survival advantage was associated with resection of 98% or more of the tumor volume, and generally, gross total tumor resection led to longer life expectancy.

The efficacy of chemotherapy has been steadily improving with the development of new cancer drugs. Stupp et al. [3] analyzed the data of 573 patients and showed that the median survival time (MST) was 14.6 months for patients who underwent radiotherapy plus chemotherapy with temozolomide, but only 12.1 months for those with radiotherapy alone.

All these clinical data analysis are retrospective. They have value for reference, but they are likely quite biased in nature, and cannot give any perspective prediction. In the present paper we develop a mathematical model which integrates the treatment of patients by surgery, radiotherapy and chemotherapy. The model parameters are chosen so that the simulation results fit with the patient data analysis reported in [1–3]. The purpose of the model is to suggest a combination of treatment protocols that can give patients maximal survival time.

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Materials and methods

The mathematical model describes a spherical tumor regrowing after surgical resection. The tumor contains tumor cells (x) and necrotic cells (y). The quantity x represents the number density of tumor cells (i.e., the number of tumor cells in 1 mm^3); the quantity y represents the number density of necrotic cells. It is assumed that the number density of cells in tumor is a constant [4], that is, $x + y$ = number of cells in 1 mm^3, which is 10^6 [5]. New tumor cells are produced by proliferation, and they transit to necrotic cells by lysis. The mathematical model is described in the appendix.

Tumor cells that are near to the expanding surface of the solid tumor receive more nutrients and proliferate faster than tumor cells that are near the core of the tumor. Indeed, as mentioned in Rew and Wilso [6], the proportion of proliferating cells varies considerably from the outer region to the inner region of the tumor. For simplicity we assume that the proliferation rate, λ, is constant. According to [7] and [4], $\lambda = 2 \times 10^{-2} \, h^{-1}$. We shall also assume the rate of cells becoming necrotic, δ, is constant. We take δ to be slightly smaller than λ, namely, $\delta = 1.89 \times 10^{-2} \, h^{-1}$. According to [8], necrotic cells are removed on the average of 2–3 days. We shall take the removal rate μ to be 1/72 h^{-1}.

According to Lacroix et al. [2], the median preoperative tumor volume was 34 cm^3. If we assume that the tumor is spherical, then this corresponds to radius at resection time of $R_0 = 20$ mm. In the partial resection case, a smaller ball of radius R_* is removed, and residual tumor cells remain in the region between the two concentric balls. After surgery the ball of radius R_* fills with cerebro-spinal fluid, and the residual tumor begins to grow outward, as illustrated schematically in Fig. 1. From the rate λ of the tumor cell proliferation and the reported life expectancy, we estimate that the patient dies at the time when the tumor radius reaches 40 mm; this is confirmed in [2].

According to Stupp et al. [3], within 6 weeks after the histologic diagnosis of glioblastoma, patients were assigned to receive standard focal radiotherapy alone or standard radiotherapy plus concomitant daily temozolomide followed by adjuvant temozolomide, whether or not they had previously undergone debulking surgery. The standard radiotherapy consists of fractionated focal irradiation at a dose of 2 Gy per fraction given daily, 5 days per week (Monday through Friday), over a period of 6 weeks, for a total dose of 60 Gy. Accordingly, we take the radiation activity function to be

$$\rho(t) = \begin{cases} 1 & \text{if } 6 \leq t \leq 12, \\ 0 & \text{otherwise.} \end{cases}$$
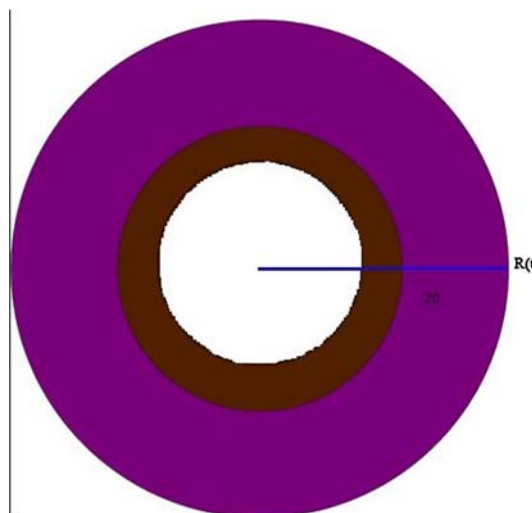

Fig. 1 The inner ball is the surgically removed part of the tumor with radius R_*, the middle concentric shell is the residual tumor, and the outer shell is the regrowth part of the tumor

We assume that the radiation kills tumor cells at a rate A, so that the death rate by radiotherapy is $A\rho(t)$. For simplicity, we lump together the cells killed by radiation with the necrotic cells.

Chemotherapy consists of temozolomide at a dose of 75 mg per square meter of body surface per day, given 7 days a week from the first day of radiation until the last day of radiation. Then, after a 4-week break, chemotherapy continues, and patients receive a double dose of temozolomide daily for 28 days. After the end of this period, another cycle of temozolomide dosing is administered at $\frac{8}{3}$ level of the original dose, that is at 200 mg per square meter. We therefore introduce the temozolomide dosing function as

$$\tau(t) = \begin{cases} 1 & \text{if } 6 \leq t \leq 12, \\ 2 & \text{if } 16 \leq t \leq 20, \\ \frac{8}{3} & \text{if } 20 \leq t \leq 40, \\ 0 & \text{otherwise.} \end{cases}$$

If chemotherapy with 75 mg dose kills tumor cells at a rate B, then the killing rate by chemotherapy treatment is $B\tau(t)$.

Albert et al. [1] provide the MST for various age groups of patients. For definiteness we consider the group of patients between the age of 20 and 39. This group is further divided in [1] into three subgroups:

(a) Patients had complete resection (no residual tumor) and undergone radiotherapy; their MST was 92 weeks.

(b) Patients had partial resection (with residual tumor) and undergone radiotherapy; their MST was 46 weeks.

(c) Patients had partial resection (with residual tumor) without radiotherapy; their MST was 15 weeks.

A recent study by Stummer et al. [9] of 243 patients compares the MST of patients who underwent complete resection versus subtotal (partial) resection: both groups received radiation therapy. Repeat surgery and/or initiation of chemotherapy were applied to some patients after tumor progression. The MST was 71 weeks for the first group and 49 weeks for the second group. By contrast with the data in Albert et al quoted above (in (a) and (b)) the study in [9] lumps together all ages ≤60; these data may indicate that older patients may not do as well as younger patients undergoing complete resection. Studies on the effect of different modes of radiation (without distinguishing between complete and subtotal resection) are reported in Werner-Wasik et al. [10], Chang et al. [11] and Sultanem et al. [12], see also [13].

It is commonly believed that by the time glioblastoma is diagnosed, some cancer cells have already migrated from the main body of the tumor. Thus, even when resection is complete there are residual tumor cells in the vicinity of the tumor. Our model accounts for these cells by defining complete resection to be the removal of not all the ball of radius R_0, but of a slightly smaller ball of radius $R_0 - \varepsilon$; we take $\varepsilon = 5$ μm, half the size of a typical cell, thereby making the implicit assumption that glioma cells in the thin shell $R_0 - \varepsilon \leq r \leq R_0$ are in "migration mode" from the solid tumor.

In the next section we use data from [1–3] to determine the parameter R_* corresponding to partial resection and the parameters A and ε.

The data analysis by Stupp et al. [3] with regard to the efficacy of chemotherapy dose not distinguish between subtotal resection and complete resection. It should be pointed out that surgical resectability is not comparable from one tumor brain case to another, but for the purpose of our analysis we lump all glioblastoma cases together. We shall arbitrarily assume that the data correspond to subtotal resection. Hence, the mean survival time for patients with subtotal resection undergoing radiotherapy and chemotherapy is 60 weeks. This information will be used to estimate the killing rate B. If more specific information than in [3] will become available in the future, we shall be able to make a better choice of B, but this should not affect our results significantly.

Our model can adapted as new radiation, chemotherapy and biotherapy are introduced. For a new radiation, or new chemotherapy, we only need to replace the radiation activity function $\rho(t)$ or drug dosing function $\tau(t)$ by the new radiation activity function or new drug dosing function. For a biotherapy, we need to add a new biotherapy killing term in our model Eqs. 6 and 7.

Results

In all the numerical simulations discussed below we assume that the initial density of tumor cells in the shell $R_* \leq r \leq R_0$, or $R_* - \varepsilon \leq r \leq R_0$, is nine times higher than the density of the necrotic cells.

Figure 2 shows the growth of the tumor radius $R(t)$ without any therapy if $R_* = 18$ mm (partial resection). The time T at which $R(T)$ becomes 40 mm, that is the survival time, is approximately 15 weeks, as reported for the subgroup (c) above. This agreement validates our choice of R_*. We note that the initial growth of the tumor is extremely fast. Thus although our simulation begins with tumor radius of 18 mm, the radius very quickly arises to over 20 mm. The same holds for the subsequent figures.

Figure 3 shows the growth of the tumor radius $R(t)$ if we take in our model the radiation killing rate $A = 1.0$ and partial resection $R_* = 18$ mm. We see that $R(T) = 40$ mm at approximately $T = 46$, as reported for the subgroup (b). This validates the choice of the parameter value $A = 1.0$. Note that the tumor radius begins growing until the start of radiation. Radiation treatment decreases the radius, but as soon as radiation is stopped, the tumor begins to grow again.
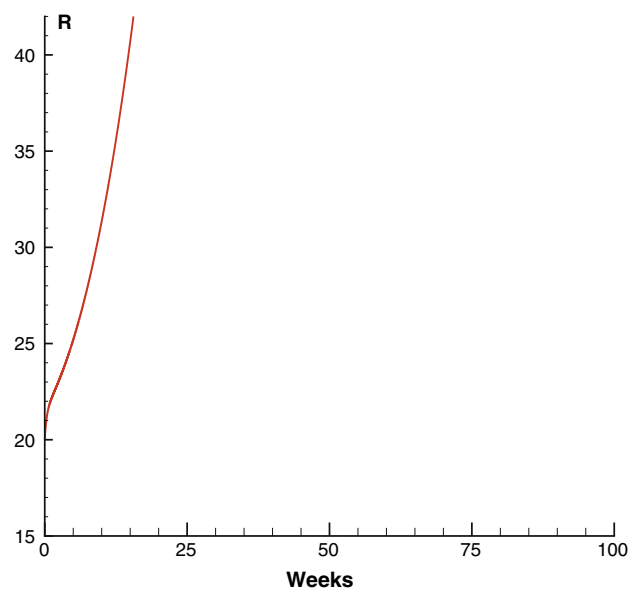

Fig. 2 Partial resection $R_* = 18$ mm: residual tumor regrowth without radiotherapy and chemotherapy
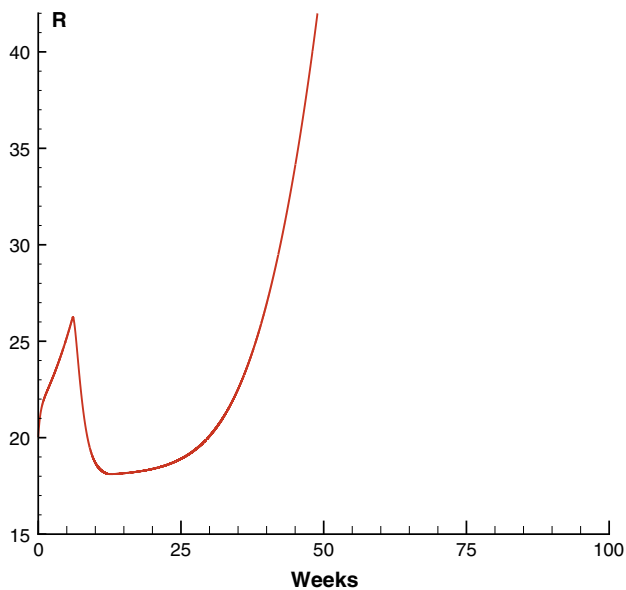
Fig. 3 Partial resection $R_* = 18$ mm: residual tumor regrowth with radiotherapy only, at regular strength ($A = 1.0$)
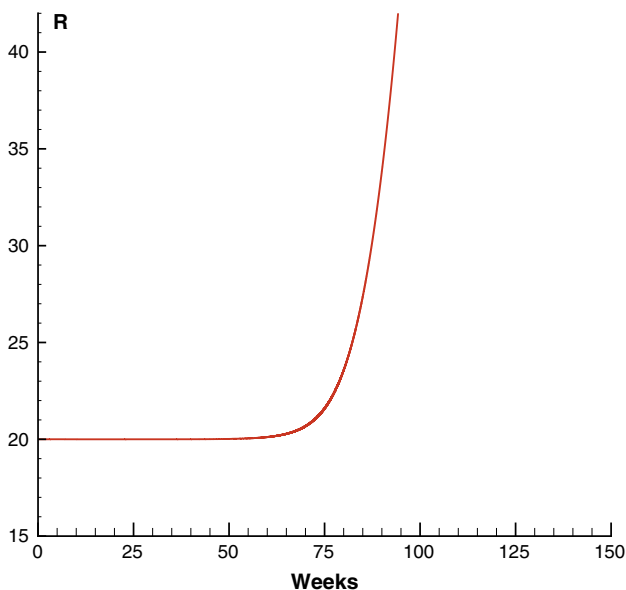

Fig. 4 Complete resection with radiotherapy only, at regular strength ($A = 1.0$)

Figure 4 shows the growth of $R(t)$ after the complete resection (that is, $R(0) = R_0 - \varepsilon$) and radiotherapy. We see that $R(T) = 40$ mm at $T = 92$ weeks which is in agreement with the MST reported for the subgroup (a). This agreement validates the choice of the parameter ε.

We next use the mathematical model to explore the effect of different radiation protocols and resections.

The standard radiation is given for a period of 6 weeks. In Fig. 5 we see the result of giving the same total amount
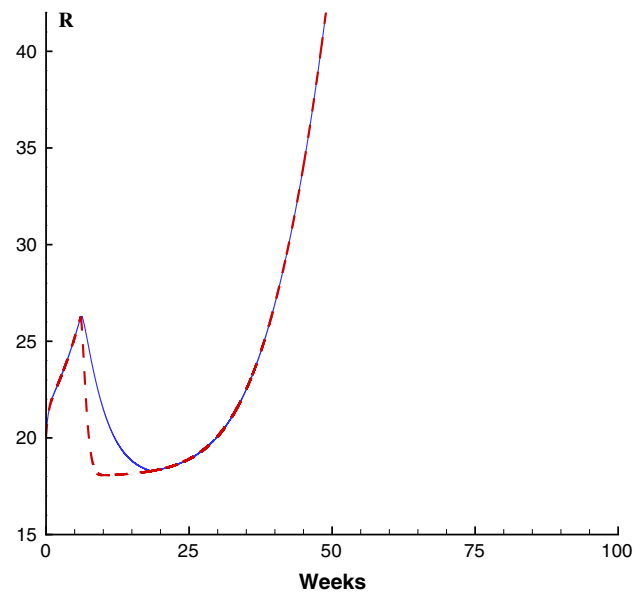

Fig. 5 Radiation with $R_* = 18$ mm. Protocol 1 (dashed line): radiotherapy only, at double strength, half time. Protocol 2 (solid line): radiotherapy only, at half strength, double time

60 Gy of radiation within 3 weeks instead of 6 weeks, and of giving the same total amount distributed over 12 weeks; both profiles are computed for the residual case. The survival time increases in the first case from 46 weeks to 50 weeks, and in the second case from 46 weeks to 49.5 weeks. Thus both procedures are somewhat advantageous in comparison with the standard procedure of 6 weeks. It should be pointed out that the use of 60 Gy is actually radiobiologically impertinent as it ignores overriding issues of normal cerebral toxicity and radioresistance, but is interesting to consider in the abstract.

There have been recent studies aimed at possible advantages of shortening the hypofractionated radiotherapy treatment from 6 weeks to 4 weeks (in 20 fractions) with $2\frac{1}{2}$ Gy or 3 Gy per day [11] [12]. These studies do not distinguish between complete or subtotal resection, they indicate low level of toxic side effects, but no clear advantage in increasing the MST. Our model is based on a different set of patients, all who undergone subtotal resection and of age between 20 and 39.

Our model can be extended to explore the effect of chemotherapy. As in the case of radiotherapy, chemotherapy kills tumor cells at some rate B. Figure 6 profiles $R(t)$ in the residual tumor case. By choosing $B = 0.03$ we achieve survival time of 60 weeks as given in Stupp et al. [3]. We see that chemotherapy has very little benefits compared to radiotherapy (i.e., $B = 0.03$ is much smaller that $A = 1.0$).

In Table 1 we have collected the model parameters and their numerical values. These parameter values can adjusted as more data become available.
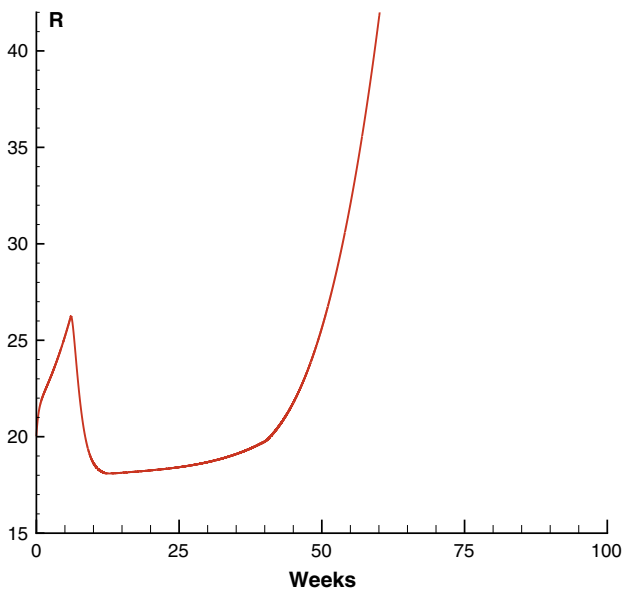
Fig. 6 Residual tumor, $R_* = 18$ mm, regrowth with radiotherapy at regular strength ($A = 1.0$) and chemotherapy at strength $B = 0.03$
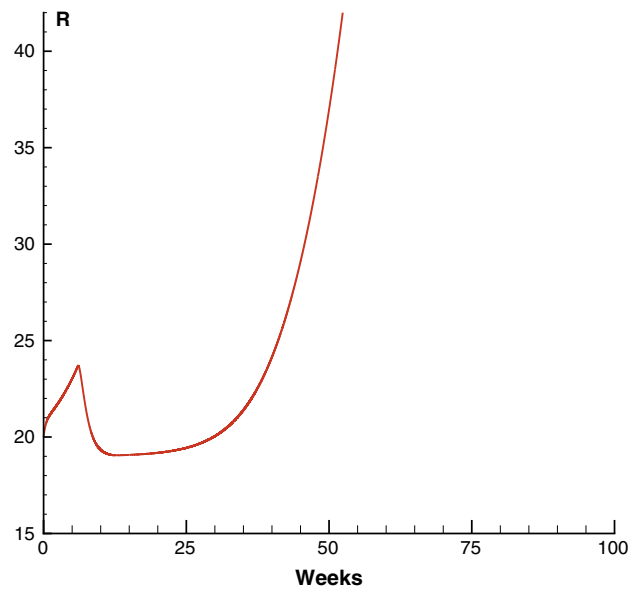

Fig. 7 Residual tumor, $R_* = 19$ mm, regrowth with radiotherapy at regular strength ($A = 1.0$) but no chemotherapy

Discussion

We have developed a mathematical model of glioblastoma treatment by radiotherapy and chemotherapy, which also incorporates the size of the tumor which is removed by surgery. The model can be used to explore the benefits of different protocols of treatment. In particular we have shown that somewhat greater benefits incur if the same total amount of radiation is given over a period of 12 weeks instead of over 6 weeks.

We have also shown that the benefits of chemotherapy are very little for patients already undergoing radiotherapy.

Subtotal resection occurs either by design (if the tumor borders a critically essential part of the brain) or because of failure of the surgeon to determine the precise boundary of the tumor. We have estimated the average diameter for the residual tumor at $R_* = 18$ mm, when the tumor size is $R_0 = 20$ mm. Our model can predict the benefits that will occur if the resection will be more complete, or if the radiation dose is increased. For example, Fig. 7 shows that resection with $R_* = 19$ mm followed by radiotherapy yields survival time of 52 weeks as compared to 46 weeks when $R_* = 18$ mm, and 92 weeks when resection is

complete. Figure 8 shows, in the case of residual resection ($R_* = 18$ mm), that if in the standard radiation treatment the amount of dose is doubled, then the MST will increase from 46 weeks to 80 weeks. But this of course does not take into account toxic side effects due to increased radiation.

If instead of using the data of the group of patients between the age of 20 and 39 in Albert et al. [1] we use the patients data of different age groups in [1] or the patients data of Stummer et al. [9] for the age group ≤60, we obtain slightly different parameters A, B, ε, but this does not affect the qualitative conclusions as described in Figs. 2–8.

The present paper is based on data from [1–3]. A recent article by Gorlia et al. [14] provides similar data which agree with those of [1–3] in the case of patients who undergone partial resection with radiotherapy and with or without chemotherapy. However it gives a shorter MST for patients who undergone complete resection with radiotherapy. This inconsistency may be the result of how one interprets complete resection. Our model parameters can be adjusted to the data in [14], but the qualitative results described in Figs. 2–8 will not be affected.

We conclude with the interesting observation common to all the figures shown above: the tumor appears to be in

Table 1 Parameters and their values

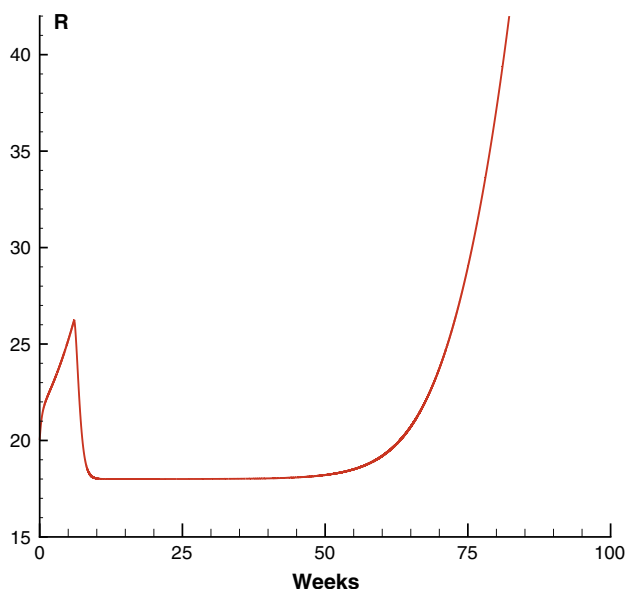| Parameters	Description	Numerical values	dimensions
λ	Proliferation rate of tumor cells	2×10^{-2}	$1/h$
δ	tumor cell lysis rate	1.89×10^{-2}	$1/h$
μ	Removal rate of necrotic cells	$\frac{1}{72}$	$1/h$
A	Radiation killing rate	1.0	$1/h$
B	Temozolomide killing rate	0.03	$1/h$

Fig. 8 Radiation protocol 3: $R_* = 18$ mm with radiotherapy only as in standard radiation treatment, but with double strength dosage

steady state with nearly the same radius until just a few weeks before the patient dies; during these last few weeks the radius increases exponentially fast.

Appendix

Consider a radially symmetrical tumor and denote by r the distance from a point to the origin. We denote the boundary of the tumor by $r = R(t)$. Set

x = number density of tumor stem cells,

y = number density of dead cells.

The proliferation and removal of cells cause a movement of cells within the tumor, with a convection term, for tumor cells x, in the form $\frac{1}{r}\frac{\partial}{\partial r}[r^2u(r,t)x(r,t)]$, where $u(r,t)$ is the radial velocity; $u(R_*,t) = 0$ since the tumor does not grow inward. By mass conservation law,

$$\frac{\partial x(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2u(r,t)x(r,t)) = \lambda x(r,t) - \delta x(r,t), \quad (1)$$

Similarly,

$$\frac{\partial y(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2u(r,t)y(r,t)) = \delta x(r,t) - \mu y(r,t). \quad (2)$$

We assume that the total density of tumor and necrotic cells is constant through the tumor, that is, $x(r,t) + y(r,t) = \text{const} = \theta$, and $\theta = 10^6/\text{mm}^3$ [5]. By adding

Eqs. (1) and (2) together, we obtain an equation for the radial velocity:

$$\frac{\theta}{r^2}\left(\frac{\partial}{\partial r}r^2u\right) = (\lambda + \mu)x(r,t) - \mu\theta. \quad (3)$$

The tumor radius evolves according to

$$\frac{dR}{dt} = u(R(t),t). \quad (4)$$

We assume that,

$$x(r,0) = \frac{9}{10}\theta, \text{ for } R_* \leq r \leq R_0, \quad (5)$$

that is, initially 90% of cells are tumor cells, and 10% are necrotic cells.

We need to solve Eqs. (1), (3) in $R_* \leq r \leq R(t)$ with the initial condition (5) and with the tumor growth condition (4).

The above model does not include radiotherapy and chemotherapy. If the standard radiotherapy is administered over a period of 6 weeks during the time period $6 \leq t \leq 12$ and the temozolomide is given for 40 weeks, Eqs. (1) and (2) are replaced by

$$\frac{\partial x(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2u(r,t)x(r,t))$$
$$= \lambda x(r,t) - \delta x(r,t) - A\rho(t)x(r,t) - B\tau(t)x(r,t), \quad (6)$$

$$\frac{\partial y(r,t)}{\partial t} + \frac{1}{r^2}\frac{\partial}{\partial r}(r^2u(r,t)y(r,t))$$
$$= \delta x(r,t) + A\rho(t)x(r,t) + B\tau(t)x(r,t) - \mu y(r,t). \quad (7)$$

By adding the two equations, we obtain the same Eq. (3), as before, for the velocity $u(r,t)$.

Figures (1)–(7) are based on solving Eqs. (6) and (3) in $R_* \leq r \leq R(t)$ together with (4) and (5).

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