

Analysis and comparison of multimodal cancer treatments

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We analyse the sequence in which the three most commonly prescribed cancer treatments—surgery (S), chemotherapy (C) and radiotherapy (R)—should be administered. A system of ordinary differential equations is formulated that captures the various local and systemic effects of the three modes of treatment, as well as the first-order effects of the inter-relationship between the primary tumour and the distant metastatic tumours, including primary tumour shedding and the primary tumour's effect on the rate of angiogenesis in the metastatic tumours. Under a set of stated assumptions on the parameter values, we find the exact cancer cure probability (subject to toxicity constraints) for the six permutation schedules (i.e. SCR, CSR, CRS, SRC, RSC, RCS) and for two novel schedules, SRCR and RSCR, that apply radiotherapy in disjoint, optimally timed portions. We show analytically that SRCR and RSCR are the two best-performing (i.e. highest cure probability) schedules among the eight considered. Further, SRCR is shown to be optimal among all possible schedules, provided a modest condition is satisfied on the delay of initial angiogenesis experienced by the patient's dormant tumours.

Keywords: cancer treatments; metastasis; dynamic modelling; queueing theory.

1. Introduction

When a patient is diagnosed with cancer (e.g. of the breast, prostate or head and neck), three main therapy modalities are available: the local (i.e. at the site of the primary tumour) treatments, surgery (S) and radiotherapy (R), and the systemic (i.e. local and distant) treatment, chemotherapy (C). The decision facing the practitioner is how much local and systemic treatment to apply and when to apply it. At the crux of this sequencing decision is the fact that most cancer deaths are caused by metastatic (i.e. distant) disease, even though the majority of cancer patients do not have clinically detectable metastases at the time of presentation (DeVita *et al.*, 1993).

Our motivation for studying this problem is twofold: first, the clinical research community has not converged on agreed-upon sequencing protocols. Although the debate continues for most types of cancers, we illustrate this point with breast cancer, perhaps the most intensely studied form of this disease. The focus before 1975 was on locoregional control of tumours using surgery and adjuvant (i.e. postsurgical) radiotherapy, perhaps

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followed by chemotherapy (Thürlimann & Senn, 1996); in the two subsequent decades, the benefits of adjuvant chemotherapy became more apparent, while the marginal benefit of adjuvant radiotherapy after a total mastectomy was brought into question (Early Breast Cancer Trialists' Collaborative Group, 1995) and was not shown to improve survival until 1997 (Overgaard *et al.*, 1997; Ragaz *et al.*, 1997). Not until 1996 were the results of a prospective trial published that was aimed at the sequencing decision (Recht *et al.*, 1996); in our notation, this study showed that SCR was better than SRC for patients at substantial risk for metastatic disease. In addition, neoadjuvant (i.e. preoperative) chemotherapy has been championed by the Milan Cancer Institute group and appears to be efficacious in women with large tumours (Bonadonna *et al.*, 1998).

In addition to the lack of consensus in the clinical community, our second motivation for studying this problem is the deep understanding of the relationship between angiogenesis and metastasis that has emerged in recent years, due largely to Judah Folkman's laboratory (Weidner *et al.*, 1991; O'Reilly *et al.*, 1994; Holmgren *et al.*, 1995). The paradigm shift caused by tumour angiogenesis research has recently led to a rethinking of the detailed timing of chemotherapy schedules (Browder *et al.*, 2000). This leads us to believe that incorporating angiogenesis-related mechanisms, which are described in the next section, into the sequencing decision makes the sequencing problem sufficiently complex that a mathematical analysis has the potential to shed new light that may otherwise elude the clinical research community.

Mathematical modelling has been applied extensively to the detailed temporal scheduling of radiotherapy (see, for example, Fowler, 1989; Sachs *et al.*, 1997) and chemotherapy (Norton & Simon, 1977; Coldman & Goldie, 1983; Dibrov *et al.*, 1985; Day, 1986; Skipper, 1986; Swan, 1990; Adam & Panetta, 1995; Costa & Boldrini, 1997 to name a few). In contrast, very little modelling work has been undertaken for multimodal therapy. Insights from the linear-quadratic model of radiobiology—if not the mathematical model itself—have been used to suggest that the time delays between these three modes of treatment should be kept to a minimum (Peters & Withers, 1997). However, all of the aforementioned papers consider only the primary tumour, even though metastases are responsible for most cancer mortality. Several researchers have developed stochastic simulation models of breast cancer that incorporate the primary tumour and metastases, and have calibrated their models to clinical data to generate some insights into the efficacy of chemotherapy and the nature of the metastatic spread (Koscielny *et al.*, 1985; Retsky *et al.*, 1987; Yorke *et al.*, 1993; Speer *et al.*, 1984; Retsky *et al.*, 1997). The models of Retsky and co-workers are the most similar in spirit to ours, in that they incorporate the dormancy-followed-by-rapid-growth phenomenon revealed by Folkman's work. Although the simulation models in Koscielny *et al.* (1985); Retsky *et al.* (1987); Yorke *et al.* (1993); Speer *et al.* (1984); Retsky *et al.* (1997) are more complicated than our model, and in some cases are based on a clever statistical analysis of a wealth of data (see, for example, Koscielny *et al.*, 1984), these studies do not compare different multimodal treatments.

In this paper, we formulate the multimodal treatment problem as a control problem: maximize the cancer cure probability subject to toxicity constraints. To maintain a deterministic framework, we adopt a 'certainty equivalence' approach and use queueing theory to obtain a point estimate for the unknown amount of undetectable metastases at the time of presentation. Rather than undertake a frontal assault of this problem via control theory, we perform an exact analysis of the six permutation schedules, which in

turn suggests two novel strategies that appear worthy of consideration. We then show that these two policies are superior to the six permutation schedules, and show that one of these policies is in fact an optimal solution to the original control problem, as long as the parameter values satisfy a certain condition.

This paper is organized as follows: the underlying biology and the mathematical model are described in Section 2. In Section 3, we state and justify the assumptions on the parameter values that are imposed to derive our results. The six permutation policies are analysed in Section 4 and compared in Section 5. The two novel schedules are motivated and analysed in Section 6 and their superiority is established in Section 7. The results are discussed in Section 8. Readers who are not interested in the mathematical derivations may want to skip Section 4 and read only Propositions 4–10 in Sections 5–7 before turning to Section 8.

2. The model

Model overview

Our model is a set of ordinary differential equations (ODEs) that tracks the dynamics of a primary tumour and its associated metastases, which are subject to a multimodal treatment of surgery, radiotherapy and chemotherapy. Our desire to maintain analytical tractability while covering a broad range of phenomena (e.g. angiogenesis, metastasis, three treatment modalities) necessitates the use of a simple model that captures only first-order effects. Consequently, we ignore the detailed aspects incorporated into the state-of-the-art spatial models on individual facets of tumour growth and cancer treatments; see, for example, the references in Orme & Chaplain, 1997 (angiogenesis); Perumpanani *et al.*, 1996 (metastasis); Jackson & Byrne, 2000 (chemotherapy); Wein *et al.*, 2000 (radiotherapy) and Adam & Bellomo, 1997 (surgery). However, we hypothesize that many of these details are not required—indeed, not appropriate—for a study that is aimed at the strategic and rather crude decisions related to the ordering of the three treatment options.

The following salient features are captured in our model; the model's limitations are discussed in Section 8. The disease involves a primary tumour (e.g. in the breast or prostate) and possibly secondary tumours incident elsewhere in the body (e.g. in the lungs, liver, and/or kidneys). Vascularized (primary and secondary) tumours shed cells that travel to a distant site, and grow into secondary tumours called *metastases*. After reaching a moderate size, metastatic tumours undergo a latent (non-growing) period referred to as *dormancy*, where cell division is balanced by cell death caused by apoptosis and necrosis (Holmgren *et al.*, 1995). This dormant state is due to a lack of nutrients, and dormant tumours are clinically undetectable. Rapid growth resumes after the metastasis recruits nearby endothelial cells to form blood vessels around the tumour, in a process called *angiogenesis* (Folkman, 1995). The possibly prolonged period of time between the onset of dormancy and the eventual vascularization of the metastasis is referred to as the *angiogenic delay*. Recent evidence indicates that the presence of the vascular primary tumour actually prolongs the angiogenic delays experienced by dormant metastases, and the removal of the vascular primary tumour (e.g. by surgery) reduces the angiogenic delays, causing metastases to more rapidly emerge from their dormancy (O'Reilly *et al.*, 1994; Holmgren *et al.*, 1995).

Our model begins at the time of presentation, when the clinician observes a vascular primary tumour and any clinically detectable distant metastases. The clinician quantifies the size of these tumours, and uses this information to estimate the amount of subclinical metastases that is undetectable at the time of presentation. The patient then undergoes multimodal treatment consisting of the surgical removal of the primary tumour, radiotherapy treatment that acts locally on the primary tumour, and chemotherapy that acts systemically on all cancer in the body. The goal of our analysis is to compare the efficacy of different schedules that vary as to the order of the three treatment modalities.

The model equations

Although we will not be using control theory, it is useful to view this problem from a control-theoretic point of view. Let $r(t)$ equal one if radiotherapy is being administered at time t , and let it equal zero otherwise. Similarly, let $c(t)$ be a 0–1 control variable describing the chemotherapy regimen. Our third decision variable is the time of surgery, t_s . We want to choose these decision variables to maximize the probability of cancer cure, subject to toxicity constraints. Our model tracks the number of cells in the primary tumour ($p(t)$), the number of cells in dormant metastases ($d(t)$), and the number of cells in nondormant (i.e. growing) metastases ($m(t)$). Note that $m(t)$ contains avascular metastases (metastases that have no more than \bar{v} cells) as well as postdormant tumours that have undergone angiogenesis. We assume that at time 0, the clinician observes $p(0)$ and the number and size of all metastases comprising $m(0)$, and uses this information to estimate the initial amount of dormant metastases. In the spirit of the certainty equivalence principle that allows for the separation of estimation and control (Bertsekas, 1976), we substitute this point estimate for the unobservable quantity, $d(0)$, into our optimization problem.

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

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

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

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

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

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

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

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

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

and

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

Model description

Primary tumour growth. The primary tumour in (2) is assumed to grow exponentially at rate γ . Its regrowth rate after treatment is also γ (Brown *et al.*, 1987). Although tumours are often assumed to follow Gompertzian growth (Norton, 1988), the exponential assumption is reasonable over the time horizon of treatment (roughly nine months).

Treatment. We assume that the ‘log cell kill’ hypothesis (Skipper *et al.*, 1964), which states that a given dose of chemotherapy kills a fixed fraction of remaining cancer cells (with exponential killing rate k_c), holds in all three compartments in (2)–(4). We assume that radiotherapy also kills a fixed fraction of remaining cells, with exponential killing rate k_r . Radiotherapy is active against the primary tumour, but not against the distant metastases. Although we are ignoring the quadratic killing term in the linear-quadratic model that is used in the radiobiology community, the great majority of cell killing under standard fractionation schedules is due to the linear term (Fowler, 1989). However, our model is attempting to capture neither the details of radiotherapy fractionation schedules nor other temporal details of multimodal scheduling, such as breaks between rounds of chemotherapy and healing periods between modes of treatment. Rather, in (5)–(7), we assume that radiotherapy and chemotherapy are administered for exactly R and C time units, respectively, and they cannot be given simultaneously (Stewart, 1991). Surgery is instantaneous and kills a fixed fraction e^{-s} of the primary tumour. For cases such as breast cancer, in which surgical removal of lymph nodes is possible, the nodes are considered part of the primary tumour; smaller values of s correspond to nodes that go undetected at the time of surgery. Note that nothing can be gained by inserting rest periods into the treatment schedules, and so it is without loss of generality that our toxicity constraints restrict an optimal multimodal treatment to last $R + C$ time units.

Cancer cure probability. We model the cancer cure probability using the Poisson model, which has been widely used to compute the tumour control probability in the radiobiology community (Tucker & Taylor, 1996). According to this model, f is the fraction of (primary and metastatic) tumour cells that are clonogenic (i.e. capable of tumour regeneration), the number of remaining cells at each point in time has a Poisson probability distribution, and a cure is achieved if all clonogenic cells are destroyed. This approach, together with the queuing theory analysis at the end of this section, allows us to avoid tracking individual metastases in our model. To see this, suppose there are m_{i0} cells in metastasis i before treatment and we administer some chemotherapy just before time t , so that $m_i(t) = m_{i0}e^{-k}$. Then the instantaneous cancer cure probability at time t is the probability that all the clonogenic cells in these metastases are killed. Assuming that the growth and killing rates of these metastases are independent, this quantity is $\prod_{i=1} \exp(-f m_{i0}e^{-k}) = \exp(-f m_0 e^{-k}) = \exp(-f m(t))$, where $m_0 = \sum_i m_{i0}$ and $m(t) = \sum_i m_i(t)$. Hence, we only need to keep track of the total number of metastatic cells.

A similar argument holds for the dormant compartment. Hence, the instantaneous cancer cure probability at time t is $e^{-f[p(t)+d(t)+m(t)]}$, which only depends on the total number of cells, $p(t) + d(t) + m(t)$, a quantity we refer to as the *cancer burden*. According to the Poisson model, each tumour cell is either clonogenic or not, and hence the instantaneous cure probabilities at different time points are highly dependent. Therefore, in the radiobiology literature, the tumour cure probability for radiation monotherapy is taken to be the maximum (over $t \in [0, R]$) instantaneous cure probability, and this maximum is attained at the end of treatment (i.e. at $t = R$); if the instantaneous tumour cure probabilities were independent (they clearly are not), then it would be more appropriate to integrate over time, rather than maximize over time. In contrast, the instantaneous cancer cure probability in our problem is not necessarily maximized at the end of treatment (i.e. at $t = R + C$); for example, it is possible that cell killing by postsurgical radiotherapy is more than offset by metastatic growth. Hence, in (1) we need to perform the inner maximization over $t \in [0, R + C]$ to find the probability of cancer cure.

Shedding of metastases. We assume that the primary tumour is vascular at time t if and only if it satisfies $p(t) > \bar{v}$. A vascularized tumour sheds cells at rate $\lambda p(t)^\beta$, where $\lambda > 0$ and $\beta \in [0, 1]$. For mathematical simplicity, we do not subtract the shedding term, which represents a negligible fraction of primary tumour cells, from (2). Although our results do not depend upon a specific value of β , because cells are shed from the tumour surface and the probability of shedding is linear in the microvessel count (Weidner *et al.*, 1991), a natural choice is $\beta = 2/3$ (Landry *et al.*, 1982). Metastases are the result of a multistage process in which most shed cells successfully escape, survive in circulation, extravasate, and migrate to a conducive location in the host organ, but most solitary cells remain dormant and most micrometastases do not continue to grow (Chambers *et al.*, 1995; Luzzi *et al.*, 1998). We assume that all the requisite steps successfully occur with a fixed probability, which is incorporated into the constant λ .

Metastatic growth. Cells that are shed from the primary tumour enter the metastatic compartment, where they are assumed to grow exponentially at rate γ_m . We now make two crucial assumptions to avoid tracking the evolution of avascular metastases into dormant

metastases when they reach size \bar{v} , thereby maintaining analytical tractability. First, we assume that all unobservable metastases at time 0 have exactly \bar{v} cells. That is, they are all dormant, and undergoing a delay until the angiogenic switch is turned on; consequently, $m(0)$ is indeed observable. In reality, some of these unobservable metastases may have not yet attained \bar{v} cells, while others may be vascularized but not yet detectable. This assumption is not too unreasonable, because the angiogenic delay in the presence of a primary tumour is typically of the order of several years (Hanahan & Folkman, 1996), whereas the time for an avascular metastasis to grow from a single cell to \bar{v} cells, and the time for a postdormant metastasis to grow from \bar{v} cells to the level of detection are both of the order of months (Demicheli *et al.*, 1998). Second, we do not account for entry into the dormant compartment of newly shed metastases that reach \bar{v} cells. This omission is justified because the growth of a metastasis is typically not fast enough for a single metastatic cell to grow to \bar{v} cells during the multimodal treatment. Chemotherapy treats metastases, so the only time in which growth can occur unabated is during radiotherapy. For a shed cell to become \bar{v} cells within R time units, we must have $\gamma_m R \geq \ln \bar{v}$. However, taking the metastatic doubling time to be seven days (the shortest estimate in the literature, Demicheli *et al.*, 1998) and \bar{v} to be 10^5 cells (Folkman, 1995), R needs to be at least $\ln \bar{v} / \gamma_m = 116.3$ days, which is more than twice as long as standard fractionation schedules for radiotherapy (Fowler, 1989).

At time 0, the dormant compartment consists of a (possibly empty) set of metastases that each contain \bar{v} cells. If chemotherapy is given before radiotherapy, then these dormant metastases will be smaller than \bar{v} cells at time C , and during radiotherapy will grow exponentially at rate γ_m , but not beyond the size of \bar{v} cells. It is mathematically convenient to incorporate this regrowth into the dormant compartment, and as explained later, the indicator function $I_{\{d(t) < \bar{d}(t)\}}$ in (3) disallows the regrowth of depleted dormant metastases beyond \bar{v} cells.

Angiogenesis of dormant metastases. The onset of angiogenesis experienced by dormant metastases occurs at rate a_v when the primary tumour is vascular, and at the faster rate a when the primary tumour is avascular. We are assuming that the reduced angiogenic delay is due solely to having an avascular tumour (defined by $p(t) \leq \bar{v}$), regardless of how tumour shrinkage was achieved. While this phenomenon is well documented for surgical removal of the primary tumour (Weidner *et al.*, 1991; O'Reilly *et al.*, 1994; Holmgren *et al.*, 1995) and for radiotherapy (Camphausen *et al.*, 2001), it is not yet known whether this reduction in angiogenic delay also occurs for tumour shrinkage achieved by chemotherapy.

Angiogenic threshold. We now explain the role of the indicator function $I_{\{t \geq t_a\}}$ in (3), (4). Standard ODE models can give drastically misleading results by allowing an infinitesimal population to move from a populated compartment (i.e. the dormant compartment) to an initially unpopulated compartment (i.e. the metastatic compartment) and then experience fast exponential growth in the latter compartment. Motivated by movements from a wild-type compartment to a mutant compartment in an immune response model, Kepler & Perelson (1995) developed a deterministic threshold model to circumvent this shortcoming. We adapt their technique, which allows us to delay the first metastatic vascularization until time t_a , which is defined in (9). To derive (9), we assume that avascular metastasis i has

size $d_i(t) \in (0, \bar{v}]$ (recall that chemotherapy may shrink these dormant metastases to below the size of \bar{v} cells). We assume that the angiogenesis rate for metastasis i at time t is

$$\frac{d_i(t)}{\bar{v}} [a_v I_{\{p(t) > \bar{v}\}} + a I_{\{p(t) \leq \bar{v}\}}]. \quad (11)$$

For each of these avascular metastases, we envision a different angiogenesis clock ticking with an exponentially distributed duration with rates given by (11), and we are interested in the time at which the first clock expires. Note that full-size dormant metastases (i.e. $d_i(t) = \bar{v}$) experience the standard angiogenesis rate of $[a_v I_{\{p(t) > \bar{v}\}} + a I_{\{p(t) \leq \bar{v}\}}]$, whereas smaller metastases have proportionately smaller rates, and hence longer expected delays (because in reality they need to grow to the size of \bar{v} first, although this is not directly incorporated into our model). Following Kepler & Perelson (1995), we let $P(t)$ denote the probability that none of these dormant tumours have undergone angiogenesis by time t . The function $P(t)$ satisfies $P(0) = 1$ and is nonincreasing in t . Once $P(t)$ reaches the prespecified value $1/e$ (see Kepler & Perelson, 1995 for a justification of this value), which is defined to occur at time t_a , then for all $t \geq t_a$ we allow the cells from the dormant compartment to trickle into the metastatic compartment at the rate a_v or a , depending upon the size of the primary tumour. In computing $P(t)$, we obtain a form amenable to an aggregation of the individual metastases:

$$\begin{aligned} P(t) &= \prod_i \exp \left(-\frac{1}{\bar{v}} \int_0^t d_i(\tau) [a_v I_{\{p(\tau) > \bar{v}\}} + a I_{\{p(\tau) \leq \bar{v}\}}] d\tau \right), \\ &= \exp \left(-\frac{1}{\bar{v}} \int_0^t d(\tau) [a_v I_{\{p(\tau) > \bar{v}\}} + a I_{\{p(\tau) \leq \bar{v}\}}] d\tau \right), \end{aligned} \quad (12)$$

where $d(t) = \sum_i d_i(t)$. Setting $P(t_a) = 1/e$ in (12) and simplifying yields (9).

Regrowth of dormant metastases. Now we return to the indicator function $I_{\{d(t) < \bar{d}(t)\}}$ in the regrowth term in (3). Recall that the regrowth term allows dormant metastases, which have been shrunk to below \bar{v} cells by chemotherapy, to regrow to their original size. The quantity $\bar{d}(t)$ in (10) is equal to the size of the initial dormant population $d(0)$ less any dormant cells that have departed from the dormant compartment due to angiogenesis. Because the dormant compartment does not include any newly shed metastases from the metastatic compartment, this upper limit on $d(t)$ limits the regrowth of shrunk dormant metastases to precisely their original size.

Shedding by vascular metastases. Shedding by vascular metastases is captured by the model, because an incipient metastasis behaves exactly as an existing nondormant metastatic tumour: the growth rate and the effects of treatment experienced by incipient and existing nondormant metastatic tumours are identical, meaning that no information is lost by keeping such shed cells aggregated into the nondormant metastatic compartment. This argument tacitly invokes the earlier assumption that incipient metastases are not able to reach dormancy before the end of treatment.

Estimation of undetectable metastases. At the time of presentation, the clinician observes $p(0)$ cells in the primary tumour and the number and size of each of the detectable metastases comprising $m(0)$. Given this information, we now derive the expected size of the dormant compartment at the time of presentation, which is given in (8).

As mentioned earlier, we assume that all unobservable metastases at time 0 have exactly \bar{v} cells. Hence, our estimate of $d(0)$ is \bar{v} multiplied by the number of undetectable metastases at the time of presentation. We can view the estimation of this last quantity in the context of queueing theory (Kelly, 1979), where arrivals correspond to the shedding of cells by the primary tumour, and services correspond to the time between being shed as a solitary metastatic cell and reaching a clinically detectable size. More specifically, we consider a dynamic stochastic system where arrivals to the queue consist of shed cells and occur according to a nonhomogeneous Poisson process at rate $\lambda p(\tau)^\beta$. Departures from the system occur when a metastasis in the system reaches a detectable size. We assume that metastases reach a detectable size after a random amount of time with mean μ^{-1} . If D is the detection limit in terms of cells, then $\mu^{-1} = a_v^{-1} + \gamma_m^{-1} \ln D$. Service (growth to detection) for each metastasis begins as soon as the metastasis enters the system (is shed) and the service time is assumed to be independent from that of other metastases.

The queue length $Q(\tau)$ for the infinite-server queue described above is precisely the number of undetected metastases at time τ . Foley (1982) showed that $Q(\tau)$ is independent of the departure process from this queue prior to time τ . Note that according to our deterministic growth model, the size of each observable detectable metastasis at the time of presentation can be mapped into the time that it reached the detection limit D . That is, observing the size and number of clinical metastases corresponds in our queueing system to observing the departure process up to the time of presentation. Hence, Foley’s result implies that the number of undetectable metastases at the time of presentation is independent of the number and size of detectable metastases at the time of presentation. Furthermore, Keilson & Servi (1994) show that, if this queue is initially empty and has an arrival rate $A(\tau)$ and service time cumulative distribution function $S(\tau)$, then the queue length at time τ has a Poisson distribution with mean $\int_0^\tau A(z)[1 - S(\tau - z)] dz$. Thus, we need to specify $S(\tau)$ to derive an explicit formula for $E[Q(\tau)]$. To obtain a relatively simple expression, we follow the tradition in queueing theory and assume that service times are exponential. If we let $\tau = 0$ correspond to the time when the primary tumour becomes vascularized, then $p(\tau) = \bar{v}e^{\gamma\tau}$ and

$$\begin{aligned}
 E[Q(\tau)] &= \int_0^\tau \lambda \bar{v}^\beta e^{\beta\gamma z} e^{-\mu(\tau-z)} dz \\
 &= \frac{\lambda \bar{v}^\beta}{e^{\mu\tau}} \left(\frac{e^{(\beta\gamma + \mu)\tau} - 1}{\beta\gamma + \mu} \right).
 \end{aligned}
 \tag{13}$$

Since we assume vascularization occurs for tumours consisting of \bar{v} cells, at the time of presentation the primary tumour has been shedding cells for $\ln(p(0)/\bar{v})/\gamma$ time units, i.e. the length of time it took the primary tumour to grow from \bar{v} cells to $p(0)$ cells. Hence, the expected amount of dormant metastases present at the time of presentation is $\bar{v}E\left[Q\left(\frac{\ln(p(0)/\bar{v})}{\gamma}\right)\right]$, which, upon simplification of (13), yields (8).

3. Assumptions on the parameters

To enable an analytical comparison of the schedules, we make the following five assumptions.

ASSUMPTION 1 $\frac{\bar{v}}{p(0)} \geq \max\{e^{-s}, e^{(\gamma-k_c)C}, e^{(\gamma-k_r)R}\}$: surgery, the full regimen of chemotherapy and the full regimen of radiotherapy are each effective enough to shrink the initial primary tumour to an avascular size. If we take typical values of $\bar{v} = 10^5$ cells and $p(0) = 10^9$ cells, then these therapies need to achieve at least four logs of cell kill. Representative schedules of 30×2 Gy for radiotherapy (Hall, 1994) and eight rounds of CMF 420 (Ragaz *et al.*, 1997) can typically achieve more than four logs of cell kill (Hall, 1994; Skipper & Schabel, 1982; Steel, 1977).

ASSUMPTION 2 $(k_c - \gamma_m)C \geq \gamma_m R$: dormant metastatic tumours treated with the full regime of chemotherapy do not grow back to their pre-chemotherapy size during the subsequent full regime of radiotherapy. In other words, the full regimen of chemotherapy is able to offset R days of unabated growth. This is perhaps the most debatable of our five assumptions. Using Ragaz *et al.* (1997); Recht *et al.* (1996), we let $C = 165$ days and $R = 33$ days. Estimates for the metastatic growth rate vary from $\gamma_m = 0.01 \text{ day}^{-1}$ (which corresponds to a doubling time of about 2.5 months; Koscielny & Tubiana, 1999) to 0.1 day^{-1} (a doubling time of seven days; Demicheli *et al.*, 1998). By Assumption 2, we need $k_c \geq 0.012 \text{ day}^{-1}$ (if $\gamma_m = 0.01 \text{ day}^{-1}$) or $k_c \geq 0.12 \text{ day}^{-1}$ (if $\gamma_m = 0.1 \text{ day}^{-1}$), which corresponds to a $21(k_c - \gamma_m) = 0.042$ log drop (if $\gamma_m = 0.01 \text{ day}^{-1}$) or 0.42 log drop (if $\gamma_m = 0.1 \text{ day}^{-1}$) for each cycle of chemotherapy. Estimates for the log cell kill for each round of chemotherapy vary from 0.3 (Retsky *et al.*, 1993) to 0.6 (Skipper & Schabel, 1982). Hence, this assumption is satisfied by most, but perhaps not all, tumours.

ASSUMPTION 3 $\frac{\lambda(p(0)^\beta - \bar{v}^\beta)}{\beta(k_r - \gamma)} \leq p(0) e^{(\gamma - k_r)R} (1 - e^{-s + (\gamma - k_c)C})$: the number of cells shed by the primary tumour during an initial treatment by radiotherapy is less than or equal to the number of primary cells killed by surgery and chemotherapy following radiotherapy. While it is difficult to find data to confirm or refute this assumption, recall that shed cells in our model correspond to those that have successfully escaped from the primary tumour, survived during transport, extravasate, migrate to a metastatic location, and grow beyond the micrometastatic size. Given the low probability of this string of events (Chambers *et al.*, 1995; Luzzi *et al.*, 1998), together with the efficacy of surgery and chemotherapy, this assumption seems incontrovertible.

ASSUMPTION 4 $k_r \geq k_c$: the kill rate of radiotherapy is greater than or equal to the kill rate of chemotherapy. This assumption is supported by the literature (Hall, 1994; Skipper & Schabel, 1982; Steel, 1977).

ASSUMPTION 5 $\gamma_m \geq \gamma$: metastatic tumours grow at least as fast as the primary tumour. This assumption is satisfied by estimates from the literature (Demicheli *et al.*, 1998; Koscielny & Tubiana, 1999).

4. Analysis of permutation schedules

In this section, we analyse the six permutation schedules. Because e^{-fx} is decreasing in $x > 0$, maximizing the cancer cure probability is equivalent to minimizing the cancer

burden; i.e. for any given schedule, we can replace the inner maximization in (1) by $\min_{t \in [0, R+C]} p(t) + d(t) + m(t)$; we refer to the resulting minimal value as a schedule's *nadir*. Our approach is to determine the nadirs for all six permutation schedules in this section and to compare these nadirs, and hence compare the efficacies of these schedules, in Section 5.

Because surgery is instantaneous, for purposes of analysis it is convenient to group the schedules into two groups: the three CR schedules (SCR, CSR, CRS) and the three RC schedules (SRC, RSC, RCS), which are analysed in Sections 4.1 and 4.2, respectively.

4.1 Nadirs of CR schedules

The analysis in this section is enabled by the key observation that we can combine the dormant and metastatic compartments for CR schedules. To see this, note that throughout chemotherapy, both the dormant and the metastatic compartments experience a net (negative) growth rate of $\gamma_m - k_c$. During the subsequent radiotherapy, the metastatic compartment regrows freely at rate γ_m , while the dormant population regrows at rate γ_m until (possibly) hitting the threshold $\bar{d}(t)$, $t \in [C, C+R]$. However, the dormant population never regrows to the threshold during $[C, C+R]$ because, during this time interval,

$$\begin{aligned} d(t) &= d(0) \exp \left(- \int_0^t \left(a_v I_{\{p(\tau) > \bar{v}\}} + a I_{\{p(\tau) \leq \bar{v}\}} \right) I_{\{\tau \geq t_a\}} d\tau \right) \\ &\quad \times \exp \left(\int_0^t [\gamma_m I_{\{d(\tau) < \bar{d}(\tau)\}} - k_c c(\tau)] d\tau \right) \quad \text{by solving (3),} \\ &= \bar{d}(t) \exp \left(\int_0^t [\gamma_m I_{\{d(\tau) < \bar{d}(\tau)\}} - k_c c(\tau)] d\tau \right) \quad \text{by (10),} \\ &\leq \bar{d}(t) e^{\gamma_m t - k_c C} \quad \text{because at most } t - C \text{ days of regrowth have occurred,} \\ &\leq \bar{d}(t) \quad \text{by Assumption 2.} \end{aligned} \tag{14}$$

Hence, the cells in the dormant and metastatic compartments exhibit precisely the same behaviour during CR strategies, and separating these compartments and keeping track of angiogenesis is not necessary for computing the nadirs of CR schedules. Consequently, the model dynamics for the SCR, CSR and CRS schedules simplify to the following two ODEs:

$$\dot{p}(t) = [\gamma - k_c I_{\{t \in [0, C)\}} - k_r I_{\{t \in [C, C+R]\}} - s I_{\{t = t_s\}}] p(t), \tag{15}$$

$$(d + m)(t) = \lambda p(t)^\beta I_{\{p(t) > \bar{v}\}} + [\gamma_m - k_c I_{\{t \in [0, C)\}}] (d + m)(t). \tag{16}$$

SCR. Under SCR, surgery is performed at time 0, driving $p(0)$ below \bar{v} by Assumption 1. By Assumptions 2, 4 and 5, $k_r \geq k_c > \gamma$, and thus subsequent chemotherapy and radiotherapy both shrink the primary tumour. Hence, initial surgery eliminates shedding for the duration of the entire schedule. Discarding the shedding term and solving (15), (16)

yields

$$p(t) = \begin{cases} p(0) e^{-s+(\gamma-k_c)t} & \text{if } t \in [0, C); \\ p(0) e^{-s+(\gamma-k_c)C+(\gamma-k_r)(t-C)} & \text{if } t \in [C, C+R], \end{cases}$$

$$(d+m)(t) = \begin{cases} (d(0) + m(0)) e^{(\gamma_m-k_c)t} & \text{if } t \in [0, C); \\ (d(0) + m(0)) e^{(\gamma_m-k_c)C+\gamma_m(t-C)} & \text{if } t \in [C, C+R]. \end{cases}$$

Because $\dot{p}(t)$ and $(d+m)(t)$ are negative for all $t \in [0, C)$, it follows that the cancer burden hits its nadir in the interval $[C, C+R]$. If we define the cancer burden at time $t = C+u \in [C, C+R]$ by $b_{\text{SCR}}(u)$, then

$$b_{\text{SCR}}(u) = p(0) e^{-s+(\gamma-k_c)C+(\gamma-k_r)u} + [d(0) + m(0)] e^{(\gamma_m-k_c)C+\gamma_m u}, \quad (17)$$

$$\dot{b}_{\text{SCR}}(u) = (\gamma - k_r)p(0) e^{-s+(\gamma-k_c)C+(\gamma-k_r)u} + \gamma_m[d(0) + m(0)] e^{(\gamma_m-k_c)C+\gamma_m u},$$

$$\ddot{b}_{\text{SCR}}(u) = (\gamma - k_r)^2 p(0) e^{-s+(\gamma-k_c)C+(\gamma-k_r)u} + \gamma_m^2[d(0) + m(0)] e^{(\gamma_m-k_c)C+\gamma_m u}. \quad (18)$$

The function $b_{\text{SCR}}(u)$ is convex in $u \in [0, R]$ by (18), and solving $\dot{b}_{\text{SCR}}(u) = 0$ gives

$$\hat{u} = (\gamma_m - \gamma + k_r)^{-1} \ln \left[\frac{(k_r - \gamma)p(0) e^{-s+\gamma C}}{\gamma_m[d(0) + m(0)] e^{\gamma_m C}} \right].$$

The convexity of $b_{\text{SCR}}(u)$ implies that the nadir for the SCR schedule is

$$n_{\text{SCR}} = p(0) e^{-s+(\gamma-k_c)C+(\gamma-k_r)u^*} + [d(0) + m(0)] e^{(\gamma_m-k_c)C+\gamma_m u^*}, \quad (19)$$

where

$$u^* = \begin{cases} 0 & \text{if } d(0) + m(0) \geq \frac{p(0)}{\gamma_m} (k_r - \gamma) e^{-s+(\gamma-\gamma_m)C}; \\ R & \text{if } d(0) + m(0) \leq \frac{p(0)}{\gamma_m} (k_r - \gamma) e^{-s+(\gamma-\gamma_m)(C+R)-k_r R}; \\ \frac{\ln \left[\frac{(k_r - \gamma)p(0) e^{-s+\gamma C}}{\gamma_m[d(0) + m(0)] e^{\gamma_m C}} \right]}{(\gamma_m - \gamma + k_r)} & \text{otherwise.} \end{cases} \quad (20)$$

The value u^* is the amount of radiotherapy we can apply before the rate of metastatic growth outstrips the rate of primary tumour reduction.

CSR. Under schedule CSR, shedding occurs until chemotherapy is able to drive the primary tumour below \bar{v} (see Assumption 1), which occurs at time $t_c = (\gamma - k_c)^{-1} \ln(\bar{v}/p(0))$. For $t \in [0, C)$, (15) for the primary tumour is solved by $p(t) = p(0) e^{(\gamma-k_c)t}$. Substituting this expression into (16) gives the linear ODE

$$(d+m)(t) = \lambda[p(0) e^{(\gamma-k_c)t}]^\beta + [\gamma_m - k_c](d+m)(t) \quad \text{for } t \in [0, t_c),$$

which has the solution

$$(d+m)(t) = \frac{\lambda p(0)^\beta [e^{(\gamma_m-k_c)t} - e^{(\gamma-k_c)\beta t}]}{(k_c - \gamma)\beta + \gamma_m - k_c} + [d(0) + m(0)] e^{(\gamma_m-k_c)t}. \quad (21)$$

The second term in the right side of (21) describes treatment of the original (dormant and nondormant) metastases. The first term corresponds to incipient metastases caused by shedding and their subsequent growth; if we denote this term by

$$h_c(t) = \begin{cases} \frac{\lambda p(0)^\beta [e^{(\gamma_m - k_c)t} - e^{(\gamma - k_c)\beta t}]}{(k_c - \gamma)\beta + \gamma_m - k_c} & \text{if } t < t_c; \\ \frac{\lambda p(0)^\beta [e^{(\gamma_m - k_c)t} - e^{(\gamma - k_c)\beta t_c + (\gamma_m - k_c)(t - t_c)}]}{(k_c - \gamma)\beta + \gamma_m - k_c} & \text{if } t_c \leq t \leq C, \end{cases} \quad (22)$$

then

$$(d + m)(t) = h_c(t) + (d(0) + m(0)) e^{(\gamma_m - k_c)t} \quad \text{for } t \in [t_c, C].$$

Following the arguments in the SRC case, we solve the linear ODEs (15), (16) for $t \in [C, C + R]$ and define the cancer burden at time $C + v$ to be

$$b_{CSR}(v) = p(0) e^{-s + (\gamma - k_c)C + (\gamma - k_r)v} + [d(0) + m(0)] e^{(\gamma_m - k_c)C + \gamma_m v} + h_c(C) e^{\gamma_m v}. \quad (23)$$

The derivative of $b_{CSR}(v)$ vanishes at

$$\hat{v} = (\gamma_m - \gamma + k_r)^{-1} \ln \left[\frac{(k_r - \gamma)p(0)e^{-s + (\gamma - k_c)C}}{\gamma_m h_c(C) + \gamma_m [d(0) + m(0)] e^{(\gamma_m - k_c)C}} \right].$$

By the convexity of $b_{CSR}(v)$, it follows that the CSR nadir is

$$n_{CSR} = p(0) e^{-s + (\gamma - k_c)C + (\gamma - k_r)v^*} + [d(0) + m(0)] e^{(\gamma_m - k_c)C + \gamma_m v^*} + h_c(C) e^{\gamma_m v^*}, \quad (24)$$

where

$$v^* = \begin{cases} 0 & \text{if } d(0) + m(0) + h_c(C) \geq \frac{p(0)}{\gamma_m} (k_r - \gamma) e^{-s + (\gamma - \gamma_m)C}; \\ R & \text{if } d(0) + m(0) + h_c(C) \leq \frac{p(0)}{\gamma_m} (k_r - \gamma) e^{-s + (\gamma - \gamma_m)(C + R) - k_r R}; \\ (\gamma_m - \gamma + k_r)^{-1} \ln \left[\frac{(k_r - \gamma)p(0) e^{-s + (\gamma - k_c)C}}{\gamma_m h_c(C) + \gamma_m [d(0) + m(0)] e^{(\gamma_m - k_c)C}} \right] & \text{otherwise.} \end{cases} \quad (25)$$

CRS. Because schedules CRS and CSR both apply surgery after the primary tumour has been driven below \bar{v} and shedding has ceased, the dormant and metastatic compartments of CRS and CSR undergo identical primary shedding and treatment. Hence, the two schedules' $d + m$ solutions are the same. As in the previous cases, the nadir is achieved in $[C, C + R]$. Solving (15) under CRS during $t \in [C, C + R]$ yields

$$p(t) = \begin{cases} p(0) e^{(\gamma - k_c)C + (\gamma - k_r)(t - C)} & \text{for } t \in [C, C + R); \\ p(0) e^{-s + (\gamma - k_c)C + (\gamma - k_r)R} & \text{if } t = C + R. \end{cases}$$

Define the cancer burden function at time $t = C + w$ for $w \in [0, R)$ by

$$b_{\text{CRS}}(w) = p(0) e^{(\gamma - k_c)C + (\gamma - k_r)w} + [d(0) + m(0)] e^{(\gamma_m - k_c)C + \gamma_m w} + h_c(C) e^{\gamma_m w},$$

and let \hat{w} be the point where $\dot{b}_{\text{CRS}}(w)$ vanishes. We find that

$$\hat{w} = (\gamma_m - \gamma + k_r)^{-1} \ln \left[\frac{(k_r - \gamma) p(0) e^{(\gamma - k_c)C}}{\gamma_m h_c(C) + \gamma_m [d(0) + m(0)] e^{(\gamma_m - k_c)C}} \right].$$

The nadir could be achieved at time $C + R$ with the application of surgery; because the computation of \hat{w} does not take this into account, we need to compare the three-part solution (analogous to (20) and (25)) with the $w = R$ case. After making this comparison, we find that the CRS nadir is

$$\begin{aligned} n_{\text{CRS}} &= p(0) e^{-sI_{\{w^*=R\}} + (\gamma - k_c)C + (\gamma - k_r)w^*} + h_c(C) e^{\gamma_m w^*} \\ &\quad + (d(0) + m(0)) e^{(\gamma_m - k_c)C + \gamma_m w^*}, \end{aligned} \tag{26}$$

where $w^* = R$ if

$$\begin{aligned} &p(0) e^{(\gamma - k_c)C + (\gamma - k_r)\hat{w}^*} (1 - e^{-s + (\gamma - k_r)(R - \hat{w}^*)}) \\ &\quad + [h_c(C) e^{\gamma_m \hat{w}^*} + [d(0) + m(0)] e^{(\gamma_m - k_c)C + \gamma_m \hat{w}^*}] (1 - e^{\gamma_m (R - \hat{w}^*)}) > 0, \end{aligned}$$

and otherwise $w^* = \hat{w}^*$, where

$$\hat{w}^* = \begin{cases} 0 & \text{if } d(0) + m(0) + h_c(C) \geq \frac{p(0)}{\gamma_m} (k_r - \gamma) e^{(\gamma - \gamma_m)C}; \\ R & \text{if } d(0) + m(0) + h_c(C) \leq \frac{p(0)}{\gamma_m} (k_r - \gamma) e^{(\gamma - \gamma_m)(C+R) - k_r R}; \\ (\gamma_m - \gamma + k_r)^{-1} \ln \left[\frac{(k_r - \gamma) p(0) e^{(\gamma - k_c)C}}{\gamma_m h_c(C) + \gamma_m [d(0) + m(0)] e^{(\gamma_m - k_c)C}} \right] & \text{otherwise.} \end{cases}$$

4.2 Nadirs of RC schedules

SRC. Under the SRC strategy, the primary tumour satisfies $p(t) = p(0) e^{-s + (\gamma - k_r)t}$ for $t \in [0, R]$. The solutions for the other two compartments depend on whether or not angiogenesis occurs before time R . In the former case, by Assumption 1 and (3) and (9), the time that angiogenesis is initiated in the dormant compartment is given by

$$t_{\text{sr}} = \frac{\bar{v}}{ad(0)}.$$

We need to consider two cases: $t_{\text{sr}} \leq R$ and $t_{\text{sr}} > R$. For $t_{\text{sr}} \leq R$, we have

$$\begin{aligned} d(t) &= \begin{cases} d(0) & \text{if } t \in [0, t_{\text{sr}}); \\ d(0) e^{-a(t - t_{\text{sr}})} & \text{if } t \in [t_{\text{sr}}, R], \end{cases} \\ m(t) &= \begin{cases} m(0) e^{\gamma_m t} & \text{if } t \in [0, t_{\text{sr}}); \\ g_{\text{sr}}(t) + d(0) + m(0) e^{\gamma_m t} & \text{if } t \in [t_{\text{sr}}, R], \end{cases} \end{aligned}$$

where

$$g_{sr}(t) = \begin{cases} 0 & \text{if } t < t_{sr}, \\ \frac{d(0)}{a + \gamma_m} [ae^{\gamma_m(t-t_{sr})} + \gamma_m e^{-a(t-t_{sr})}] - d(0) & \text{if } t_{sr} \leq t, \end{cases} \quad (27)$$

which is the offspring, up to time t , of cells that transitioned from dormancy via angiogenesis. Hence, the cancer burden in $[0, R]$ can be succinctly stated as

$$p(t) + d(t) + m(t) = p(0) e^{-s+(\gamma-k_r)t} + d(0) + g_{sr}(t) + m(0)e^{\gamma_m t}, \quad (28)$$

where $g_{sr}(t)$ takes on the case-dependent value in (27).

As in the CR schedules, we combine the dormant and metastatic compartments by noting that they undergo exactly the same experience during $(R, R + C]$ of the SRC schedule. Hence, for $t \in (R, R + C]$, we have

$$p(t) = p(0)e^{-s+(\gamma-k_r)R+(\gamma-k_c)(t-R)}, \quad (29)$$

$$(d + m)(t) = [d(R) + m(R)] e^{(\gamma_m - k_c)(t-R)}. \quad (30)$$

Turning to the case $t_{sr} > R$, we find that no angiogenesis occurs in the dormant compartment, and the solution given in (28) holds for $t \in [0, R]$. Similarly, as in (29), (30), the cancer burden for $t \in [R, R + C]$ is given by

$$p(t) + d(t) + m(t) = p(0) e^{-s+(\gamma-k_r)R+(\gamma-k_c)(t-R)} + [d(0) + g_{sr}(R) + m(0) e^{\gamma_m R}] e^{(\gamma_m - k_c)(t-R)}. \quad (31)$$

PROPOSITION 1 The nadir for SRC occurs at time $R + C$.

Proof. We show that the SRC cancer burden for all $t \in [0, R + C)$ is bounded below by the cancer burden at time $R + C$. For $t \in [0, R)$,

$$\begin{aligned} & p(0) e^{-s+(\gamma-k_r)t} + d(0) + g_{sr}(t) + m(0) e^{\gamma_m t} \\ & \geq p(0) e^{-s+(\gamma-k_r)t+(\gamma-k_c)C} + d(0) + g_{sr}(t) + m(0) e^{\gamma_m t} \\ & \quad \text{since } \gamma < k_c \text{ by Assumptions 2 and 5,} \\ & \geq p(0) e^{-s+(\gamma-k_r)t+(\gamma-k_c)C} + d(0) + m(0) e^{\gamma_m t} \quad \text{since } g_{sr}(t) \geq 0, \\ & \geq p(0) e^{-s+(\gamma-k_r)t+(\gamma-k_c)C} + d(0) e^{\gamma_m(R+C)-k_c C} + m(0) e^{\gamma_m(R+C)-k_c C} \\ & \quad \text{by Assumption 2,} \\ & \geq p(0) e^{-s+(\gamma-k_r)t+(\gamma-k_c)C} + [d(0) + g_{sr}(R)] e^{(\gamma_m - k_c)C} + m(0) e^{\gamma_m(R+C)-k_c C} \\ & \quad \text{since } t_{sr} \geq 0 \text{ implies } d(0) + g_{sr}(R) < d(0) e^{\gamma_m R}, \\ & \geq p(0) e^{-s+(\gamma-k_r)R+(\gamma-k_c)C} + [d(0) + g_{sr}(R)] e^{(\gamma_m - k_c)C} + m(0) e^{\gamma_m(R+C)-k_c C} \\ & \quad \text{since } \gamma \leq k_r \text{ by Assumptions 2, 4 and 5,} \\ & = p(R + C) + d(R + C) + m(R + C) \quad \text{by (31).} \end{aligned}$$

To understand the second-to-last inequality, note that $t_{sr} \geq 0$; that is, a delay may occur before the original $d(0)$ cells begin to enter the metastatic compartment. Hence, $d(0) +$

$g_{\text{sr}}(t)$, which is the number of dormant cells plus the number of offspring from dormant-then-angiogenic cells, is less than or equal to $d(0)e^{\gamma_m t}$.

For $t \in [R, R + C)$, we have, by Assumptions 2 and 5,

$$\begin{aligned} p(t) + d(t) + m(t) &\geq p(t)e^{(\gamma - k_c)(R+C-t)} + d(t)e^{(\gamma_m - k_c)(R+C-t)} + m(t)e^{(\gamma_m - k_c)(R+C-t)}, \\ &= p(R + C) + d(R + C) + m(R + C), \end{aligned}$$

which completes the proof. \square

Hence, the nadir for SRC is given by

$$n_{\text{SRC}} = p(0)e^{-s+(\gamma - k_r)R+(\gamma - k_c)C} + [d(0) + g_{\text{sr}}(R)]e^{(\gamma_m - k_c)C} + m(0)e^{\gamma_m(R+C) - k_c C}. \quad (32)$$

RSC. Because this schedule begins with radiotherapy, our analysis must account for shedding. Analogous to t_c , define $t_r = (k_r - \gamma)^{-1} \ln[p(0)/\bar{v}]$, which is the time it takes for presurgical radiotherapy to drive the primary tumour to the avascular size \bar{v} . Assumption 1 implies that $t_r < R$ for strategies RSC and RCS.

The analysis of RSC over $[0, R)$ proceeds, as in the SRC case, by breaking the time axis at points where the equations for d and m change. For RSC, these break points occur at time t_r and also at time t_{rs} provided $t_{\text{rs}} < R$, where t_{rs} is the time that angiogenesis is initiated in the dormant compartment.

By analysing (9), we find that

$$t_{\text{rs}} = \begin{cases} \frac{\bar{v}}{a_v d(0)} & \text{if } \frac{\bar{v}}{a_v d(0)} \leq t_r; \\ \frac{\bar{v}}{ad(0)} \left(1 - \frac{t_r a_v d(0)}{\bar{v}}\right) & \text{if } \frac{\bar{v}}{a_v d(0)} > t_r \text{ and } \frac{\bar{v}}{ad(0)} \left(1 - \frac{t_r a_v d(0)}{\bar{v}}\right) < R, \end{cases}$$

and $t_{\text{rs}} \geq R$ if $\frac{\bar{v}}{a_v d(0)} > t_r$ and $\frac{\bar{v}}{ad(0)} \left(1 - \frac{t_r a_v d(0)}{\bar{v}}\right) \geq R$. Hence, we have three cases to analyse. After working out these cases, we can express the cancer burden succinctly in terms of two case-dependent auxiliary functions,

$$g_{\text{rs}}(t) = \begin{cases} 0 & \text{if } t < t_{\text{rs}}; \\ \frac{d(0)}{a + \gamma_m} [ae^{\gamma_m(t-t_{\text{rs}})} + \gamma_m e^{-a(t-t_{\text{rs}})}] - d(0) & \text{if } t_r \leq t_{\text{rs}} \leq t; \\ \frac{d(0)}{a_v + \gamma_m} [a_v e^{\gamma_m(t-t_{\text{rs}})} + \gamma_m e^{-a_v(t-t_{\text{rs}})}] - d(0) & \text{if } t_{\text{rs}} \leq t \leq t_r; \\ \frac{a_v d(0)}{a_v + \gamma_m} [e^{\gamma_m(t_r-t_{\text{rs}})} - e^{-a_v(t_r-t_{\text{rs}})}] e^{\gamma_m(t-t_r)} \\ \quad + \frac{d(0)e^{-a_v(t_r-t_{\text{rs}})}}{a + \gamma_m} [ae^{\gamma_m(t-t_r)} + \gamma_m e^{-a(t-t_r)}] - d(0) & \text{if } t_{\text{rs}} \leq t_r < t, \end{cases} \quad (33)$$

which quantifies the offspring of dormant cells that undergo angiogenesis when

radiotherapy is applied before surgery, and

$$h_r(t) = \begin{cases} \frac{\lambda p(0)^\beta [e^{\gamma_m t} - e^{(\gamma - k_r)\beta t}]}{(k_r - \gamma)\beta + \gamma_m} & \text{if } t < t_r; \\ \frac{\lambda p(0)^\beta [e^{\gamma_m t} - e^{(\gamma - k_r)\beta t_r + \gamma_m(t - t_r)}]}{(k_r - \gamma)\beta + \gamma_m} & \text{if } t \geq t_r, \end{cases} \quad (34)$$

which corresponds to the incipient metastases caused by shedding and its subsequent growth. The cancer burden for RSC is given by (the details are straightforward and are omitted)

$$p(t) + d(t) + m(t) = p(0) e^{(\gamma - k_r)t} + d(0) + g_{rs}(t) + h_r(t) + m(0) e^{\gamma_m t} \quad \text{for } t \in [0, R), \quad (35)$$

$$p(t) + d(t) + m(t) = p(0)e^{-s + (\gamma - k_r)R + (\gamma - k_c)(t - R)} + [d(0) + g_{rs}(R) + h_r(R) + m(0) e^{\gamma_m R}] e^{(\gamma_m - k_c)(t - R)} \quad \text{for } t \in [R, R + C]. \quad (36)$$

PROPOSITION 2 The nadir for RSC occurs at time $R + C$.

Proof. The approach here is the same as for Proposition 1. For notational simplicity, we define $\hat{h}_r(t)$ to be the number of individual metastases shed by the primary tumour up to time t , so that $\hat{h}_r(t_r) = \int_0^{t_r} \lambda p(0)^\beta e^{(\gamma - k_r)\beta \tau} d\tau$, which equals the left side of Assumption 3. Note that $\hat{h}_r(t)$ counts the number of cells shed, whereas $h_r(t)$ in (34) and (58) incorporates these cells plus their progeny. For $t \in [0, R)$,

$$\begin{aligned} & p(0) e^{(\gamma - k_r)t} + d(0) + g_{rs}(t) + h_r(t) + m(0) e^{\gamma_m t} \\ & \geq p(0) e^{(\gamma - k_r)t + (\gamma - k_r)(R - t)} + d(0) + m(0) e^{\gamma_m t} \\ & \quad \text{since } (\gamma - k_r)(R - t) < 0, \text{ and } h_r(t), g_{rs}(t) \geq 0, \\ & \geq p(0) e^{(\gamma - k_r)R} + \hat{h}_r(t_r) - p(0) e^{(\gamma - k_r)R} (1 - e^{-s + (\gamma - k_c)C}) + d(0) + m(0) e^{\gamma_m t} \\ & \quad \text{by Assumption 3,} \\ & = p(0) e^{-s + (\gamma - k_r)R + (\gamma - k_c)C} + \hat{h}_r(t_r) + d(0) + m(0) e^{\gamma_m t}, \\ & \geq p(0) e^{-s + (\gamma - k_r)R + (\gamma - k_c)C} + \hat{h}_r(t_r) e^{\gamma_m R + (\gamma_m - k_c)C} + d(0) e^{\gamma_m R + (\gamma_m - k_c)C} \\ & \quad + m(0) e^{\gamma_m(R + C) - k_c C} \quad \text{by Assumption 2,} \\ & \geq p(0) e^{-s + (\gamma - k_r)R + (\gamma - k_c)C} + h_r(t_r) e^{\gamma_m(R - t_r) + (\gamma_m - k_c)C} + d(0) e^{\gamma_m R + (\gamma_m - k_c)C} \\ & \quad + m(0) e^{\gamma_m(R + C) - k_c C} \\ & \quad \text{since each shed cell can grow for at most } t_r \text{ days by time } t_r, \\ & \geq p(0) e^{-s + (\gamma - k_r)R + (\gamma - k_c)C} + h_r(t_r) e^{\gamma_m(R - t_r) + (\gamma_m - k_c)C} \\ & \quad + [d(0) + g_{rs}(R)] e^{(\gamma_m - k_c)C} + m(0) e^{\gamma_m(R + C) - k_c C} \\ & \quad \text{since } t_{rs} \geq 0 \text{ implies } d(0) + g_{rs}(R) < d(0) e^{\gamma_m R}, \\ & = p(R + C) + d(R + C) + m(R + C) \quad \text{by (34) and (36).} \end{aligned}$$

For $t \in [R, R + C)$ the same argument as for SRC in Proposition 1 holds, completing the proof. □

Hence, the nadir for RSC is

$$n_{\text{RSC}} = p(0) e^{-s+(\gamma-k_r)R+(\gamma-k_c)C} + [d(0) + g_{\text{rs}}(R) + h_{\text{r}}(R) + m(0) e^{\gamma_m R}] e^{(\gamma_m-k_c)C}. \quad (37)$$

RCS. The analysis of the RCS policy is summarized in the following proposition.

PROPOSITION 3 $n_{\text{RCS}} = n_{\text{RSC}}$.

Proof. First, we claim that the sum of the d and m compartments are equal for the RSC and RCS schedules. To see this, note that these two schedules are identical during the interval $[0, R)$, so the cancer burdens prior to time R are the same. Assumption 1 implies that the primary tumour is driven below \bar{v} by time R in both policies; consequently, the behaviour of the d and m compartments of RCS are again the same as RSC even during $[R, R + C]$. This follows from observing that, once flipped, the primary vascular/shedding ($> \bar{v}$) switch stays off, because $p(t)$ is a decreasing function.

Furthermore, we claim that the nadir for RCS occurs at time $R + C$. The proof of this claim is the same as for Proposition 2, except that we include the surgery event before the final inequality in the analysis for $t \in [R, R + C)$. Hence, it suffices to show that the cancer burden of RCS at time $R + C$ is the same as that of RSC at time $R + C$. We already know that the sum of their d and m components are the same; clearly, their p compartments are also identical, since, by time $R + C$, both schedules have applied surgery, R days of radiotherapy and C days of chemotherapy to the primary tumour. \square

5. Comparison of permutation schedules

In this section, we compare the performance of the six permutation schedules. We compare the three CR schedules in Section 5.1 and the three RC schedules in Section 5.2. The two most widely used multimodal schedules, SCR and SRC, are compared in Section 5.3.

5.1 CR schedules

The following proposition provides simple dominance relations among the three CR strategies. Throughout the paper, 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.

PROPOSITION 4 Earlier surgery is more effective for CR strategies; that is,

$$n_{\text{SCR}} \leq n_{\text{CSR}} \leq n_{\text{CRS}}.$$

Proof. Define the function

$$\psi(x_1, x_2) = \min_{0 \leq t \leq R} \{x_1 e^{(\gamma-k_r)t} + x_2 e^{\gamma_m t}\}. \quad (38)$$

Note that $x_1 \geq y_1, x_2 \geq y_2$ implies that $\psi(x_1, x_2) \geq \psi(y_1, y_2)$. By (19) and (24), we have

$$n_{\text{SCR}} = \psi(p(0) e^{-s+(\gamma-k_c)C}, [d(0) + m(0)] e^{(\gamma_m-k_c)C}),$$

and

$$n_{CSR} = \psi(p(0) e^{-s+(\gamma-k_c)C}, [d(0) + m(0)] e^{(\gamma_m-k_c)C} + h_c(C)), \tag{39}$$

which implies $n_{SCR} \leq n_{CSR}$. Also,

$$\begin{aligned} n_{CSR} &\leq \min\{\psi(p(0) e^{(\gamma-k_c)C}, [d(0) + m(0)] e^{(\gamma_m-k_c)C} \\ &\quad + h_c(C)), p(0) e^{-s+(\gamma-k_c)C+(\gamma-k_r)R} \\ &\quad + [(d(0) + m(0)) e^{(\gamma_m-k_c)C} + h_c(C)] e^{\gamma_m R}\} \text{ by (38), (39),} \\ &= n_{CRS} \text{ by (26),} \end{aligned}$$

which completes the proof. □

5.2 RC schedules

Recall that $n_{RSC} = n_{RCS}$ by Proposition 3. In other words, delaying surgery until the end of radiotherapy produces the same cure probability as delaying surgery until after radiotherapy and chemotherapy. To determine if delayed surgery is useful in any RC schedules, we use (32) and (37) to compute

$$n_{SRC} - n_{RSC} = [g_{sr}(R) - g_{rs}(R) - h_r(R)] e^{(\gamma_m-k_c)C},$$

implying that RSC is favoured over SRC if

$$g_{sr}(R) - g_{rs}(R) > h_r(R); \tag{40}$$

that is, if the number of offspring from dormant-then-vascular cells when surgery is performed first is greater than the number of cells produced by shedding before the primary tumour is shrunk to an avascular size plus the number of offspring of dormant-then-vascular cells when surgery is postponed until radiotherapy is complete. Note that $g_{sr}(R) \geq g_{rs}(R)$ because the dormant population undergoes angiogenesis more slowly when surgery is delayed. Unfortunately, the many cases inherent in the definitions of $g_{sr}(t)$, $g_{rs}(t)$ and $h_r(t)$ in (27), (33), (34) prevent us from sharpening the result in (40).

5.3 SCR versus SRC

In this section, we compare the two most widely used multimodal schedules, SCR and SRC.

PROPOSITION 5 If

$$m(0) \geq \frac{p(0)(k_r - \gamma) e^{-s+(\gamma-\gamma_m)C}}{\gamma_m} - \frac{\lambda \bar{v}[p(0)^\beta - \bar{v}^{\beta+\frac{\mu}{\gamma}} p(0)^{\frac{-\mu}{\gamma}}]}{\beta\gamma + \mu} \tag{41}$$

and

$$\begin{aligned} m(0) &\geq \frac{p(0) e^{-s+(\gamma-\gamma_m)C} (1 - e^{(\gamma-k_r)R})}{e^{\gamma_m R} - 1} \\ &\quad - \frac{\bar{v}\lambda[p(0)^\beta - \bar{v}^{\beta+\frac{\mu}{\gamma}} p(0)^{\frac{-\mu}{\gamma}}](ae^{\gamma_m(R-t_{sr})} + \gamma_m e^{-a(R-t_{sr})} - a - \gamma_m)I_{\{t_{sr} \leq R\}}}{(\beta\gamma + \mu)(a + \gamma_m)(e^{\gamma_m R} - 1)}, \end{aligned} \tag{42}$$

where

$$t_{sr} = \frac{\bar{v}}{ad(0)} = \frac{\beta\gamma + \mu}{a\lambda[p(0)^\beta - \bar{v}^{\beta+\frac{\mu}{\gamma}} p(0)^{\frac{-\mu}{\gamma}}]}, \tag{43}$$

or if $p(0)$ is sufficiently large to satisfy

$$p(0)^{\beta-1} - \bar{v}^{\beta+\frac{\mu}{\gamma}} p(0)^{-(1+\frac{\mu}{\gamma})} \geq \frac{(k_r - \gamma) e^{-s+(\gamma-\gamma_m)C} (\beta\gamma + \mu)}{\gamma_m \bar{v}\lambda} \tag{44}$$

and

$$\begin{aligned} [p(0)^{\beta-1} - \bar{v}^{\beta+\frac{\mu}{\gamma}} p(0)^{-(1+\frac{\mu}{\gamma})}] & (ae^{\gamma_m(R-t_{sr})} + \gamma_m e^{-a(R-t_{sr})} - a - \gamma_m) I_{\{t_{sr} \leq R\}} \\ & \geq \frac{e^{-s+(\gamma-\gamma_m)C} (1 - e^{(\gamma-k_r)R}) (\beta\gamma + \mu) (a + \gamma_m)}{\bar{v}\lambda}, \end{aligned} \tag{45}$$

then SCR is more effective than SRC.

Proof. By (19) and (32),

$$\begin{aligned} n_{SCR} - n_{SRC} &= p(0) e^{-s+(\gamma-k_c)C} (e^{(\gamma-k_r)u^*} - e^{(\gamma-k_r)R}) \\ &+ e^{(\gamma_m-k_c)C} [d(0) e^{\gamma_m u^*} - (d(0) + g_{sr}(R))] + m(0) e^{(\gamma_m-k_c)C} (e^{\gamma_m u^*} - e^{\gamma_m R}). \end{aligned} \tag{46}$$

Our analysis involves two steps: first we prove that either (41) or (44) imply that $u^* = 0$ in (20), and then we show that the quantity in (46) is negative in the $u^* = 0$ case if either (42) or (45) hold.

Substituting (8) into the $u^* = 0$ condition in (20) yields, after some simplification, condition (41). Alternatively, if $m(0) = 0$ then (41) is satisfied if

$$\frac{\lambda \bar{v} [p(0)^\beta - \bar{v}^{\beta+\frac{\mu}{\gamma}} p(0)^{\frac{-\mu}{\gamma}}]}{\beta\gamma + \mu} \geq \frac{p(0)(k_r - \gamma) e^{-s+(\gamma-\gamma_m)C}}{\gamma_m}. \tag{47}$$

The left side of (47) increases in $p(0)$ without bound, while Assumption 1 implies that the right side is bounded above by $\gamma_m^{-1} (k_r - \gamma) \bar{v} e^{(\gamma-\gamma_m)C}$. Consequently, we can rearrange (47) to get (44).

Turning to the second part of our argument, we set $u^* = 0$ in (46) to get

$$\begin{aligned} n_{SCR} - n_{SRC} &= p(0) e^{-s+(\gamma-k_c)C} (1 - e^{(\gamma-k_r)R}) - g_{sr}(R) e^{(\gamma_m-k_c)C} \\ &+ m(0) e^{(\gamma_m-k_c)C} (1 - e^{\gamma_m R}). \end{aligned}$$

This quantity is negative if

$$m(0) \geq \frac{p(0) e^{-s+(\gamma-\gamma_m)C} (1 - e^{(\gamma-k_r)R}) - g_{sr}(R)}{e^{\gamma_m R} - 1}. \tag{48}$$

Substituting in for $g_{sr}(R)$ using (27) and (8), we find that (48) can be expressed as (42), (43).

Using an argument analogous to that used in deriving (44), we take $m(0) = 0$ and find that (48) is satisfied if

$$g_{\text{sr}}(R) \geq p(0) e^{-s+(\gamma-\gamma_m)C} (1 - e^{(\gamma-k_r)R}). \quad (49)$$

Recalling that g_{sr} represents the number of offspring of dormant-then-vascular cells and that this quantity is increasing with $d(0)$ (once $d(0)$ is large enough to make $t_{\text{sr}} < R$), we can use (27) and (8) to show that $g_{\text{sr}}(R)$ increases without bound as $p(0)$ increases. Because the right side of (49) is bounded above by $\bar{v}e^{(\gamma-\gamma_m)C}(1 - e^{(\gamma-k_r)R})$ (by Assumption 1 again), condition (49) holds if $p(0)$ is sufficiently large; more precisely, condition (45) is derived by substituting (27) and (8) into (49), thereby completing the proof. \square

In words, Proposition 5 states that SCR is favoured over SRC if the initial metastatic population $m(0)$ is sufficiently large relative to the initial primary tumour size $p(0)$ (as given by (41)–(43)) or if the initial primary tumour is sufficiently large (as dictated by (44), (45)). It is desirable to use chemotherapy before radiotherapy to suppress either the large metastatic population (in the former case) or the large dormant population (in the latter case).

On the other hand, the dominance can swing the other way for patients at low metastatic risk. Referring to (46), note that $p(0)$ small enough makes $g_{\text{sr}}(R) = 0$ and $m(0)$ small enough makes the final term negligible; consequently, SRC is favoured over SCR for $p(0)$ and $m(0)$ sufficiently small.

6. Analysis of RCR schedules

The two RCR schedules are motivated in Section 6.1 and analysed in Sections 6.2 and 6.3, respectively.

6.1 Motivation

To motivate the SRCR schedule, we return to our comparison of SCR and SRC in Section 5.3. A close examination of (46) reveals that metastatic growth during radiotherapy is of central concern. More specifically, only existing vascular metastases and newly dormant-then-vascular tumours grow during SRC's radiotherapy, whereas dormant regrowth causes all metastatic tumours to grow during SCR's radiotherapy. Consequently, due to dormancy during SRC's radiotherapy, less systemic growth occurs during SRC's radiotherapy than during SCR's radiotherapy. Equation (46) also shows that SRC applies the full R days of radiotherapy and achieves its nadir at the end of treatment, while SCR mitigates the effect of its larger systemic growth during radiotherapy by achieving its nadir before applying the full allotment of radiotherapy, when radiation's effectiveness is eclipsed by increases due to systemic growth.

Schedule SRCR combines these advantages of SCR and SRC. By performing radiotherapy first we ensure that the severity of the systemic growth during radiotherapy is the same as that of SRC, but, using our analytical results, we time the duration of radiotherapy applied to mimic how SCR applies pre-nadir radiotherapy only while the net effect of radiotherapy on the nadir is desirable, i.e. radiotherapy's effectiveness is able

to offset systemic growth. Note that the inevitable conclusion to this is that sometimes the systemic growth may be so significant that it overcomes the usefulness of prenadir radiotherapy before R days of radiotherapy are applied, and the schedule foregoes the remaining radiotherapy until after chemotherapy.

The motivation for RSCR is analogous to that for SRCR, only this time the advantages of CSR and RSC are combined. For the same reasons that RSC can outperform SRC, delayed surgery is a viable option for RCR schedules and RSCR will at times outperform SRCR.

6.2 Nadir of SRCR schedule

Consider a generic SRCR schedule that begins with surgery, then administers radiotherapy for t time units, is followed by the full regimen of chemotherapy, and concludes with $R - t$ time units of radiotherapy. Under this schedule, the cancer burden at time $t + C$ is

$$b_{\text{SRCR}}(t) = p(0) e^{-s+(\gamma-k_r)t+(\gamma-k_c)C} + [d(0) + g_{\text{sr}}(t)] e^{(\gamma_m-k_c)C} + m(0) e^{\gamma_m t+(\gamma_m-k_c)C}, \quad (50)$$

where $g_{\text{sr}}(t)$ is defined in (27). We analyse a specific SRCR schedule, namely the one that applies R_1 time units of radiotherapy before chemotherapy and $R - R_1$ time units of radiotherapy after chemotherapy, where

$$R_1 = \arg \min_{0 \leq t \leq R} b_{\text{SRCR}}(t); \quad (51)$$

that is, the SRCR schedule minimizes the cancer burden at the time when chemotherapy is completed.

If $R_1 < R$ then regrowth of dormant cells occurs during $[R_1 + C, R + C]$ until the dormant compartment size at some time $t \in [R_1 + C, R + C]$ reaches the upper bound imposed by $\bar{d}(t)$. But, as with the CR schedules, we can show that this regrowth during SRCR never attains the level $\bar{d}(t)$ because

$$\begin{aligned} d(t) &= \bar{d}(t) e^{\gamma_m(t-R_1)+(\gamma_m-k_c)C} \quad \text{for } t \in [R_1 + C, R + C] \text{ by (14),} \\ &\leq \bar{d}(t) e^{\gamma_m(R+C)-k_c C} \quad \text{since } t - R_1 \leq R \text{ for } t \in [R_1 + C, R + C], \\ &\leq \bar{d}(t) \quad \text{by Assumption 2.} \end{aligned}$$

Hence, for SRCR during $[R_1 + C, R + C]$, the d and m compartments experience growth at rate γ_m and can be grouped for computing the cancer burden within this interval. Therefore, for $t \in [R_1 + C, R + C]$, we have

$$p(t) = p(0) e^{-s+(\gamma-k_r)R_1+(\gamma-k_c)C+(\gamma-k_r)(t-R_1-C)}, \quad (52)$$

$$(d+m)(t) = [(d(0) + g_{\text{sr}}(R_1)) e^{(\gamma_m-k_c)C} + m(0) e^{\gamma_m R_1+(\gamma_m-k_c)C}] e^{\gamma_m(t-R_1-C)}. \quad (53)$$

Although a closed-form solution for R_1 in (51) cannot, in general, be found, this optimization problem can be easily solved using standard numerical techniques. Nonetheless, we can prove the following proposition.

PROPOSITION 6 Schedule SRCR achieves its nadir at time $R_1 + C$.

Proof. Consider the schedule SR_1C , which is shorthand for an SRC policy that employs only R_1 time units of radiotherapy. We claim that this schedule attains its nadir at time $R_1 + C$ as a consequence of Proposition 1. To see this, note that the proof of Proposition 1 did not assume anything about the length of R , it did not use the radiotherapy part of Assumption 1, and, although Assumption 2 was used, this assumption still holds for radiotherapy of duration $R_1 < R$. Furthermore, Proposition 1's use of solutions based on the SRC analysis are valid for SR_1C , because these solutions did not rely on a particular choice of R nor the radiotherapy part of Assumption 1. Hence, the minimum cancer burden of schedule SRCR up to time $R_1 + C$ occurs at time $R_1 + C$.

To conclude the proof, we need only show that, when $R_1 < R$, the cancer burden of SRCR actually increases during $[R_1 + C, R + C]$. Using (52) and (53), we get that, for $C + t \in [R_1 + C, R + C]$,

$$\begin{aligned} \dot{b}_{\text{SRCR}}(t) &= (\gamma - k_r)p(0) e^{-s+(\gamma-k_r)R_1+(\gamma-k_c)C+(\gamma-k_r)t} \\ &\quad + \gamma_m[(d(0) + g_{\text{sr}}(R_1)) e^{(\gamma_m-k_c)C} + m(0) e^{\gamma_m R_1+(\gamma_m-k_c)C}] e^{\gamma_m t}, \\ \ddot{b}_{\text{SRCR}}(t) &= (\gamma - k_r)^2 p(0) e^{-s+(\gamma-k_r)R_1+(\gamma-k_c)C+(\gamma-k_r)t} \\ &\quad + \gamma_m^2[(d(0) + g_{\text{sr}}(R_1)) e^{(\gamma_m-k_c)C} + m(0) e^{\gamma_m R_1+(\gamma_m-k_c)C}] e^{\gamma_m t}. \end{aligned} \quad (54)$$

But $\dot{b}_{\text{SRCR}}(R_1) \geq 0$ by the definition of R_1 (note that $\dot{b}_{\text{SRCR}}(R_1) > 0$ if $R_1 = 0$), and $\ddot{b}_{\text{SRCR}}(t) \geq 0$ for $t \in [R_1, R]$ by (54), which completes the proof. \square

Using Proposition 6, we get that

$$\begin{aligned} n_{\text{SRCR}} &= p(0) e^{-s+(\gamma-k_r)R_1+(\gamma-k_c)C} \\ &\quad + [d(0) + g_{\text{sr}}(R_1)] e^{(\gamma_m-k_c)C} + m(0) e^{(\gamma_m-k_c)C+\gamma_m R_1}. \end{aligned} \quad (55)$$

6.3 Nadir of RSCR schedule

The development and analysis of RSCR is analogous to that of SRCR. Let

$$\begin{aligned} b_{\text{RSCR}}(t) &= p(0) e^{(\gamma-k_r)t-s+(\gamma-k_c)C} + [d(0) + g_{\text{rs}}(t) + h_r(t)] e^{(\gamma_m-k_c)C} \\ &\quad + m(0) e^{\gamma_m t+(\gamma_m-k_c)C} \quad \text{for } t \in [0, R], \end{aligned} \quad (56)$$

and define

$$\hat{R}_1 = \arg \min_{0 \leq t \leq R} b_{\text{RSCR}}(t).$$

Applying a similar analysis and arguments used for SRCR with b_{RSCR} and \hat{R}_1 in place of b_{SRCR} and R_1 (the analysis of RSCR requires noting that neither Proposition 2 nor the solutions for RSC rely on the radiation portion of Assumption 1, and that Assumption 3 is satisfied for $\hat{R}_1 < R$), we find that the nadir of RSCR occurs at time $\hat{R}_1 + C$, and thus

$$\begin{aligned} n_{\text{RSCR}} &= p(0) e^{-s+(\gamma-k_r)\hat{R}_1+(\gamma-k_c)C} + [d(0) + g_{\text{rs}}(\hat{R}_1) + h_r(\hat{R}_1)] e^{(\gamma_m-k_c)C} \\ &\quad + m(0) e^{(\gamma_m-k_c)C+\gamma_m \hat{R}_1}. \end{aligned}$$

7. Dominance of RCR schedules

In Propositions 7 and 8 below, we prove what was conjectured in Section 6.1: SRCR combines the best elements of SCR and SRC, and RSCR combines the best of CSR and RSC. The dominance of the RCR schedules is summarized in Proposition 9, and these two strategies are compared in Proposition 10.

PROPOSITION 7 $n_{\text{SRCR}} \leq n_{\text{SCR}}, n_{\text{SRC}}$.

Proof. Using (32) and (55), we get

$$n_{\text{SRCR}} = b_{\text{SRCR}}(R_1) \leq b_{\text{SRCR}}(R) = n_{\text{SRC}},$$

by our choice of R_1 .

To prove $n_{\text{SRCR}} \leq n_{\text{SCR}}$, note that

$$\begin{aligned} b_{\text{SRCR}}(t) &= p(0) e^{-s+(\gamma-k_c)C+(\gamma-k_r)t} + [d(0) + g_{\text{sr}}(t)] e^{(\gamma_m-k_c)C} \\ &\quad + m(0) e^{(\gamma_m-k_c)C+\gamma_m t} \text{ by (50),} \\ &\leq p(0) e^{-s+(\gamma-k_c)C+(\gamma-k_r)t} + d(0) e^{\gamma_m t} e^{(\gamma_m-k_c)C} + m(0) e^{(\gamma_m-k_c)C+\gamma_m t} \\ &\quad \text{since } t_{\text{sr}} \geq 0 \text{ implies } d(0) + g_{\text{sr}}(t) < d(0) e^{\gamma_m t}, \\ &= b_{\text{SCR}}(t) \text{ for all } t \in [0, R] \text{ by (17).} \end{aligned} \tag{57}$$

But inequality (57) implies that

$$n_{\text{SRCR}} = \min_{0 \leq t \leq R} b_{\text{SRCR}}(t) \leq \min_{0 \leq t \leq R} b_{\text{SCR}}(t) = n_{\text{SCR}}.$$

□

PROPOSITION 8 $n_{\text{RSCR}} \leq n_{\text{CSR}}, n_{\text{RSC}}$.

Proof. By Proposition 2, we have

$$n_{\text{RSCR}} = \min_{0 \leq t \leq R} b_{\text{RSCR}}(t) \leq b_{\text{RSCR}}(R) = n_{\text{RSC}}.$$

Showing $n_{\text{RSCR}} \leq n_{\text{CSR}}$ is trickier; we begin by establishing the inequality $h_r(t) e^{(\gamma_m-k_c)C} \leq h_c(C) e^{\gamma_m t}$, where $t \in [0, R]$. For $t \in [0, t_r]$, it is easiest to derive this inequality by using the following integral versions of $h_r(t)$ and $h_c(C)$, which follow from first principles and are consistent with the previous definitions in (22) and (34):

$$h_r(t) = \int_0^t e^{\gamma_m(t-\tau)} \lambda p(0)^\beta e^{(\gamma-k_r)\beta\tau} d\tau, \tag{58}$$

$$h_c(C) = e^{(\gamma_m-k_c)(C-t_c)} \int_0^{t_c} e^{(\gamma_m-k_c)(t_c-\tau)} \lambda p(0)^\beta e^{(\gamma-k_c)\beta\tau} d\tau. \tag{59}$$

Then, for $t \in [0, t_r]$,

$$\begin{aligned}
h_r(t) e^{(\gamma_m - k_c)C} &= e^{(\gamma_m - k_c)C} \int_0^t e^{\gamma_m(t-\tau)} \lambda p(0)^\beta e^{(\gamma - k_r)\beta\tau} d\tau \quad \text{by (58),} \\
&\leq e^{\gamma_m t} e^{(\gamma_m - k_c)C} \int_0^t \lambda p(0)^\beta e^{(\gamma - k_r)\beta\tau} d\tau, \\
&\leq e^{\gamma_m t} e^{(\gamma_m - k_c)C} \int_0^{t_c} \lambda p(0)^\beta e^{(\gamma - k_r)\beta\tau} d\tau \\
&\quad \text{since } k_c \leq k_r \text{ (by Assumption 4) implies } t_r \leq t_c, \\
&\leq e^{\gamma_m t} e^{(\gamma_m - k_c)(C - t_c)} \int_0^{t_c} e^{(\gamma_m - k_c)(t_c - \tau)} \lambda p(0)^\beta e^{(\gamma - k_r)\beta\tau} d\tau \\
&\quad \text{since } k_c > \gamma_m \text{ by Assumption 2,} \\
&\leq e^{\gamma_m t} e^{(\gamma_m - k_c)(C - t_c)} \int_0^{t_c} e^{(\gamma_m - k_c)(t_c - \tau)} \lambda p(0)^\beta e^{(\gamma - k_c)\beta\tau} d\tau \\
&\quad \text{since } k_c \leq k_r \text{ by Assumption 4,} \\
&= e^{\gamma_m t} h_c(C) \quad \text{by (59).} \tag{60}
\end{aligned}$$

For $t_r < t \leq R$,

$$\begin{aligned}
h_r(t) e^{(\gamma_m - k_c)C} &= h_r(t_r) e^{\gamma_m(t-t_r)} e^{(\gamma_m - k_c)C} \quad \text{by (34),} \\
&\leq h_c(C) e^{\gamma_m(t-t_r)} e^{\gamma_m t_r} \quad \text{by (60),} \\
&= h_c(C) e^{\gamma_m t}.
\end{aligned}$$

We use the above inequality, along with the fact that $t_{rs} \geq 0$ implies that $d(0) + g_{rs}(t) < d(0) e^{\gamma_m t}$, to show

$$\begin{aligned}
b_{\text{CSR}}(t) &= p(0) e^{-s + (\gamma - k_c)C + (\gamma - k_r)t} + d(0) e^{(\gamma_m - k_c)C + \gamma_m t} + h_c(C) e^{\gamma_m t} \\
&\quad + m(0) e^{(\gamma_m - k_c)C + \gamma_m t} \quad \text{by (23),} \\
&\geq p(0) e^{-s + (\gamma - k_c)C + (\gamma - k_r)t} + [d(0) + g_{rs}(t)] e^{(\gamma_m - k_c)C} + h_r(t) e^{(\gamma_m - k_c)C} \\
&\quad + m(0) e^{(\gamma_m - k_c)C + \gamma_m t}, \\
&= b_{\text{RSCR}}(t) \quad \text{by (56).}
\end{aligned}$$

The proof is completed by

$$n_{\text{CSR}} = \min_{0 \leq t \leq R} b_{\text{CSR}}(t) \geq \min_{0 \leq t \leq R} b_{\text{RSCR}}(t) = n_{\text{RSCR}}.$$

□

The next proposition combines the earlier results to show that one of the two RCR schedules is always superior to the six permutation schedules.

PROPOSITION 9 If $n_{\text{SRCR}} \leq n_{\text{RSCR}}$, then SRCR is better than all six permutation schedules; otherwise, RSCR is better than all six permutation schedules.

Proof. The SRCR schedule is better than the three CR schedules by Propositions 4 and 7, and it is better than SRC by Proposition 7. The RSCR schedule is better than the other two permutation schedules: it is better than RSC by Proposition 8 and better than RCS by Proposition 3. Hence, the better of the two RCR schedules is better than all six permutation schedules. \square

While it is difficult to compare the two RCR schedules in full generality, we derive in the next proposition a condition under which SRCR dominates not only RSCR but all feasible schedules. Although this condition is likely to hold in the clinic, it is actually motivated by analytical tractability of the optimization problem (51). Note that for $t \in [0, t_{sr}]$, equations (27) and (50) imply

$$\dot{b}_{\text{SRCR}}(t) = (\gamma - k_r)p(0) e^{-s+(\gamma-k_c)C+(\gamma-k_r)t} + \gamma_m m(0) e^{(\gamma_m-k_c)C+\gamma_m t}. \quad (61)$$

If we let $\tilde{\tau}$ equal the minimum of R and the time at which (61) vanishes (taking $-\ln(0) = \infty$), then

$$\tilde{\tau} = \min \left\{ R, \frac{\ln \left(\frac{(k_r-\gamma)p(0)e^{-s+(\gamma-\gamma_m)C}}{\gamma_m m(0)} \right)}{\gamma_m - \gamma + k_r} \right\}.$$

If $\tilde{\tau} \leq t_{sr}$, then $R_1 = \tilde{\tau}$ is the closed-form solution to (51). A weaker version of the condition $\tilde{\tau} \leq t_{sr}$ is that, when surgery is performed first, the first angiogenesis of a dormant tumour occurs sometime *after* R days. Given that R is likely to be in the range of 33–40 days, and the postsurgical angiogenesis of dormant tumours typically takes several months (Demicheli *et al.*, 1998), this is not an unreasonable assumption.

PROPOSITION 10 If

$$\min \left\{ R, \frac{\ln \left(\frac{(k_r-\gamma)p(0)e^{-s+(\gamma-\gamma_m)C}}{\gamma_m m(0)} \right)}{\gamma_m - \gamma + k_r} \right\} \leq \frac{\bar{v}}{ad(0)} \quad (\text{i.e. } \tilde{\tau} \leq t_{sr}),$$

then SRCR is optimal among all possible schedules that satisfy constraints (2)–(10).

Proof. We need to show that SRCR is at least as good as any schedule, say schedule B, in which surgery, C days of chemotherapy and R days of radiotherapy are interspersed in some general way.

The proof is by contradiction: consider a schedule B in which surgery, C days of chemotherapy and R days of radiotherapy are interspersed in some general way, and assume that B is optimal. Let t^* denote the time of schedule B’s nadir, with R_C and R_B the cumulative durations of chemotherapy and radiotherapy (respectively) applied up to time t^* , and B_s a 0–1 indicator equal to 1 if B applies surgery prior to t^* . Further, let

- x_1 = number of cells remaining at time t^* that were produced by dormant regrowth during periods of radiotherapy after chemotherapy;
- x_2 = number of offspring cells, remaining at time t^* , that were produced by any dormant cells that underwent angiogenesis during $[0, t^*]$;
- x_3 = number of cells remaining at time t^* produced by any primary tumour shedding during $[0, t^*]$. This includes both the shed cells and their offspring.

Then we can write

$$\begin{aligned}
n_B &= p_B(t^*) + d_B(t^*) + m_B(t^*), \\
&= p(0) e^{-sB_s + (\gamma - k_c)C_B + (\gamma - k_r)R_B} + d(0) e^{(\gamma_m - k_c)C_B} + x_1 + x_2 + x_3 \\
&\quad + m(0) e^{(\gamma_m - k_c)C_B + \gamma_m R_B} \\
&\geq p(0) e^{-sB_s + (\gamma - k_c)C_B + (\gamma - k_r)R_B} + d(0) e^{(\gamma_m - k_c)C_B} + m(0) e^{(\gamma_m - k_c)C_B + \gamma_m R_B} \\
&\quad \text{since } x_i \geq 0 \text{ for } i = 1, 2, 3, \\
&\geq p(0) e^{-s + (\gamma - k_c)C_B + (\gamma - k_r)R_B} + d(0) e^{(\gamma_m - k_c)C_B} + m(0) e^{(\gamma_m - k_c)C_B + \gamma_m R_B} \\
&\quad \text{because } s \geq 0 \text{ by Assumption 1,} \\
&\geq p(0) e^{-s + (\gamma - k_c)C_B + (\gamma - k_c)(C - C_B) + (\gamma - k_r)R_B} + d(0) e^{(\gamma_m - k_c)C_B + (\gamma_m - k_c)(C - C_B)} \\
&\quad + m(0) e^{(\gamma_m - k_c)C_B + (\gamma_m - k_c)(C - C_B) + \gamma_m R_B} \\
&\quad \text{since } C_B \leq C, \text{ and } \gamma < k_c, \gamma_m < k_c \text{ by Assumptions 2 and 5,} \\
&= p(0) e^{-s + (\gamma - k_c)C + (\gamma - k_r)R_B} + d(0) e^{(\gamma_m - k_c)C} + m(0) e^{(\gamma_m - k_c)C + \gamma_m R_B}, \\
&\geq p(0) e^{-s + (\gamma - k_c)C + (\gamma - k_r)\tilde{\tau}} + d(0) e^{(\gamma_m - k_c)C} + m(0) e^{(\gamma_m - k_c)C + \gamma_m \tilde{\tau}} \\
&\quad \text{by the definition of } \tilde{\tau}, \\
&= b_{\text{SRCR}}(\tilde{\tau}) \text{ by (50),} \\
&= n_{\text{SRCR}}.
\end{aligned}$$

Hence, SRCR is optimal among all feasible policies. \square

8. Discussion

Approach. We have formulated a mathematical model that to our knowledge is the first to explicitly address the age-old question in cancer treatment: how to sequence surgery, radiotherapy and chemotherapy (McCormick, 1996). Our model attempts to incorporate all of the salient mechanisms underlying the interrelated dynamics associated with a primary tumour and its shedding, angiogenesis of the primary tumour and its impact on metastatic dormancy and growth, and the impact of local (surgery and radiotherapy) and systemic (chemotherapy) treatment. Despite trying to keep our model as simple as possible, it still has 14 parameters. Moreover, some of these parameter values are only known to within an order of magnitude, and most of them have considerable interpatient heterogeneity, sometimes in a complicated manner; that is, due to specific mutations and the microenvironment, the radiosensitivity, chemosensitivity, shedding rate, growth rates, and angiogenesis rates may be correlated (see, for example Tubiana & Koscielny, 1991; Lewis *et al.*, 1996). Hence, in our view, it would be difficult if not impossible to validate this 14-parameter model (due to the many degrees of freedom in the parameter value selection) using clinical data. Without a model validation, any conclusions derived from a computational study would not (with good reason) persuade a skeptical clinical research community. Therefore, we have employed a purely analytical approach to this problem. In Section 3, we impose five assumptions on the parameter values, and in Proposition 10 we add a sixth condition to prove the global optimality of a specific policy. These six

inequalities can be expressed in simple biological terms, so that a clinical researcher can easily decide whether our sequencing results are credible.

Results. For the three RC schedules, we prove that earlier surgery is preferred; i.e. SCR is better than CSR, which is better than CRS. To understand this result, note the tradeoff inherent in the timing of surgery: earlier surgery prevents shedding of the primary tumour, while later surgery acts as a ‘poor man’s antiangiogenesis’ by slowing the rate of vascularization of dormant metastatic tumours. In our model, the avascular and vascular metastatic tumours behave identically during CR schedules: they both shrink during chemotherapy, and both grow during radiotherapy (an avascular tumour’s growth during radiotherapy is regrowth toward its dormant ceiling size of \bar{v} cells, but Assumption 2 prevents them from attaining this level during treatment). In these circumstances, efforts to prevent angiogenesis of dormant metastases by delaying surgery are fruitless. Hence, delayed surgery offers no antiangiogenic advantage to offset the accompanying primary shedding, and so earlier surgery is preferable.

The suboptimality of CSR is perhaps surprising in light of the ongoing clinical trial of this schedule by the Milan Cancer Institute (Bonadonna, 1996). There are three factors not included in our model that could bias our results against the CSR regimen. First, by assuming that surgery is instantaneous, we ignore the unchecked metastatic growth that may occur during the several-week healing period between surgery and adjuvant chemotherapy in SCR; however, we note that delays of up to four weeks cause no significant difference in outcome (The Ludwig Breast Cancer Study Group, 1988; Sertoli *et al.*, 1995). Also, one of the rationales of the Milan group is that chemotherapy is likely to face a smaller drug-resistant population in the neoadjuvant setting (Bonadonna *et al.*, 1998). Finally, their biggest motivation for administering at least a few rounds of chemotherapy before surgery was to increase the likelihood of breast-conserving surgery.

In contrast to the CR schedules, the timing of surgery does influence the behaviour of dormant metastases during RC schedules. Vascular metastatic tumours grow during RC’s radiotherapy, while dormant tumours remain latent at their ceiling size. According to (40), RSC is favoured over SRC (i.e. delayed surgery is preferable) if the increase in the number of offspring from dormant-then-vascular cells during radiotherapy when surgery is performed first rather than delayed (recall that the angiogenesis rate is higher after surgery) is greater than the amount of incipient metastases caused by primary shedding and its subsequent growth during radiotherapy if surgery is delayed. Computational results (not shown here) using representative parameter values from the literature and a variety of initial conditions did not allow us to conclude that one of these two schedules consistently dominated the other.

The two most commonly used multimodal schedules from a historical perspective are SCR and SRC. Proposition 5 shows that SCR is preferred to SRC if, at the time of presentation, the detectable metastasis is sufficiently large relative to the primary tumour, or if the primary tumour is sufficiently large. In these two cases, chemotherapy should be given before radiotherapy to suppress the vascular metastatic population and the dormant metastatic population, respectively. In contrast, if the primary tumour is sufficiently small and there is no detectable metastasis, then SRC is favoured over SCR. This result is consistent with Recht *et al.* (1996), which showed that SCR is preferable to SRC for breast

cancer patients receiving conservative surgery who are at substantial risk for systemic metastases (as determined by the presence of positive nodes, a negative estrogen receptor test, or invaded lymphatic vessels).

A close examination of the comparison of SCR and SRC led us to consider SRCR, which maintains the relatively low systemic growth during SRC's radiotherapy, while adopting SCR's approach of achieving its nadir when radiotherapy's effectiveness is offset by systemic growth. In a similar manner, we hypothesized that RSCR combines the best of CSR and RSC. Although neither of these novel policies always dominates the other, we prove that it is always the case that the better of these two schedules is preferable to all six permutation schedules. Furthermore, under the additional condition that vascularization of dormant metastatic tumours does not occur within the first R (≈ 40) days after surgery, then SRCR is optimal over all possible schedules that employ surgery, R days of radiotherapy and C days of chemotherapy. A noteworthy feature of this result is its simplicity: one only needs to split radiotherapy into two disjoint segments to attain optimality, and more sophisticated strategies, such as the integrated alternating regimen in Tubiana *et al.* (1985), need not be considered. A second interesting aspect of this result is that SRCR has the same cure probability in our model as a SR_1C policy that employs $R_1 \leq R$ time units of radiotherapy. Nonetheless, applying the remaining $R - R_1$ time units of radiotherapy after chemotherapy may improve locoregional control and delay the onset of metastasis in cases where a cure is not achieved.

Finally, as a side benefit of our analysis, we note that our estimation of the amount of subclinical dormant metastases at the time of presentation appears to be new. Applying existing results in queueing theory, where shed cells from the primary tumour correspond to arrivals to the waiting line, and services correspond to the time between being shed as a solitary metastatic cell and reaching a clinically detectable size, we derive the counter-intuitive result that the knowledge of the number and size of clinically detectable metastases at the time of presentation does not influence the estimate for the expected number of dormant metastases at the time of presentation. This result requires only two mild probabilistic assumptions: shedding occurs according to a nonhomogeneous Poisson process, which follows (asymptotically, as the number of cells gets large; Çinlar, 1972) if each cell metastasizes independently of one another, and all service times are independent and identically distributed.

Limitations. Our model, despite containing 14 parameters, is a gross caricature of physical reality. First and foremost, most tumours are a heterogeneous collection of cells that accumulate mutations (e.g. p53), which are partially dictated by the tumour's microenvironment (e.g. the oxygen level; Graeber *et al.*, 1996) and the treatment (particularly chemotherapy) regimen (i.e. Coldman–Goldie's acquired resistance hypothesis; Coldman & Goldie, 1983). These mutations in turn may cause changes in the radiosensitivity, chemosensitivity, shedding rate, growth rate, and angiogenesis rate of the primary and metastatic tumours. It is difficult to predict how our model's exclusion of this heterogeneity might bias the results. One could argue that giving chemotherapy early may be desirable because the tumour cells have not accumulated too many mutations, while it could also be argued that it is preferable to delay chemotherapy, and hence acquired drug

resistance. Either way, our omission of these factors requires our results to be interpreted with caution.

As mentioned earlier, our model also glosses over the detailed timing issues, such as the healing periods between modes of treatment, and the pharmacokinetics of chemotherapy. Also, there are some chemotherapeutic agents that appear to act in a synergistic or antagonistic manner with radiotherapy. However, these interactions are drug-specific and often depend upon the detailed timing of the schedule. Finally, the process of tumour angiogenesis is extremely complex, involving the regulation of dozens of factors (Hanahan & Folkman, 1996), and our modelling of it is necessarily simplistic.

Despite these biological simplifications, perhaps the biggest shortcoming in our model—which is shared by the majority of mathematical models in the cancer treatment literature—is the modelling of a dynamic stochastic decision problem with imperfect but accumulating information by a dynamic deterministic control problem with perfect information. In particular, the effectiveness of our two novel schedules requires the clinician to observe the point in time when the metastatic growth begins to outweigh the radiation killing, something that is impossible with today's technology. Consequently, it is important to reflect on how—and if—the results derived here can be applied to the actual clinical problem. We envision that the insights from this analysis could be operationalized in the following manner, which is illustrated with the SRCR schedule. First, a statistical model (along the lines developed in Koscielny *et al.*, 1984; Koscielny & Tubiana, 1999) could be used to map the information gained at the time of presentation and at surgery (e.g. size of the primary tumour, amount of detectable metastases, histological grade, presence of margins, node involvement, hormonal tests such as psa for prostate cancer or estrogen receptor for breast cancer) to estimate a one-dimensional quantity called the metastatic potential (e.g. the probability of detectable metastases within five years). This information is then used in the context of our results: if the metastatic potential is very small then use SRC, if it is very large use SCR, and if it is intermediate in value then use a version of SRCR. Of course, the refinement and validation (via simulation initially) of such a model would entail a significant independent study in itself. If new information arises during treatment, then the schedule can be altered accordingly; for example, if a patient presents with metastases during the radiation portion of SRC, radiotherapy would be immediately truncated in favour of chemotherapy.

Conclusion. In summary, our model and analysis provides a systematic framework for thinking about the sequencing of the three traditional cancer treatments in multimodal therapy. Our analysis elucidates the tradeoffs inherent in this complex problem, and unearthed two novel schedules, SRCR and RSCR, which may be capable of generating clinical benefits. In addition to further studies that might validate and operationalize our results (as described above), an obvious extension is to incorporate angiogenesis inhibitors as a fourth mode of treatment; initial results of angiostatin and radiotherapy on mice are intriguing (Gorski *et al.*, 1998; Mauceri *et al.*, 1998). To generalize our model in this direction without sacrificing analytical tractability would probably require a modelling approach in the spirit of Hahnfeldt *et al.* (1999), rather than the more detailed spatial models that dominate the mathematical literature (Orme & Chaplain, 1997).

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