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Mathematical modeling of ovarian cancer treatments: Sequencing of surgery and chemotherapy

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Abstract

Ovarian cancer has long been one of the most common forms of cancer in women. The main treatment for ovarian cancer comprises a combination of surgery and chemotherapy. In an effort to improve treatment strategies, a variety of mathematical models have been developed in the literature. In this paper, we consider a simple mathematical model that incorporates tumor growth as well as the effects of chemotherapeutic and surgical treatments in ovarian cancer. We consider several growth models and combine them with different cell-kill hypotheses. Surgery is assumed to eliminate a fixed fraction of tumor cells instantaneously. We discuss how different models predict the optimal sequencing of chemotherapeutic and surgical treatments. This work has been carried out in the context of ovarian cancer; however, the results may also be useful for other kind of cancers.

Keywords: Mathematical modeling; Tumor growth; Ovarian cancer

1. Introduction

Ovarian cancer is a malignant growth that begins in the ovaries. It can be divided into three broad subgroups: epithelial, stromal, and germ cell tumors. Epithelial ovarian cancer is the most common disease and develops from tissue on the ovarian surface. Detecting ovarian cancer is, in general, difficult, because of the lack of effective screening tests. If the disease is discovered when confined to the ovaries, surgery alone is curative in more than 90% of patients; however, in most patients, diagnosis only occurs after dissemination beyond the ovaries. In these cases, a combined treatment of surgery and chemotherapy is necessary.

One of the most important prognostic factors in the treatment of advanced ovarian cancer is the amount of residual tumor after the initial surgery (Griffiths, 1975; Hacker et al., 1983; Delgado et al., 1984; Bertelsen, 1990; Hoskins et al., 1994; Bristow et al., 2002). Patients in whom the diameter of the remaining tumor is no more than 1–2 cm tend to have longer survival times (Hoskins et al., 1994). Progression-free survival (the length of time from start of treatment to disease progression) and overall survival (the length of life after starting treatment) are improved in all patients who are subsequently treated with chemotherapy; however, the impact is most pronounced in those patients who are optimally debulked (Markman et al., 2001; Muggia et al., 2000; Mutch, 2002; Agarwal and Kaye, 2003; Rose et al., 2004).

Chemotherapeutic drugs usually destroy cancer cells by preventing them from growing and dividing rapidly; unfortunately, those drugs also target normal cells. The choice of chemotherapies, dosage, and timing are determined by many factors including patient's response and the stage of the ovarian cancer. Standard combination chemotherapy consists of drugs that contain platinum agents such as cisplatin and carboplatin, and taxane compounds such as paclitaxel and cyclophosphamide. Recent studies have addressed modifications of the

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chemotherapy regimen, see, for example, Hoskins et al. (2000) and the references therein.

Although, there have been a wide variety of studies carried out on ovarian cancer, the answers to some key questions related to the optimal sequencing and scheduling of chemotherapy and surgery are far from resolved. In a clinical setting, it has been a long held belief that the optimal therapeutic strategy is to maximally debulk a cancerous tumor followed by chemotherapy. Interval debulking is also deemed appropriate if the initial surgery is sub-optimal. However, in recent years, there has been a shift in opinion to up-front neo-adjuvant chemotherapy (NACT), followed by surgery and then more chemotherapy (Jacob et al., 1991; Surwit et al., 1996; Vergote et al., 1998; Schwartz et al., 1999; Kayikcioglu et al., 2001; Kuhn et al., 2001; Mazzeo et al., 2003; Steed et al., in press). There is no clear evidence to suggest that this should be the preferred approach and, in fact, the factors driving this change are in part pragmatic (lack of availability of surgery time) and in part clinical (easier to perform surgery if the diseased tumor bulk is reduced). However, it is far from clear if this change in sequence is better or worse in terms of patient outcome. There is currently a large multicenter randomized clinical trial (EORTC 55971) addressing this question but the data will not be available in the near future. Therefore, the development of mathematical models to address this question would appear to be very appropriate and timely.

There have been a wide range of mathematical models on cancer and tumor growth; however, only a few investigations have been particularly concerned with ovarian cancer. Recently, Panetta (1997) presented a mathematical model and used it to study breast and ovarian cancer treatment with paclitaxel. Using this mathematical model (Panetta, 1997; Webb, 1992; Panetta and Adam, 1995), he discussed how varying the treatment period, drug infusion time, the dose strength, and proliferating fraction of the cancer mass affect the outcome of the treatment. Montalenti et al. (1998) simulated cancer-cell kinetics after drug treatment (in particular, the effects of cisplatin on ovarian carcinomas). Recently, Marcu et al. (2005) also studied the biological effects of cisplatin and simulated the consequence of cisplatin resistance on tumor control.

Much of the experimental data that exist has been modeled using purely time-dependent growth laws based on either exponential or Gompertzian growth. In the simplest approach, tumor growth is assumed to be exponential; however, these models are characterized by the property of unbounded growth (there is no upper limit). Although exponential growth serves as an appropriate model for the early stages of tumor growth, it is generally the case that the doubling time of a tumor begins to increase as the tumor grows larger. Gompertzian growth takes this into account, with tumor size a function of the time, initial size N_0, limiting size N_∞, and growth rate β (Laird, 1964; Norton et al., 1976; Norton, 1988; Retsky et al., 1990). Other most commonly used growth models are logistic growth, generalized logistic growth (Heitjan, 1991), and power law growth (West et al., 2001; Guiot et al., 2003; Retsky, 2004); these are discussed in the next section. On the other hand, several approaches have been developed for modeling chemotherapeutic induced cell-kill. One of the original assumptions, referred to as the log-kill hypothesis, is that cell-kill by many drugs is proportional to the tumor population (Skipper et al., 1964). This implies that smaller tumors are more easily eradicated with drugs than larger tumors. Later, Norton and Simon (1977, 1986) proposed that the cell-kill is proportional to the growth rate (e.g., exponential, logistic or Gompertz) of the tumor. A third hypothesis notes that some chemotherapeutic drugs must be metabolized by an enzyme before being activated. This reaction is saturable due to a fixed amount of enzyme. Thus, Holford and Sheiner (1981) developed the so-called E_{max} model which assumes that the cell-kill is proportional to a saturable function of mass. Recently, Fister and Panetta (2003) used optimal control techniques to study these three cell-kill models. They showed that there are qualitatively different treatment schemes for each model, in particular, the log-kill model requires less drug compared to the Norton–Simon model to reduce the cancer an equivalent amount over the same treatment interval.

When drugs are given in combination, determining the effects of each drug can be difficult. However, some of the chemotherapeutic drugs are given as a single agent, and thus, to avoid difficulties with drug combinations and to reduce the number of assumptions and parameters in the model, we only consider the effects of a single drug agent. On the other hand, some of the drugs interfere with cell division processes (G_0, a period where cells exist in a quiescent state, G_1, the first growth phase, S, during which the DNA is replicated, G_2, the second growth phase, and M phase or mitosis). These cell-cycle specific drugs tend to be very schedule dependent, because the only way to increase the total cell kill is by extending the duration of exposure, not by increasing the dose. Hence, it is important to consider different phases in the mathematical model, especially the active (proliferating) phase and resting (quiescent) phase (Panetta, 1997). Our primary aim is to develop a simple mathematical model that incorporates tumor growth as well as the effects of chemotherapeutic and surgical treatments and to study the optimal sequencing of these modes of treatments. Thus, we study a non-cell-cycle phase specific drug and consider only one population of tumor cells in the mathematical modeling. The generalization of the model to a two compartment model (in order to take into account proliferating and quiescent phases) is discussed in the conclusion.

2. Mathematical model

A number of mathematical models for tumor growth have been proposed in the past to describe tumor growth

kinetics. The more popular models are based on exponential (generalized) logistic, and Gompertzian growth laws. The justification for these models mainly depends on how well they fit the survival curves of the particular tumor system under consideration. The general form of the growth model can be written as

$$\frac{dN}{dt} = f(N) \quad \text{with } N(0) = N_0, \tag{1}$$

where $f(N)$ describes the tumor cell growth dynamics. For exponential growth, the simplest possible growth, $f(N) = kN$, where k is the proliferation rate. Exponential growth is cellular division with a constant dividing time. The Gompertz model is a modification of exponential growth, with the addition of a decreasing growth rate over time. This decelerated growth causes the cancer to asymptotically approach a limiting size, referred to as its carrying capacity. Another commonly used growth model, which incorporates the assumption of limiting cell number, is the generalized logistic model. We consider a general form for the function $f(N)$,

$$f(N) = \alpha_1 N - \alpha_2 N^{v+1}. \tag{2}$$

Clearly, $\alpha_2 = 0$ is equivalent to exponential growth. With the choice of $\alpha_1 = \beta/v$ and $\alpha_2 = \beta/(vN_\infty^v)$, where N_∞ is the limiting population size of the tumor, we obtain generalized logistic growth ($v > 0$),

$$f(N) = \left(\frac{\beta N}{v}\right)\left[1 - \left(\frac{N}{N_\infty}\right)^v\right]. \tag{3}$$

The case of $v = 1$ is the usual logistic growth. One should also note that for $v \ll 1$, generalized logistic growth reduces to Gompertzian growth, in which $f(N)$ is given by

$$f(N) = -\beta N \ln\frac{N}{N_\infty}. \tag{4}$$

Recently, West et al. (2001) proposed a general model for the ontogenetic growth of living organisms using basic cellular mechanisms. They showed that the same universal exponential curve fits the ontogenetic growth data on mammals, birds, fish, and molloscs, providing masses and growth times for the different organisms are properly rescaled. Guiot et al. (2003) extended this model to the growth of solid malignant tumors and compared it to a variety of data. As pointed out by Retsky (2004), it is generally difficult to prove that tumor growth follows a "universal law". Mathematically, their model is equivalent to $f(N) = aN^p - bN$. Requiring that the limiting size of the tumor is N_∞, we obtain $b = aN_\infty^{p-1}$, thus ($p < 1$):

$$\frac{dN}{dt} = aN^p\left[1 - \left(\frac{N}{N_\infty}\right)^{1-p}\right]. \tag{5}$$

Guiot et al. (2003) used the above growth model with $p = \frac{3}{4}$ to fit the data. One can show that Eq. (5) reduces to Gompertzian growth for p close to one and $a = \beta/(1-p)$.

We now proceed by considering the effects of surgery and chemotherapy. We consider the case of a single, non-cell-cycle specific, drug agent. As discussed earlier, different cell-kill models have been proposed to study the effects of chemotherapy on tumor growth. In the log-kill hypothesis, it is assumed that cell-kill is proportional to tumor population (Skipper et al., 1964). This means that a given dose of chemotherapy kills a fixed fraction of the remaining cells. The Norton and Simon (NS) model (Norton and Simon, 1997, 1986) considers the cell-kill to be proportional to the growth rate. A third popular model is the E_{max} model, where cell-kill is proportional to a saturable function of Michaelis–Menton form Holford and Sheiner (1981). Surgery, on the other hand, is instantaneous and kills a fixed fraction $\exp(-k_s)$ of the tumor cells (Bell and Wien, 2001, 2002), where k_s is related to the fraction of the removed tumor cells (smaller values of k_s correspond to cases where more cells go undetected at the time of surgery). Thus, the number of cells at time t is given by the following differential equation:

$$\frac{dN}{dt} = f(N) - G(t,N) - k_s I(t = t_{surgery})N, \tag{6}$$

where $I(t = t_{surgery})$ is the indicator function; it is one if $t = t_{surgery}$ and zero otherwise. The function $G(t,N)$ describes the pharmacokinetic and pharmacodynamic effects of the drug on the system. In this study, we consider three cell-kill strategies as the following:

$$G(t,N) = \begin{cases} c(t)N & \text{log-kill,} \\ c(t)f(N) & \text{NS model,} \\ c(t)N/(N+\delta) & E_{max} \text{ model.} \end{cases} \tag{7}$$

The function $c(t)$ is proportional to the drug concentration, $c(t) = 0$ implies no drug effect is present and $c(t) > 0$ gives the amount or strength of the drug effect. In general, the function $c(t)$ can take many different forms; one popular choice is the on–off type, where the drug is active or inactive (Panetta, 1997).

3. Results

In this section, we consider different growth models combined with the cell-kill hypothesis given in the previous section, and study the optimal sequencing of chemotherapy and surgery. Thus, we consider two schedules: (a) chemotherapy and surgery (CS), and (b) surgery and chemotherapy (SC), see Fig. 1.

3.1. Log-kill model

We first consider Gompertzian growth and the log-kill model. Thus, the governing ordinary differential equation is given by

$$\frac{dN}{dt} = -\beta N \ln\frac{N}{N_\infty} - c(t)N - k_s I(t = t_{surgery})N. \tag{8}$$

(i) *Sequencing of CS, see Fig.* 1a: For $t < t_0$, where $t_0 = t_{chemo}$, there is no chemotherapy or surgery, so $N(t)$ is simply the solution of the Gompertz growth model. At

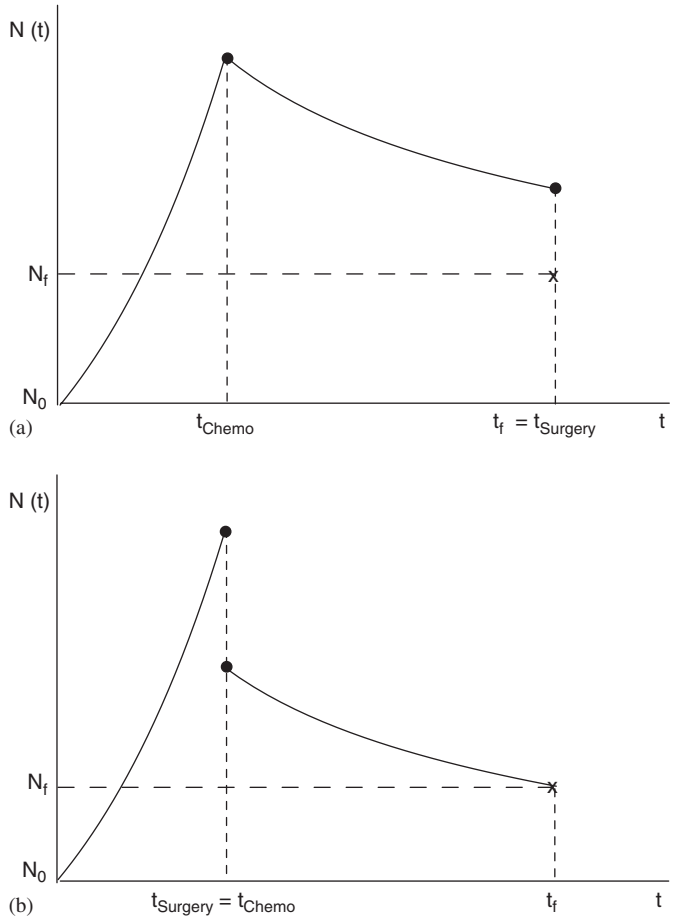

Fig. 1. A schematic diagram of sequences of treatments: (a) chemotherapy and surgery and (b) surgery and chemotherapy.

$t = t_0$, we obtain

$$N(t_0) = N_\infty \left(\frac{N_0}{N_\infty}\right)^{\exp(-\beta t_0)}. \tag{9}$$

For $t_0 < t < t_f$, where chemotherapy is applied, the solution of Eq. (8) for a general $c(t)$, and with the above initial condition at t_0, is

$$N(t) = N_\infty \exp\left\{ e^{-\beta t}\left(c_1(t) + \ln\frac{N_0}{N_\infty}\right)\right\}, \tag{10}$$

where $c_1(t)$ is defined as

$$c_1(t) = -\int_{t_0}^{t} c(t)\, e^{\beta t}\, dt. \tag{11}$$

Assuming that surgery at $t_f = t_{surgery}$ kills $\exp(-k_s)$ of the cells, we obtain

$$\frac{N_{CS}}{N_\infty} = \exp\left[e^{-\beta t_f}\left(c_1(t_f) + \ln\frac{N_0}{N_\infty}\right) - k_s\right]. \tag{12}$$

(ii) *Sequencing of SC, see Fig.* 1b: In this case surgery is performed first, thus after surgery the number of cells at t_0 is given by

$$N(t_0) = N_\infty e^{-k_s}\left(\frac{N_0}{N_\infty}\right)^{\exp(-\beta t_0)}. \tag{13}$$

For $t_0 < t < t_f$, where chemotherapy is given, the solution (at $t = t_f$) of Eq. (8) with the above initial condition is

$$\frac{N_{SC}}{N_\infty} = \exp\left[e^{-\beta t_f}\left(c_1(t_f) + \ln\frac{N_0}{N_\infty} - k_s e^{\beta t_0}\right)\right]. \tag{14}$$

Dividing Eqs. (12) and (14), we obtain

$$\frac{N_{CS}(t_f)}{N_{SC}(t_f)} = \exp\{-k_s(1 - e^{\beta(t_0 - t_f)})\}. \tag{15}$$

This equation indicates that in the Gompertz growth model, and for a general form of the drug concentration function, $N_{CS} < N_{SC}$. This means that sequencing of chemotherapy followed by surgery is a better strategy than sequencing surgery followed by chemotherapy.

For generalized logistic growth model, we can perform similar analytical calculations, assuming that $c(t) = c_0$ (i.e., where the drug concentration remains constant throughout the time of chemotherapy). However, the results are more complicated and we do not present them here although we arrive at the same conclusion of $N_{CS} < N_{SC}$ for these models. Clearly, the exponential growth model predicts $N_{CS} = N_{SC}$.

3.2. Norton and Simon model

For the NS model, in which the cell-kill is proportional to the growth rate, combining Eqs. (7) and (6), we have

$$\frac{dN}{dt} = -\beta N \ln\frac{N}{N_\infty}[1 - c(t)] - k_s I(t = t_{surgery})N. \tag{16}$$

If we follow the same procedure as the log-kill hypothesis, for sequencing of CS we obtain

$$\frac{N_{CS}}{N_\infty} = \exp\left[e^{-\beta t_f + c_2(t)} \ln\frac{N_0}{N_\infty} - k_s\right], \tag{17}$$

where $c_2(t)$ is given by

$$c_2(t) = \beta \int_{t_0}^{t} c(t)\, dt, \tag{18}$$

and for sequencing of SC,

$$\frac{N_{SC}}{N_\infty} = \exp\left[e^{-\beta(t_f - t_0) + c_2(t_f)}\left(e^{-\beta t_0} \ln\frac{N_0}{N_\infty} - k_s\right)\right]. \tag{19}$$

Again, dividing Eqs. (17) and (19) results in

$$\frac{N_{CS}(t_f)}{N_{SC}(t_f)} = \exp\{-k_s(1 - e^{-\beta(t_f - t_0) + c_2(t_f)})\}. \tag{20}$$

This equation implies that $N_{CS} < N_{SC}$ if $\int_{t_0}^{t_f} c(t)\, dt < t_f - t_0$, which again implies that sequencing chemotherapy first followed by surgery is a better strategy. For $c(t) = c_0$, the above condition reduces to $c_0 < 1$. One should note that the strength of chemotherapy should be more than one to be effective (see Eq. (16)); however, as mentioned earlier, chemotherapy is usually given as an on–off type function. For example, a patient with ovarian cancer usually receive 6 cycles of chemotherapy every 21 days (Steed et al., in press), where drug infusion times vary from 1 to 96 h and

doses range from 75 to 300 mg/m^2 (Panetta, 1997). Thus, in a clinical situation, and for a reasonable range of parameters, the condition $\int_{t_0}^{t_f} c(t)\,dt < t_f - t_0$ is usually satisfied.

For the generalized logistic growth model, our analytical calculations (for $c(t) = c_0$) predicted the same results that $N_{CS} \leqslant N_{SC}$ for $c_0 < 1$, where we have equality for exponential growth.

3.3. E_{max} model

We now consider the E_{max} model of Eq. (7), for which

$$\frac{dN}{dt} = f(N) - c(t)\frac{N}{N+\delta} - k_s I(t = t_{surgery})N. \quad (21)$$

In this case, in the absence of an analytical solution for the equation, we performed numerical integration. As might be expected, we obtained different results for the optimal sequence, for all the growth models (including exponential growth), by varying the parameters.

If we consider the doubling time for ovarian cancer cells to be roughly 9.22 days, as given in Panetta (1997), this leads to $\beta \approx 0.075$ (1/day). One can also assume that the total number of tumor cells is about $N_0 \sim 10^{10}$ at detection and the total number of cells at death is about $N_\infty \sim 10^{13}$. Using the above parameters in the numerical integration and applying 6 cycles of chemotherapy every 21 days (as given to ovarian cancer patients), with a reasonable choice of the chemotherapy strength, we find that the E_{max} model also predicts that sequencing of chemotherapy followed by surgery is a better strategy.

4. Discussion and conclusion

Primary cytoreductive surgery followed by platinum-based combination chemotherapy represents the current "standard of care" for patients with advanced ovarian cancer (Griffiths, 1975; Hacker et al., 1983; Delgado et al., 1984; Bertelsen, 1990; Hoskins et al., 1994; Bristow et al., 2002). The rationale for this sequence of care is based on several non-randomized studies that have shown survival is improved in patients with less than 1–2 cm diameter of residual tumor after primary surgery, compared to patients with greater size of residual disease (Markman et al., 2001; Muggia et al., 2000; Mutch, 2002; Agarwal and Kaye, 2003; Rose et al., 2004). Even with improved intraoperative and post-operative care it is not possible, in advanced stage disease, to surgically remove all disease. An alternative to "conventional primary debulking surgery" is neo-adjuvant chemotherapy (NACT) where the sequence of care is initial chemotherapy followed by surgery and then further chemotherapy. One reason is that NACT decreases tumor volume and increases the chances of maximal tumor resection.

Several clinical studies have addressed the sequencing of surgery and chemotherapy (Jacob et al., 1991; Surwit et al., 1996; Vergote et al., 1998; Schwartz et al., 1999; Kayikcioglu et al., 2001; Kuhn et al., 2001; Mazzeo et al., 2003; Steed et al., in press). In an analysis by Surwit et al. (1996) the median survival of 29 patients who underwent primary chemotherapy was 22 months, similar to that of patients who undergo primary surgery. In another retrospective study (Schwartz et al., 1999), progression-free and overall survival were compared between patients treated with NACT followed by interval debulking surgery and those treated by primary cytoreductive surgery; despite the fact that the former group was older and had a poorer performance status, they concluded that while progression-free and overall survival were equivalent in the two groups, quality of life in the latter group was superior. In a recent study, Kayikcioglu et al. (2001) compared NACT and primary surgery in advanced epithelial ovarian carcinoma and reported that patients who received NACT improved more rapidly when the cancer was sensitive to the chemotherapy compared with those who underwent extensive primary cytoreductive surgery. In the NACT patients, a smaller amount of disease was much easier to resect. In other words, NACT patients needed less aggressive surgery. Mazzeo et al. (2003) also report results of NACT in patients with advanced-stage ovarian cancer. They conclude that NACT followed by optimal debulking may be a safe and valuable treatment alternative in patients with primarily unresectable advanced-stage bulky ovarian cancer. Patients with an objective response to chemotherapy or absence of macroscopic residual tumor after surgery have a better outcome. In a very recent study, Steed et al. (in press) also compared progression free survival and overall survival of ovarian cancer patients treated with NACT and surgery to primary surgery and post-operative chemotherapy. According to their results, primary surgery should be considered in all patients; however, NACT may be an alternative in a subset of women with the intent to also perform interval debulking.

Clearly, additional clinical studies are required to evaluate the role of NACT and interval debulking surgery. As mentioned earlier, a large multicenter clinical trial (EORTC 55971) to more accurately address the question of sequencing of therapies is underway, but there are numerous challenges and it will be many years before the results of this trial are available. Thus, a validated mathematical model may provide guidance as to the optimal design of clinical trials and hopefully lead to improvement in initial treatment planning.

In this paper, we have presented a simple mathematical model to study the effects of sequencing surgical and chemotherapeutic treatments in ovarian cancer. Our primary aim was to develop a simple model that incorporates the tumor growth kinetics as well as the effects of the treatments. We used Gompertzian and generalized Logistic growth models, and combined them with different cell-kill hypotheses. Surgery was assumed to kill $\exp(-k_s)$ of the tumor cells at time of treatment. Our results showed that for both Gompertzian and generalized logistic growth models: (i) Using the log-kill hypothesis,

sequencing of chemotherapy first followed by surgery is always the optimal one. According to the Gompertzian (or logistic) growth model, larger tumors grow much slower than smaller ones. On the other hand, the log-kill hypothesis assumes that the cell-kill is proportional to tumor size, thus larger tumors are more effectively reduced by the drug. So, we can expect that sequencing of CS will be the better strategy. This supports the idea of NACT followed by the surgery. (ii) For the Norton and Simon hypothesis, the cell-kill is proportional to the growth rate (its effect is smaller near the carrying capacity). In this case, the sequencing is dependent on the drug concentration function. If $\int_{t_0}^{t} c(t)\,dt < t_f - t_0$, where less total drugs would need to be administered, sequencing of chemotherapy first followed by surgery is a better strategy. For both hypotheses, the exponential growth model gives identical results for CS or SC. (iii) For the E_{max} hypothesis, different situations can pertain, for all of the growth models, depending on the choice of parameters. If we use some realistic schedules for the chemotherapy, for the range of parameters relevant to ovarian cancer, all three cell-kill hypotheses predict that the sequencing of chemotherapy followed by surgery is a better strategy. Clearly, more detailed studies are necessary to validate this prediction.

Our results also indicate that the effects of chemotherapy are more pronounced for larger k_s, which means that more of the tumor is debulked during surgery. One of the main difficulties in modeling tumor growth and treatment is the estimation of parameters in the mathematical models. The results presented here for a class of simple models are mostly general and independent of a particular choice of parameters, as a result these models may be useful for understanding the effects of sequencing different treatment strategies.

As mentioned in the introduction, some anticancer agents induce cytotoxic effects during specific phases of the cell cycle. These cell cycle specific drugs tend to be very schedule dependent, because the only way to increase the total cell-kill is by extending the duration of exposure, not by increasing the dose. Thus, it is important to consider different phases in the mathematical model. Generalization of our model to two compartment models is straightforward. Although, it does not affect our results on optimal sequencing of surgery and chemotherapy, it is important to consider it in order to determine some treatment strategies such as treatment period and drug infusion time (Panetta, 1997).

In future work we intend to include other effects into the model, in particular the spatial dependence of the cell as well as the details of nutrient supply, oxygen flow and tumor response to the nutrients. Another interesting problem would be to consider the effects of radiotherapy and find the optimal sequencing of multimodal cancer treatments, see, for example, Bell and Wien (2001, 2002). A problem with Gompertzian (or generalized logistic) growth models is that they do not allow for the temporary dormancy of a tumor (Retsky, 2004). A modified Gompertz model with a stochastic growth rate has been developed to allow for a stepwise growth pattern and possibility of dormant phases in breast cancer (Retsky et al., 1990; Heuser et al., 1979; Speer et al., 1984). Including such effects in the mathematical model is another direction we intend to pursue in future work.

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