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Report

Sequencing surgery, radiotherapy and chemotherapy: insights from a mathematical analysis

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Summary

We present results from a mathematical analysis that is aimed at finding the best way to sequence the three traditional cancer treatments: surgery (S), chemotherapy (C), and radiotherapy (R). The mathematical model tracks the temporal evolution of the primary tumor and its associated metastases, and incorporates the primary tumor's effect on the dormancy and growth of the metastases. We show that the SCR schedule (i.e., surgery followed by chemotherapy followed by radiotherapy) achieves a higher cure probability than SRC if the primary tumor is sufficiently large or if the metastatic population is sufficiently large relative to the primary tumor. We also show that a novel schedule, SRCR, which splits the radiotherapy regimen into two disjoint portions, is optimal among all schedules, provided that the patient's dormant metastatic tumors do not become vascularized within about 40 days after surgery.

Introduction

For decades, the main treatment modalities for most solid tumors have been surgery, radiotherapy and chemotherapy. However, for some forms of cancer, a consensus has not been reached for the optimal sequencing of these three modes of treatment; for example, see [1, 2] for candidate sequences in breast cancer. This difficult sequencing decision has become further complicated in recent years as the relationship between angiogenesis and metastasis has been revealed [3–7]. Angiogenesis research has led to a rethinking of the detailed scheduling of chemotherapy [8], and it is conceivable that it should also shed new light on the sequencing decision.

In an attempt to better understand this sequencing decision, we formulate a mathematical model that follows a primary tumor and its secondary metastases during the course of multimodal treatment, and incorporates the primary tumor's effect on the dormancy, vascularization and subsequent growth of the metastases. Under some assumptions on the parameter values, which are expressed in simple biological terms, we compare the cancer cure probabilities of the six permutation schedules (i.e., SCR, CSR, CRS, SRC, RSC, RCS) and derive a novel schedule that is optimal among all feasible strategies.

The model

Model description

The mathematical model is stated in the Appendix and described in detail in a companion paper [9]. Here, we outline the model in nonmathematical terms. Our deterministic model keeps track of the size of the primary tumor and the size and number of distant metastases. The primary tumor grows exponentially, and is affected by all three forms of treatment. Surgery is instantaneous and kills a fixed fraction of cells. Our toxicity constraints assume that radiotherapy and chemotherapy are applied at fixed dose rates for a fixed duration of time. The timing of the three treatments is arbitrary, except that they cannot be given simultaneously. Inserting rest periods in our model is not beneficial, and so we do not consider schedules that have time gaps between treatments. We assume that a given dose of chemotherapy or radiotherapy kills a

fixed fraction of remaining tumor cells. This assumption is consistent with Skipper's [10] 'log cell kill' hypothesis for chemotherapy, and our radiotherapy assumption captures the linear killing term in the linear-quadratic model of radiobiology, which is responsible for the great majority of cell killing under standard fractionation schemes [11]. While radiotherapy kills only cells in the primary tumor, chemotherapy affects both the primary and metastatic tumors (with the same killing rate).

A crucial role in our model is played by a critical tumor size that we refer to as the *vascular threshold*, which is about 10^5 cells [12]. We consider a primary or metastatic tumor to be vascular if it is larger than the vascular threshold, and avascular otherwise. A vascular (primary or metastatic) tumor sheds cells at a rate that is proportional to its size raised to a certain power. Our model allows this power coefficient to take on any value between 0 and 1, where 0 corresponds to a shedding rate that is independent of the tumor size, 1 corresponds to a shedding rate that is proportional to the tumor volume, and the intermediate value of 2/3 [13] is a natural value because the probability of shedding from the tumor surface is linear in the microvessel count [3]. Metastases are the result of a multistage process in which shed cells need to successfully escape, survive in circulation, extravasate, and migrate to a conducive location in the host organ, and where most solitary cells remain dormant and most micrometastases do not continue to grow [4, 5]. We assume that all the requisite steps successfully occur with a fixed small probability, which is incorporated into the proportionality constant of the shedding rate. Hence, each cell that successfully proceeds through these steps initiates a new metastasis, which grows exponentially (at a different rate than the primary tumor) until it reaches the vascular threshold, at which point it lays dormant; this dormancy, which is due to a lack of nutrients, is characterized by a balance between cell division and cell apoptosis and necrosis [7]. A dormant tumor incurs an *angiogenic delay* until it becomes vascularized; note that dormant tumors shrunk by chemotherapy need to regrow to the vascular threshold before returning to a state of dormancy. Following [3, 6, 7], we assume that this angiogenic delay is shorter in the presence of an avascular primary tumor and is longer when the primary tumor is vascular. While this phenomenon is well documented for surgical removal of the primary tumor [3, 7] and for radiotherapy [14], it is not yet known whether this reduction in angiogenic delay also occurs for tumor shrinkage achieved by chemotherapy. Finally, to better mimic a stochastic model and prevent misleading results, we incorporate a threshold that delays the first vascularization of a dormant tumor.

The 'Poisson model', which is commonly employed to calculate the tumor control probability in radiotherapy [15], is used to compute the cancer cure probability. According to this model, a fixed fraction of all (primary and metastatic) tumor cells are clonogenic (i.e., capable of regrowing the tumor), the number of remaining tumor cells at each point in time has a Poisson probability distribution, and a cure is achieved if all clonogenic cells are killed or removed. Because the cancer burden (i.e., total number of cancer cells) is not necessarily minimized at the end of treatment (e.g., cell killing by adjuvant radiotherapy may be less than metastatic growth), we need to find, for any given treatment schedule, the minimum cancer burden throughout the course of treatment. Because the instantaneous cure probabilities are highly dependent over time (since the same tumor cells are involved), we minimize over time rather than integrate over time (which would be appropriate if the instanteous cure probabilities were independent) in Equation (1).

The model begins at the time of presentation, when the clinician observes the size of the primary tumor and the size and number of observable metastases. To estimate the mean amount of subclinical metastases at the time of presentation, we use a dynamic stochastic model in which cells are shed according to a nonhomogeneous Poisson process (at the shedding rate described earlier) and the time for a metastasis to grow (including the angiogenic delay) from a single cell to the detection limit is an exponential random variable.

Assumptions

We now state eight assumptions that are used to enable an exact analysis of our model. The assumptions are stated in precise mathematical terms in the Appendix; Assumption 8 in the Appendix is actually less stringent than Assumption 8 below, but the version in the Appendix is difficult to state in nonmathematical terms.

> *Assumption* 1. At the time of presentation, all subclinical metastases are dormant.
>
> *Assumption* 2. A single metastatic cell cannot grow to the vascular threshold (about 10^5 cells [12]) during the full regimen of radiotherapy (about 40 days).

Assumption 3. Surgery, the full allotment of chemotherapy and the full allotment of radiotherapy are each effective enough to shrink the initial primary tumor to an avascular size (i.e., below 10^5 cells).

Assumption 4. Dormant metastatic tumors treated with the full regimen of chemotherapy do not grow back to their pre-chemotherapy size during the subsequent full regimen of radiotherapy (about 40 days).

Assumption 5. The number of cells shed by the primary tumor during an initial full regimen of radiotherapy is less than or equal to the number of primary cells killed by post-radiotherapy surgery plus chemotherapy.

Assumption 6. The kill rate of radiotherapy is greater than or equal to the kill rate of chemotherapy.

Assumption 7. Metastatic tumors grow at least as fast as the primary tumor.

Assumption 8. If treatment is initiated by surgery and is followed immediately by the full regimen of radiotherapy, then no dormant tumors become vascularized during radiotherapy (about 40 days).

Detailed justification of Assumptions 2–8 can be found in [9]. There may be some very aggressive (and probably incurable) tumors for which Assumptions 4 and 8 do not hold; otherwise, these seven assumptions are not controversial. In contrast, Assumption 1 is made for purposes of analytical tractability, and may not hold in practice. However, Assumption 1 is not too unreasonable (and is unlikely to affect our results), because the angiogenic delay for a dormant metastatic tumor in the presence of a primary tumor is usually several years [16], whereas it takes several months for a metastatic tumor to grow from a single cell to the vascular threshold, and to grow from the vascular threshold to the level of detection [17].

Results

A detailed mathematical analysis of our problem appears in [9]. The results from this analysis are summarized below. We say that schedule A is 'better' (or 'more effective') than schedule B if schedule A achieves a cancer cure probability that is at least as high as Schedule B. Result 1 uses only Assumption 1. *All other results depend upon Assumptions* 2–7, and Result 4 also relies on Assumption 1. Assumption 8 is only required for Result 8.

Estimation of dormant metastases

Our estimate of the expected number of dormant metastases at the time of presentation reveals the following surprising result.

Result 1: If the tumor shedding rate is known, then the expected number of dormant metastases at the time of presentation is independent of the number and size of vascular metastases observed at the time of presentation.

Permutation schedules

Result 2 compares the three CR permutation schedules.

Result 2: Earlier surgery is more effective for CR schedules; that is, SCR is better than CSR, which is better than CRS.

We need to introduce some notation to state Result 3, which compares the three RC permutation schedules. For an arbitrary schedule A, let n_A be the number of offspring from dormant-then-vascular cells that are produced during the radiotherapy portion of the treatment. Let s be the number of cells produced by shedding (i.e., the shed cells plus their progeny) before the primary tumor is shrunk to an avascular size by neoadjuvant radiation.

Result 3: RSC and RCS have the same effectiveness. RSC is better than SRC if $n_{\mathrm{SRC}} - n_{\mathrm{RSC}} > s$.

In Result 4, we compare the two most commonly prescribed multimodal treatments, SRC and SCR. The term 'sufficiently large' in Result 4 represents some complex mathematical inequalities (two inequalities for the primary tumor and two inequalities for the metastases relative to the primary tumor) that can be found in Proposition 5 of [9].

Result 4: If the detectable metastatic population is sufficiently large relative to the primary tumor at the time of presentation, or if the primary tumor is sufficiently large at the time of presentation, then SCR is better than SRC. If there is no detectable metastases and the primary tumor is sufficiently small at the time of presentation, then SRC is better than SCR.

Novel schedules

The detailed mathematical comparison of SCR and SRC in [9] reveals the strengths and weaknesses of each and motivates a novel schedule that combines the best of both schedules. The crux of this comparison is systemic growth during the schedules' radio-

therapy. During SRC's radiotherapy, only existing vascular metastases and newly dormant-then-vascular metastases grow. During SCR's radiotherapy, dormant regrowth also occurs because the dormant tumors were shrunk during the preceding chemotherapy, and so all metastatic tumors grow. Moreover, SRC achieves its minimum cancer burden at the end of treatment, whereas SCR mitigates the effect of its larger systemic growth during radiotherapy by achieving its cancer nadir before administering the full allotment of radiotherapy, when radiotherapy's killing is exactly balanced by metastatic growth.

We propose a schedule, SRCR, that combines the strengths of SCR and SRC. This strategy splits the allotment of radiotherapy into two disjoint pieces, which are positioned before and after chemotherapy. By initiating some adjuvant radiotherapy, SRCR prevents the prenadir regrowth of dormant metastases that hinders SCR. But SRCR mimics SCR, in that the amount of pre-chemotherapy radiation administered is chosen so that chemotherapy begins exactly when the cell killing by pre-chemotherapy radiation is offset by metastatic growth or the radiotherapy toxicity constraint is reached. We construct the novel schedule RSCR, which combines the best of CSR and RSC, in an analogous fashion; that is, the first portion of radiotherapy is administered until either cell killing equals metastatic growth or the radiotherapy toxicity constraint is reached. Just as RSC can outperform SRC (see Result 3), it is also possible for RSCR to be more effective than SRCR.

Results 5 and 6 confirm our conjectures about these novel strategies and Result 7 summarizes the superiority of these schedules.

Result 5: SRCR is better than SCR and SRC.

Result 6: RSCR is better than CSR and RSC.

Result 7: It is always the case that either SRCR or RSCR (or both) is better than all six permutation schedules.

Finally, we impose Assumption 8 to derive a stronger result.

Result 8: If Assumption 8 holds, then SRCR is best among all schedules that administer surgery and the full allotments of radiotherapy and chemotherapy.

Discussion

To our knowledge, this paper represents the first attempt to use a mathematical model to optimize the sequencing of surgery, radiotherapy, and chemotherapy. The model contains 14 parameters, many of which are difficult to measure and exhibit considerable interpatient heterogeneity in a correlated manner [18, 19]. Consequently, we believe it would be extremely difficult if not impossible to perform a traditional validation of this model using clinical data, that is, to estimate the parameter values from at least 14 reliable pieces of data, and compare the model's results to a different set of clinical data. Without a model validation, conclusions from a computational study using this model would not be persuasive. Therefore, we resorted to a purely mathematical approach: we state a number of assumptions in simple biological terms, and then derive (the mathematical proofs appear in [9]) a set of results that rely on these assumptions. Model validation under this approach is much easier and only requires an understanding of the model's structure and clinical support for our eight assumptions. The only drawback to this approach is that our results are qualitative (e.g., SCR has a higher TCP than CSR) rather than quantitative (e.g., SCR has a 20% higher TCP than CSR).

Before discussing our results, we note that our analysis determines optimal sequencing decisions as a function of the 14 parameters in the model. The values of these 14 parameters differ across patients, and these parameter values need to be estimated for each patient based on information collected at the time of presentation. This parameter estimation task is beyond the scope of this paper – except for Result 1, which was required to analyze the optimal sequencing problem – although some progress has been made in this direction ([20, 21] and references therein). We return to this issue later, when we discuss how our results might be operationalized.

Discussion of results

Result 1 states that if the tumor shedding rate is known, then the knowledge of the number and size of clinically detectable metastases at the time of presenta tion does not influence the estimate for the expected number of dormant metastases at the time of presentation. This result suggests that if the tumor shedding rate is known at the time of presentation, then it is the size of the primary tumor – and not the size and number of clinically detectable metastases – that provides the most useful information about the amount of subclinical disease. This counterintuitive result is derived using queueing theory, where shed cells from

the primary tumor correspond to the arrivals to the waiting line, and service times correspond to the time between being shed as a solitary metastatic cell and reaching a clinically detectable size. Result 1 relies on Assumption 1 plus two weak probabilistic assumptions: cells are shed from the primary tumor according to a nonhomogeneous Poisson process (this assumption is satisfied if the shedding behavior of each cell is independent of the other cells), and the service times for each metastasis are independent and identically distributed (but not necessarily exponential, as in Eq. (8)).

However, it is important to note that if the tumor shedding rate is unknown and is to be estimated from the data at the time of presentation, then it would be increasing in the number and size of clinically detectable metastases. Consequently, by Result 1 and Equation (8), the expected number of dormant metastases would also be increasing in the number and size of clinically detectable metastases. Nonetheless, Equation (8) is helpful in estimating the amount of dormant metastases at the time of presentation, by showing that this quantity depends on the clinically detectable metastases only via the latter's impact on the tumor shedding rate.

We also note that neither our model nor Result 1 is inconsistent with clinical data suggesting that the presence of metastases in the lymph nodes is a better predictor of eventual cancer death than the size of the primary tumor. For example, some primary tumors may have a large growth rate and a small shedding rate, while others may have a small growth rate and a large shedding rate. In our model, the latter set of tumors may achieve a lower cancer cure probability than the former set of tumors.

Results 2 and 3 focus on the timing of surgery. The inherent tradeoff is that later surgery acts as a 'poor man's angiogenesis' by slowing the rate of vascularization of dormant metastatic tumors, while earlier surgery reduces shedding from the primary tumor. In our model, the latter effect wins out for CR schedules (i.e., chemotherapy precedes radiation) because – by Assumption 4 – the avascular and vascular metastases behave the same under all three CR schedules; that is, delayed surgery does not reduce the growth capability of dormant tumors. In contrast, the timing of surgery does affect the rate of vascularization of dormant metastases in RC schedules, and Result 3 elucidates the tradeoff of delayed vascularization and primary shedding for the RSC versus SRC case. Although the suboptimality of CSR in Result 2 may seem surprising in light of the ongoing clinical trial of this schedule by the Milan Cancer Institute [2], their primary motivation for administering at least a few rounds of neoadjuvant chemotherapy was not to increase the cure probability, but to increase the likelihood of breast-conserving surgery [22], which is a factor omitted from our study.

Result 4 compares the two most popular multimodal schedules, SCR and SRC, and reveals that chemotherapy should be given before radiation to suppress a large vascular metastatic population or a suspected (via a large primary tumor) large dormant metastatic population. This result is consistent with [1], which shows the superiority of SCR over SRC for breast cancer patients receiving conservative surgery who are at substantial risk for systematic metastasis.

As explained earlier, a detailed investigation of SCR and SRC (CSR and RSC, respectively) led us to consider SRCR (RSCR, respectively). In these two schedules, the first portion of radiotherapy is terminated at the point when either radiation killing is offset by metastatic growth or the radiotherapy toxicity constraint is reached. Results 5 through 7 confirm the superiority of these two novel schedules, and Result 8 shows that SRCR is optimal over all possible schedules if the dormant metastases do not undergo angiogenesis within about the first 40 days after surgery. There are two noteworthy features of Result 8. First, this result suggests that optimality can be attained by simply breaking the radiotherapy regimen into two disjoint segments, and that more sophisticated strategies, such as the integrated alternating regimen in [23], need not be considered. Second, the proof of Result 8 reveals that the nadir of the cancer burden, and hence the cancer cure probability, in the SRCR schedule is achieved at the end of chemotherapy, not necessarily at the end of treatment. Nonetheless, administering any post-chemotherapy portion of the radiotherapy may prolong survival for the uncured cases by improving locoregional control and delaying the onset of metastases.

Limitations

Although our 14-parameter model captures the first-order effects of the primary tumor and its shedding, angiogenesis of the primary tumor and its impact on metastatic dormancy and growth, and the impact of local and systemic treatment, it is still a very crude representation of the clinical setting. A key omission in

our model is the mutations that tumor cells accumulate as a result of the microenvironment [24] and treatment [25]. These mutations may cause changes in the radiosensitivity, chemosensitivity, shedding rate, growth rate, and angiogenesis rate of the primary and metastatic tumors. While the microenvironment-generated mutations are implicitly and crudely captured in our model via the angiogenic delay, no attempt has been made to incorporate acquired drug resistance. It is difficult to predict how the inclusion of acquired drug resistance might affect our results. For example, it has been argued that it is preferable to administer chemotherapy earlier because the tumor cells have not accumulated too many mutations [22], and to administer it later, so as to delay acquired drug resistance. In any case, our omission of acquired drug resistance requires our results to be interpreted with caution.

Our model also ignores the detailed timing issues of treatment, such as healing periods between modes of treatment (however, delays between surgery and adjuvant chemotherapy of as much as four weeks cause no significant difference in outcome [26, 27]) and the pharmacokinetics of chemotherapy. We ignore any synergistic or antagonistic interactions between chemotherapy and radiotherapy, because these are drug-specific and often depend upon the detailed timing of the schedule. We also ignore accelerated repopulation, where the tumor growth rate increases over the course of treatment [28], and the fact that the chemotherapeutic killing rate is likely to be lower for metastatic tumors than for primary tumors. Nevertheless, neither of these omissions introduce any bias regarding treatment sequences, and so are unlikely to affect our qualitative results. Finally, tumor angiogenesis is an extremely complex process involving dozens of factors [16], and our modeling of it is necessarily simplistic.

However, perhaps the model's biggest shortcoming is not related to the tumor biology, but to the formulation of our decision problem: we model a dynamic stochastic control problem with imperfect but accumulating information by a dynamic deterministic control problem with perfect information. In particular, the two novel strategies, SRCR and RSCR, require the clinician to observe the point in time when radiation killing is dominated by metastatic growth, which is impossible with current technology. Nonetheless, knowledge of an optimal solution in the idealized case of perfect information does provide insights for managing the more realistic case of imperfect information. More specifically, our analysis could be operationalized (with considerable validation and calibration), as we outline below for the SRCR schedule. First, a statistical model (along the lines developed in [20, 21]) could be used to estimate a one-dimensional quantity representing the metastatic potential (e.g., the probability of detecting metastases within 5 years) from information accumulated by the time of surgery (e.g., size of the primary tumor, amount of detectable metastases, histological grade, presence of margins, node involvement, hormonal test results). If the metastatic potential is very high then use SCR, if it is very small use SRC, and if it is intermediate in value then use a version of SRCR. Also, the schedule can be altered during the course of treatment as new information becomes available; for example, if metastasis is observed during the radiation portion of SRC, then we update the state information and use Result 4 to immediately switch to chemotherapy.

In summary, this research provides a systematic framework for deciding on the sequence of surgery, radiotherapy, and chemotherapy. Our analysis elucidates the tradeoffs that are at the crux of this complex problem, and derives two novel schedules, SRCR and RSCR, that may have the potential to enhance cancer cure probabilities. While our two main results, Results 1 and 8, cannot be validated from existing data, they provide provocative testable hypotheses regarding the estimation of dormant metastases and the optimal sequencing regimen, respectively.

Appendix

This Appendix expresses the mathematical model as a control problem: maximize the cancer cure probability subject to toxicity constraints. Mathematically, given $p(0)$ and $m(0)$, the problem is to

$$\max_{r(t),c(t),t_s} \underbrace{\max_{t\in[0,R+C]} e^{-f[p(t)+d(t)+m(t)]}}_{\text{cancer cure probability}} \tag{1}$$

subject to

$$\underbrace{\dot{p}(t)}_{\text{primary}} = [\underbrace{\gamma}_{\text{growth}} - \underbrace{k_r r(t)}_{\text{radiotherapy}} - \underbrace{k_c c(t)}_{\text{chemotherapy}} - \underbrace{s I_{\{t_s=t\}}}_{\text{surgery}}]p(t), \tag{2}$$

$$\underbrace{\dot{d}(t)}_{\text{dormant}} = [\underbrace{\gamma_m I_{\{d(t)<\bar{d}(t)\}}}_{\text{regrowth}} - \underbrace{k_c c(t)}_{\text{chemotherapy}} - \underbrace{(a_v I_{\{p(t)>\bar{v}\}} + a I_{\{p(t)\leqslant\bar{v}\}}) I_{\{t\geqslant t_a\}}}_{\text{angiogenesis}}]d(t), \tag{3}$$

$$\underbrace{\dot{m}(t)}_{\text{metastases}} = \underbrace{\lambda(p(t))^{\beta} I_{\{p(t)>\bar{v}\}}}_{\text{metastatic shedding}} + [\underbrace{(a_v I_{\{p(t)>\bar{v}\}} + a I_{\{p(t)\leqslant\bar{v}\}}) I_{\{t\geqslant t_a\}}}_{\text{angiogenesis}}]d(t) + [\underbrace{\gamma_m}_{\text{growth}} - \underbrace{k_c c(t)}_{\text{chemotherapy}}]m(t), \tag{4}$$

$$r(t) \in \{0, 1\}, \qquad c(t) \in \{0, 1\},$$
$$r(t) + c(t) \leqslant 1, \tag{5}$$

$$\int_0^{R+C} r(t)\,\mathrm{d}t = R, \tag{6}$$

$$\int_0^{R+C} c(t)\,\mathrm{d}t = C, \tag{7}$$

$$d(0) = \frac{\lambda\bar{v}[p(0)^{\beta} - \bar{v}^{\beta+\mu/\gamma}\, p(0)^{-\mu/\gamma}]}{\beta\gamma + \mu}, \tag{8}$$

$$\underbrace{\int_0^{t_a} d(\tau)[a_v I_{\{p(\tau)>\bar{v}\}} + a I_{\{p(\tau)\leqslant\bar{v}\}}]\,\mathrm{d}\tau}_{\text{angiogenesis initiation}} = \bar{v}, \tag{9}$$

and

$$\underbrace{\bar{d}(t)}_{\text{regrowth threshold}} = \begin{cases} d(0)e^{(-\int_{t_a}^{t}[a_v I_{\{p(\tau)>\bar{v}\}} + a I_{\{p(\tau)\leqslant\bar{v}\}}]\,\mathrm{d}\tau)} & \text{if } t \geqslant t_a, \\ d(0) & \text{otherwise.} \end{cases} \tag{10}$$

The model is described in detail in [9], and here we restrict ourselves to several comments on its nonobvious features. Assumption 2 allows us to ignore the entry into the dormant compartment of newly shed metastases that reach the vascular threshold of $\bar{v}$ cells. As explained in [9], this assumption – together with the calculation of the cancer cure probability and Assumption 1 – allows us to aggregate all dormant metastases into one compartment in (3) and all growing metastases into another compartment in (4). The indicator function $I_{\{t\geqslant t_a\}}$ in (3), where the threshold t_a is defined in (9), delays the first vascularization of a dormant metastasis, so that our deterministic model mimics a stochastic model. The regrowth of dormant metastases, which have been shrunk by chemotherapy, to the vascular threshold is incorporated into the first term on the right side of (3) by the indicator function $I_{\{d(t)<\bar{d}(t)\}}$. The threshold $\bar{d}(t)$ in (10), along with Assumption 2, ensures that the shrunk dormant metastases regrow only to their original size. The estimate of the initial dormant metastases in (8) uses Assumption 1 and is the result of a queueing theory analysis. In this equation, the parameter μ is the reciprocal of the mean time that it takes for a single metastatic cell to reach the level of detection in the presence of the primary tumor; hence, if D is the detection limit in terms of cells, then $\mu^{-1} = a_v^{-1} + \ln(D)/\gamma_m$.

Below we express the eight assumptions appearing in the text more precisely in terms of the model parameters. As noted earlier, Assumption 8 below is actually less stringent than the Assumption 8 that appears in the text.

Assumption 1. At time 0, all subclinical metastases have exactly $\bar{v}$ cells.
Assumption 2. $\gamma_m R \leqslant \ln \bar{v}$.
Assumption 3. $\bar{v}/p(0) \geqslant \max\{e^{-s}, e^{(\gamma-k_c)C}, e^{(\gamma-k_r)R}\}$.
Assumption 4. $(k_c - \gamma_m)C \geqslant \gamma_m R$.
Assumption 5. $\lambda(p(0)^{\beta} - \bar{v}^{\beta})/\beta(k_r - \gamma) \leqslant p(0)e^{(\gamma-k_r)R}(1 - e^{-s+(\gamma-k_c)C})$.
Assumption 6. $k_r \geqslant k_c$.
Assumption 7. $\gamma_m \geqslant \gamma$.
Assumption 8. $\min\{R, (\ln[(k_r - \gamma)p(0)\, e^{-s+(\gamma-\gamma_m)C}] - \ln[\gamma_m m(0)])/(\gamma_m - \gamma + k_r)\} \leqslant \bar{v}/ad(0)$, where we take $-\ln(0) = \infty$.

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