The logic of containing tumors

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Abstract

Challenging the paradigm of the maximum tolerated dose, recent studies have shown that a strategy aiming for containment, not elimination, can control tumor burden more effectively *in vitro*, in mouse models, and in the clinic. These outcomes are consistent with the hypothesis that emergence of resistance to cancer therapy may be prevented or delayed by exploiting competitive ecological interactions between drug-sensitive and resistant tumor cell subpopulations. However, although various mathematical and computational models have been proposed to explain the superiority of particular containment strategies, this evolutionary approach to cancer therapy lacks a rigorous theoretical foundation. Here we combine extensive mathematical analysis and numerical simulations to establish general conditions under which a containment strategy is expected to control tumor burden more effectively than applying the maximum tolerated dose. We show that when resistant cells are present, an idealized strategy of containing a tumor at a maximum tolerable size maximizes time to treatment failure (that is, the time at which tumor burden becomes intolerable). These results are very general and do not depend on any fitness cost of resistance. We further provide formulas for predicting the clinical benefits attributable to containment strategies in a wide range of scenarios, and we compare outcomes of theoretically optimal treatments with those of more practical protocols. Our results strengthen the rationale for clinical trials of evolutionarily-informed cancer therapy.

Introduction

The justification for aggressive anti-cancer therapies is to maximize the probability of a cure [1,2]. This rationale disappears if a cure cannot be expected. In some if not many cases, treating aggressively can be suboptimal due to treatment toxicity and selection for resistance. A better strategy might be rather to use the *minimal* effective dose that contains the tumor subject to ensuring sufficient quality of life [3–5].

The logic of aiming for containment rather than elimination is based on evolutionary principles. At the beginning of therapy, a tumor contains cells with different sensitivities to treatment. An aggressive treatment eliminates the most sensitive cells but can enable resistant cells – freed from competing with sensitive cells for space and resources – to thrive uncontrollably. This phenomenon, called competitive release, is well understood in ecology and pest management [6–8]. By maintaining a large population of treatment-sensitive tumor cells, a containment strategy aims to exploit cell-cell competition to prevent or delay the emergence of resistance.

Various protocols in this spirit have been found to be superior to conventional therapy in experimental models [4, 9, 10], a preclinical trial [11], and a small clinical trial in metastatic castrate-resistant prostate cancer [12]. Other clinical trials are active or recruiting [13]. Yet even as empirical evidence accumulates in support of tumor containment strategies, the underlying evolutionary theory remains only imprecisely characterized in the cancer context. With the notable exception of Martin *et al.* (1992) [3,14], previous mathematical and simulation studies [4, 9, 10, 12, 15–22] have focussed on particular model formulations, specific therapeutic protocols, and typically untested assumptions about tumor growth rate, cell-cell interactions, treatment effects and resistance

costs. Many previous findings are not readily generalizable because they are based on simulations, rather than mathematical analysis. Sufficient conditions for successful tumor containment have not been established. Here we address this knowledge gap by synthesizing, generalizing, and extending previous results to form a solid theoretical basis for pursuing evolutionary approaches to cancer therapy. Our work thus provides timely guidance for empirical research including the design of clinical trials.

Results

When is containment optimal?

The optimal treatment strategy depends on the clinical objective. If the emphasis is on rapidly reducing tumor burden then the maximum tolerated dose (MTD) is clearly superior to containment. However, if the aim is to maximize the time to progression (defined here as the time until the tumor becomes larger than at initiation of treatment) then our formal mathematical analysis proves that containment is likely to be optimal, or at least close to optimal, in a broad range of cases.

To see why, consider a tumor containing sensitive and fully resistant cells. The growth rates of these two subpopulations are expected to depend on the subpopulation sizes, and the growth rate of sensitive cells will also vary with the treatment dose. Furthermore, if resource competition is the dominant ecological interaction between subpopulations then it is reasonable to assume that, all else being equal, the larger the sensitive population, the lower the growth rate of the resistant population. To the best of our knowledge, this latter assumption holds for all proposed mathematical models with two cell types in which the impact of mutations after treatment initiation can be neglected (see Section 1 of Supplementary material for a review of previous studies).

If the objective is to maximize time to progression then, under the above general assumptions, we find that the best possible treatment is the containment strategy that precisely maintains the original tumor burden for as long as some sensitive cells remain. We will term this the *ideal* containment strategy. Moreover, among treatment strategies that eventually eliminate the sensitive population, we find that the worst option is to maximise the cell kill rate. Instead of maximizing time to progression, an alternative objective is to maximize the time until the tumor burden exceeds a certain threshold. In this case, the optimal treatment maintains the tumor at precisely this threshold size.

The intuitive explanation is that, whereas we can always reduce the sensitive population by using a sufficiently aggressive treatment, the only way to impair the growth of resistant cells is to exploit competition with sensitive cells. By assumption, this ecological form of control is most effective when the sensitive population is as high as can be permitted. Conversely, competition is least effective when the sensitive population is smallest; that is, under MTD. Formal mathematical proofs of all these results – in very general settings – can be found in Supplementary material, Section 2.1.

Characterizing the intensity of competition between tumor cells

Although we find that the superiority of ideal containment is qualitatively very robust, the predicted magnitude of clinical benefits depends on biological assumptions and parameter values. A critical factor is the strength of competition between treatment-sensitive and resistant cells. One biologically plausible hypothesis is that the growth rate of resistant cells primarily depends on their abundance relative to sensitive cells [9,10]. In ecological parlance, this means that the fitness of resistant cells is *frequency-dependent*. If this assumption holds then the most important parameter in determining outcomes is the relative fitness of resistant cells when rare [9]. In other words, what matters is how rapidly resistant cells proliferate, relative to sensitive cells, while resistant cells make up only a tiny fraction of the tumor. The smaller this parameter value, the greater the predicted clinical gains from containment, relative to MTD.

An alternative, equally plausible hypothesis is that resistant cells fitness is primarily *density-dependent*, such that the per-cell growth rate decreases as the total tumor burden increases [3,12,14,15,23]. What matters most in this case is the strength of density dependence. In the widely-used Gompertzian model of tumor growth, the

per-cell growth rate decreases relatively rapidly with increasing tumor size, leading to a strong competition effect and substantial clinical gains for containment versus aggressive treatment. Mathematical models that describe weaker competition, such as the logistic growth model, predict smaller clinical gains [3, 14], whereas those that describe stronger competition, such as the von Bertalanffy growth model, predict larger gains (Supplementary Figs. 1a and 1b; Supplementary material, Section 4.1.1).

Important differences between model predictions underscore the need to advance understanding of the ecological interactions that govern intra-tumor dynamics [24], which remain only poorly characterized. Nevertheless, we find that what matters is not so much whether a mathematical model assumes frequency- or density-dependent fitness, but rather whether the model accurately describes the strength of this dependence.

Other important biological parameters

To illustrate how biological parameter values are predicted to influence clinical outcomes, we focus on a particular Gompertzian growth model studied by Monro and Gaffney (2009) [15] (see also Martin *et al.* (1992) [3]):

$$\begin{aligned} \dot{S}(t) &= \rho \ln(K/N(t))\,(1-\lambda C(t))S(t), \\ \dot{R}(t) &= \rho \ln(K/N(t))\,R(t), \end{aligned} \tag{Model 1}$$

where $N(t) = R(t) + S(t)$ is the total tumor burden at time t; $C(t)$ is the drug dose at time t (which is assumed to equate with treatment level, neglecting details of pharmacokinetics and pharmacodynamics); λ is a sensitivity parameter; K is the tumor carrying capacity (the hypothetical size at which the tumor would cease to grow); and ρ is the baseline per-cell growth rate. We focus on this particular model in our numerical simulations partly to facilitate comparison with previous analysis [15], and also because Gompertzian growth has been shown to describe tumor growth better than alternative models such as logistic growth [25, 26].

The ideal MTD treatment depicted in Fig. 1a (dashed line) is an idealized version of MTD which instantly eliminates sensitive cells [23, 27]. In Model 1, as in any density-dependent model, the clinical gain from this regimen, compared to no treatment, is the time it takes for the tumor to grow from R_0 (the initial resistant population) back to its initial size N_0; that is, the time taken for the resistant population to increase by a factor of N_0/R_0 after being freed from competition with sensitive cells.

In the case of ideal containment, the clinical gain is instead the duration of the stabilization phase. This is equal to the time taken for the resistant population to increase by a factor of N_0/R_0 while the tumor is maintained at the stabilization size. Because competition with sensitive cells impedes the growth of resistant cells, the gain from ideal containment is invariably greater than the gain from ideal MTD. Moreover, a larger stabilization size results in a longer stabilization phase and hence improved survival (Fig. 1b).

Simple mathematical expressions may be derived to quantify the effects of containment and MTD strategies in various density-dependent scenarios (see Supplementary material, Section 3), enabling us to examine the impact of varying any parameter on time to progression, time to treatment failure, and survival time. These three outcomes are defined, respectively, as the times until the tumor becomes larger than N_0 (the size at treatment initiation), N_{tol} (a hypothetical maximum tolerable size) and N_{crit} (the hypothetical lethal tumor size). For idealized treatments, these outcomes are independent of the treatment's mode of action (for example, whether it results in a log kill rate, a Norton-Simon kill rate proportional to the net growth rate of an untreated tumor [1], or some other effect).

For Model 1, the times to progression under ideal containment at the initial size and ideal MTD are

$$t_{prog}(idContN_0) = \frac{1}{\rho}\frac{\ln(N_0/R_0)}{\ln(K/N_0)} \quad \text{and} \quad t_{prog}(idMTD) = \frac{1}{\rho}\ln\left(1+\frac{\ln(N_0/R_0)}{\ln(K/N_0)}\right),$$

respectively, where ln is the natural logarithm. In terms of time to progression, the *absolute* clinical benefit of ideal containment over ideal MTD is the difference between these numbers; the *relative* benefit is the ratio

$$\frac{t_{prog}(idContN_0)}{t_{prog}(idMTD)} = \frac{x}{\ln(1+x)} \text{ with } x = \frac{\ln(N_0/R_0)}{\ln(K/N_0)}. \tag{1}$$

These formulas reveal the importance of three patient-specific factors: the baseline growth-rate, ρ; the initial frequency of resistant cells, R_0/N_0; and the initial tumor size compared to the carrying capacity, N_0/K.

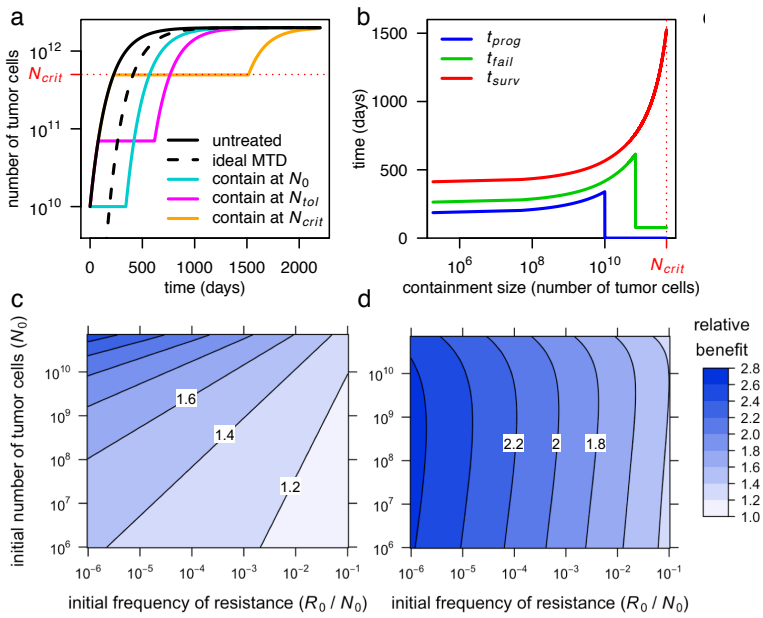

Figure 1: **Outcomes of idealised treatment strategies in Model 1. a**, Evolution of total tumor size under no treatment, ideal MTD, and ideal containment at three different tumor sizes. The patient is assumed to die shortly after tumor size becomes greater than N_{crit}. **b**, Times to progression (blue), treatment failure (green), and survival time (red) under ideal containment at a threshold size varied from R_0 to N_{crit} (ideal containment at R_0 is equivalent to ideal MTD). The time until the tumor exceeds a certain size is maximized by ideal containment at that size. **c**, Relative benefit, in terms of time to progression, for ideal containment (at size N_0) versus ideal MTD, as a function of initial tumor size and frequency of resistant cells. **d**, Relative benefit, in terms of time to treatment failure, for ideal containment (at size N_{tol}) versus ideal MTD, as a function of initial tumor size and frequency of resistant cells. Formulas are in Supplementary material, Section 3.1. Except where explicitly varied, parameter values are as in Table 2.

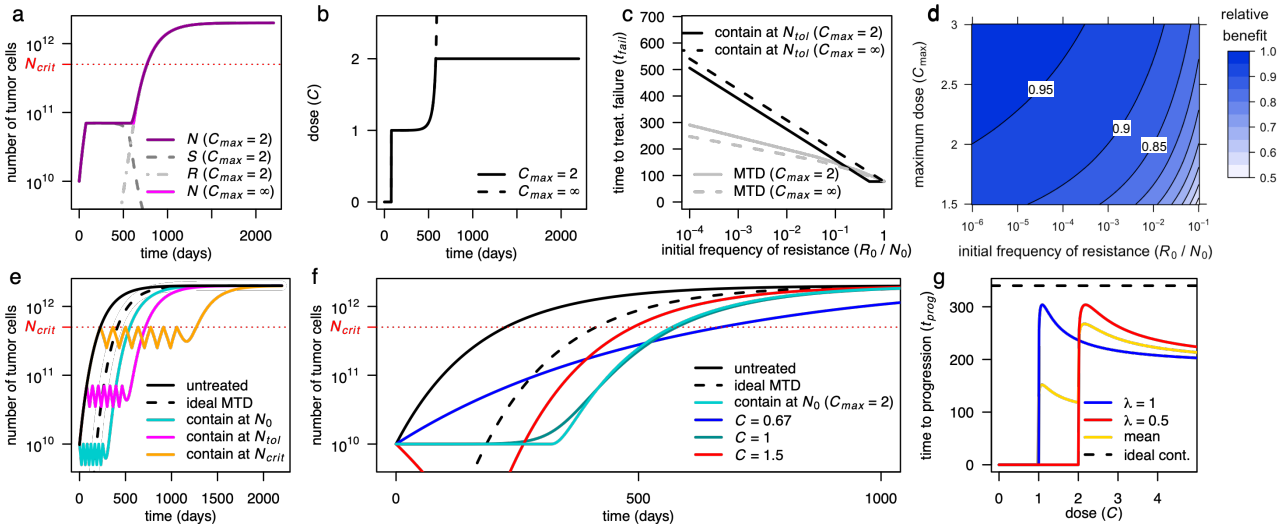

Figure 2: **Outcomes of practical treatment strategies in Model 1. a**, Tumor size under containment at the maximum tolerable size subject to maximum dose threshold $C_{max} = 2$ (purple) and $C_{max} = \infty$ (pink). The latter case corresponds to ideal containment. Sensitive (S) and resistant (R) subpopulation sizes are shown for the case $C_{max} = 2$. **b**, Treatment doses for the two strategies shown in panel a. No treatment is given until the maximum tolerable size is reached. The tumor is then stabilized by continuously increasing the dose until the dose reaches C_{max} (continuous line) or as long as some sensitive cells remain (dashed line). **c**, Time to treatment failure versus initial frequency of resistance, under containment at N_{tol}. Outcomes are shown for MTD treatment and containment at the maximum tolerable size, both in the ideal case and subject to $C_{max} = 2$. **d**, Relative benefit, in terms of time to treatment failure, for containment versus ideal containment (at size N_{tol}), as a function of maximum dose threshold (C_{max}) and initial frequency of resistant cells (formulas are in Supplementary material, Section 3.3). Contour lines are at intervals of 0.05. **e**, Ideal intermittent containment between N_{max} and $N_{min} = N_{max}/2$ for three different values of N_{max}. **f**, Tumor size for various constant dose treatments compared to containment at the initial size (subject to $C_{max} = 2$) and ideal MTD. **g**, Times to progression for two patients whose tumors differ in treatment sensitivity (parameter λ). The yellow line is the mean of the two patient outcomes and the dashed line is the time to progression under ideal containment (which is the same for both patients). Except where explicitly varied, parameter values are as in Table 2.

For idealized treatments, decreasing the growth rate parameter (ρ) has no effect on the *relative* clinical benefits of containment, but, by slowing the dynamics, leads to higher *absolute* benefits. Instead decreasing the initial frequency of resistant cells (R_0/N_0) increases both absolute and relative clinical gains of containment versus MTD. This is in part because aggressive treatments are especially suboptimal when resistance is very rare, as they then cause a drastic reduction in tumor size, which permits rapid expansion of the resistant population. Lastly, a higher value of ratio N_0/K implies more intense competition at the initial tumor size. This increases both absolute and relative benefits of containment at the initial size. Fig. 1c illustrate some of these effects for Model 1. Patterns for time to treatment failure (Fig. 1d) are more complex (Supplementary material, Section 4.1.2).

Practical treatment strategies can be close to optimal

For simplicity in the above mathematical analysis, we assumed no restriction on maximum dose, which permits the ideal containment strategy of maintaining the tumor precisely at a target size until it becomes fully resistant. In reality, toxicity constraints typically impose a maximum instantaneous dose C_{max}. Figs. 2a and 2b compare tumor dynamics and doses under ideal containment and under a containment strategy with a relatively low value of C_{max}. In the latter case, the stabilization phase is slightly shorter because it finishes before all sensitive cells have been removed, which results in slightly shorter times to progression or treatment failure (Fig. 2c and 2d; Supplementary Fig. 4). The two treatments nevertheless result in similar survival times. Differences

between ideal and non-ideal containment outcomes are discussed in greater detail in Supplementary material, Section 4.2.

An additional consideration is that a continuous containment strategy requires continuous monitoring of tumor size, which is typically infeasible. More practical protocols include intermittent containment, constant dose therapy and metronomic therapy.

Intermittent containment. The question of whether it is better to implement containment via a continuous low dose or an intermittent high dose has yet to be settled. Both strategies worked well in mice [11]. Although Zhang *et al.* (2017) [12] obtained highly promising clinical results from intermittent high dose treatment, it is plausible that a continuous low dose treatment would have performed even better (as, if anything, seems to be the case in mice [11], although the evidence is too scarce to be conclusive). Mathematical models that account for cell-cycle dynamics, pharmacodynamics, and drug-induced resistance may be able to predict the optimality of a specific intermittent treatment, provided they can be precisely parameterized. In our simple setting, however, higher tumor burden implies slower growth of resistance, and hence exact containment at an upper threshold N_{max} is better than containment between upper and lower bounds N_{max} and N_{min}. Nevertheless, as is apparent from comparing Fig. 2e and Fig. 1a, the difference between the two types of protocol is small provided that N_{min} is a large fraction of N_{max}. Indeed, decreasing tumor burden from N_{max} to N_{min} then only slightly increases the growth rate of resistant cells. Intermittent containment as in the clinical trial of Zhang *et al.* (2017) [12], which may be the only practical possibility, therefore appears to be a sound implementation of containment, as long as the lower threshold is not too low.

Constant dose. To maximize time to progression in Model 1, the optimal constant dose is slightly higher than $C = 1/\lambda$ (which corresponds to $C = 1$ in Fig. 2b). The constant dose $C = 1/\lambda$ stabilizes the sensitive population size, whereas containment uses the evolving dose $C = 1 + R/S$ to stabilize tumor size. According to our definition, the former approach leads to immediate progression because it allows the overall tumor size to increase from the start of treatment. However, provided that resistant cells are initially rare, the dose $C = 1/\lambda$ maintains tumor size close to the initial size for nearly as long as under containment (Fig. 2f). Differences that emerge after resistant cells become abundant are relatively unimportant. Thus, for a given patient, the dose $C = 1/\lambda$ is expected to lead to similar outcomes as containment at the initial size. Similarly, delaying treatment until the tumor size reaches N_{tol} and then applying dose $C = 1/\lambda$ has similar outcomes as containment at the maximum tolerable size. Table 1 gives examples of times to progression, times to treatment failure, and survival times for various constant doses and other treatments. Note that the constant dose that maximizes time to progression is slightly higher than $1/\lambda$, whereas the non-delayed constant dose that maximizes survival time is lower than $1/\lambda$ (Supplementary Table 6, Supplementary Fig. 4e). Constant dose treatments may lead to higher survival time than containment at the initial size (Fig. 2e, Supplementary Fig. 4e) but to the cost of quicker progression, and they always lead to lower survival time than containment at sufficiently higher sizes. Additional treatments are considered in Supplementary material, Sections 3.3 and 4.6.

Adaptive containment. A problem with constant dose therapy is that the parameters that determine the best dose for a particular patient are typically unknown. Giving slightly too little or too much treatment can be far from optimal (blue and red curves in Fig. 2f). Any constant dose that works relatively well for some patients will inevitably be suboptimal for others, and the constant dose that gives the best average result for a cohort of patients will typically be further from containment than the best constant dose for a single patient (Fig. 2g; Supplementary material, Section 4.6). A practical solution to this problem of inter-patient variation is to pursue an adaptive containment strategy, which will be close to optimal for every patient because it entails continuously adjusting the dose as a function of patient response, without requiring any parameter to be known in advance (except that the tolerable tumor burden N_{tol} must be chosen by the physician or revealed during treatment). Similarly (in the absence of an initial induction phase where treatment is given at MTD, which would trigger competitive release), conventional metronomic therapy – in which low doses are given at regular, predefined intervals – may look similar to intermittent containment. However, intermittent containment (a particular form of adaptive therapy [12]) has the important additional benefit of adapting doses to the evolution of the tumor and to patient-specific parameters, without knowing these parameters in advance [28].

Table 1: **Time to progression, time to treatment failure, and survival time for Model 1.** Parameter values are as in Table 2. The constant dose or delayed constant doses $C = 1.09$ and $C = 1.07$ maximize t_{prog} and t_{fail}, respectively, among all constant dose or delayed constant dose treatments. Times are measured in days.

Treatment	t_{prog}	t_{fail}	t_{surv}
No treatment	0	77	226
Ideal MTD	186	263	412
MTD ($C_{max} = 2$)	236	314	463
$C = 1.09$	303	397	549
Containment at N_0 ($C_{max} = 2$)	318	418	568
Ideal containment at N_0	340	417	566
$C = 1.07$ from $N = N_{tol}$	0	543	731
Containment at N_{tol} ($C_{max} = 2$)	0	580	767
Ideal containment at N_{tol}	0	615	764

Fitness costs of resistance are helpful but not essential

Previous studies have asserted or assumed that a necessary condition for effective tumor containment is that treatment resistance incurs a cellular fitness penalty. This is particularly true of those advocating adaptive containment strategies (for example, [4,5,10,11,28–31]). As noted in a recent review article [5], "the theory behind adaptive therapy focuses on the phenotypic costs of the molecular mechanism(s) of resistance." Importantly, none of our qualitative results depends on a fitness cost of resistance. Indeed, we find that containment can be an optimal and highly effective strategy even if resistant cells are fitter than treatment-sensitive cells in the absence of therapy.

Yet, although not required for containment to improve on aggressive treatment, fitness costs of resistance may increase clinical gains. The precise effect depends on whether the cost of resistance is constant or is higher in the presence of sensitive cells [23]. To examine this issue, let us consider the following model:

$$\begin{aligned} \dot{S}(t) &= \rho_s \ln\left(\frac{K_s}{S(t) + \alpha R(t)}\right)(1 - \lambda C(t))S(t), \\ \dot{R}(t) &= \rho_r \ln\left(\frac{K_r}{R(t) + \beta S(t)}\right) R(t). \end{aligned} \tag{Model 2}$$

Here, the baseline growth rates ρ_s, ρ_r and the carrying capacities K_s, K_r are specific to sensitive and resistant cells, respectively. In the denominators, total tumor size has been replaced by a weighted sum of the resistant and sensitive population sizes, as is commonly assumed in ecological models. The higher the competition coefficient β, the greater the impact of sensitive cells on resistant cells. If $\beta = 1$, then resistant cells are affected equally by all cells and $R + \beta S = N$, as in Model 1.

In Model 2, a resistance cost may correspond to:

- a reduction in growth rate, independent of competition intensity (low ρ_r);
- a general inability to compete with other cells (low K_r);
- a specific inability to compete with sensitive cells (high β).

All such costs increase clinical gains of any treatment by slowing the growth of resistant cells. Moreover, resistance costs reduce the expected initial fraction of resistant cells, which is good for all treatments, but especially good for containment.

Nevertheless, for a given initial fraction of resistant cells, only some types of resistance cost increase relative clinical gains of ideal containment over ideal MTD. For instance, halving ρ_r doubles times to progression under both treatments, so the absolute benefit of containment doubles, but the relative benefit is unchanged. In a model that accounts for mutation from sensitive to resistant, lowering ρ_r may even decrease the relative benefit

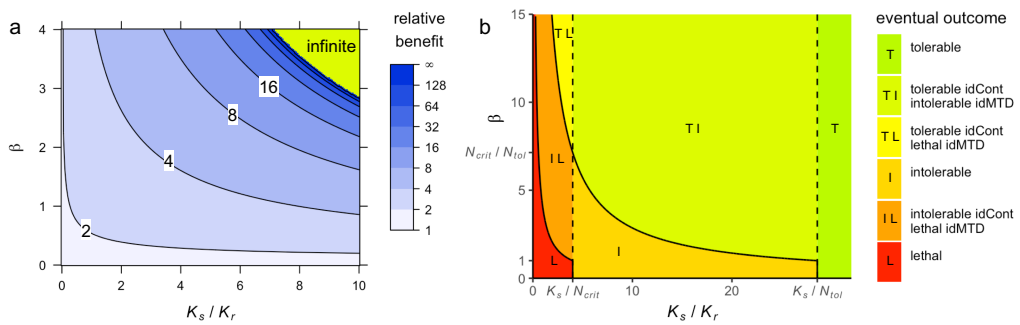

Figure 3: **Consequences of costs of resistance in Model 2. a**, Relative benefit, in terms of time to treatment failure, for ideal containment (at size N_{tol}) versus ideal MTD, for varied values of K_r and β. This figure is based on approximate formulas that are highly accurate for the selected parameter values (see Supplementary material, Section 5.2). Supplementary Fig. 6 shows an alternative version of this plot based on simulations. Contour lines are at powers of 2. **b**, Eventual outcomes of ideal containment (idCont) and ideal MTD (idMTD) treatment strategies, based on exact formulas (see Supplementary material, Section 5.1). The "infinite" region in panel a corresponds to the "TI" region in panel b. Fixed parameter values are as in Table 2.

of containment [23]. In contrast, lowering K_r or increasing β increases both absolute and relative clinical gains, because it harms resistant cells proportionally more in the presence of sensitive cells. Some of these effects are illustrated in Figure 3 (see also complementary analyses in [23, 32]).

What if all tumor cells are partially sensitive to treatment?

If resistant cells retain some sensitivity to treatment then the basic logic changes in two ways. First, if resistant cells are sufficiently sensitive then MTD can cure the tumor. This is not a case that concerns us, since our goal is to find alternative treatments when MTD is expected to fail. Second, even if a cure is impossible, there are now two ways to fight resistant cells: treating at low dose (to maintain competition with sensitive cells) or aggressively (to exploit partial sensitivity). Since competition with sensitive cells weakens as the sensitive population is depleted, treatment failure can be delayed by switching from a containment strategy to MTD at an appropriate time before treatment failure, but at the cost of increased toxicity. Whether the gain from switching to MTD is typically small or substantial remains to be investigated but, in general, the difference in outcomes for containment versus MTD is smaller when all cells are partially sensitive to treatment. If resistant cells are sufficiently sensitive then MTD may even be superior to pure containment.

If resistant cell frequency and sensitivity are unknown then we face a conundrum. Should we treat at high dose after low dose treatment failure? If the tumor is already fully resistant then any further treatment will incur needless toxicity. If resistant cells are fully resistant but some sensitive cells remain then it might be better to maintain a low dose. But if resistant cells retain some sensitivity then treating at high dose after initial treatment failure may be the best option, subject to treatment toxicity. To make the best choice, clinicians will require new methods for assessing tumor composition and sensitivity during therapy. Determining optimal strategies in the case of partial or unknown treatment sensitivity is an important topic for future theoretical research.

When can the tumor be contained forever?

In Model 2, unless a fully sensitive or fully resistant tumor is intrinsically benign ($K_s < N_{tol}$ or $K_r < N_{tol}$, respectively), indefinite containment under the maximum tolerable size requires two conditions: first, resistant cells are harmed more from competition with sensitive cells than from competition with other resistant cells ($\beta > 1$); second, the resistant population would decline in an almost fully sensitive tumor of threshold size N_{tol}.

The latter condition is equivalent to $K_r < \beta N_{tol}$. Since the resistant population's carrying capacity is likely to be significantly larger than the threshold tumor size, this condition typically requires a large competition coefficient β. Therefore, at least in this model, indefinite containment is possible only if sensitive cells greatly

impair the fitness of resistant cells (green region of Figure 3a; green and yellow regions of Figure 3b). These results are derived in Supplementary material Section 5.1.

Discussion

Theoretical support for maximum tolerated dose therapy relies on the assumption that resistant cancer cells are absent [1] or arise only during treatment [2]. Given that many if not most large solid cancers are expected to harbor pre-existing resistance [33], we have sought to build a firm theoretical foundation for understanding when containment strategies are likely to improve on the conventional approach. The logic of containing tumors is fundamentally simple: if some cells are fully resistant to treatment then the only way to fight them is via competition with sensitive cells, where "competition" includes any process that leads to a decrease in the resistant population growth rate due to the presence of sensitive cells. Moreover, given the constraint of maintaining tumor size below a certain threshold, competition is maximized under containment treatment strategies. We have shown that this logic can be formalized and given a rigorous mathematical form. It follows that model details are qualitatively irrelevant, provided that resistant cells are highly resistant and increasing the number of sensitive cells always decreases the resistant population growth rate.

Our results have implications for the design of preclinical and clinical trials of tumor containment strategies. In our simple but very general framework, the time until tumor size exceeds any particular threshold is maximized by maintaining tumor size precisely at this threshold for as long as there remain sensitive cells. This is true even if resistance has no cellular fitness cost. Our results therefore suggest that tumor containment experiments and trials should not be restricted to cases where a resistance cost is assumed to exist. Furthermore, although the ideal form of containment is impractical, our simulations and theoretical arguments predict that more feasible containment strategies will also improve substantially on conventional maximum tolerated dose (MTD) treatment. These more practical approaches include adaptive therapy [4], which has an important advantage over constant-dose or metronomic protocols, in that the optimal dose need not be known in advance. On the other hand, our theoretical results imply that an on-off implementation of adaptive therapy – as was employed in the only clinical trial of tumor containment to date [12] – may be suboptimal, because it causes tumor size to deviate substantially below the maximum tolerable threshold. Further research is needed to establish optimal dosing protocols in the presence of biological factors not accounted for in our framework. We also note that if resistant cells are only partially resistant then switching to MTD before the failure of low dose treatment may be superior to a pure containment strategy. Whether the difference in outcomes is substantial remains an important topic for further investigation.

By deriving explicit formulas for predicted clinical gains due to containment, we have shown that a crucial factor is the intensity of competition between sensitive and resistant cells. For tumors that obey the Gompertzian growth law, clinical gains are predicted to be substantial, at least when resistant cells are initially rare and the initial tumor size is not very small (at least 0.1% of carrying capacity). Less conventional tumor growth models predict either smaller or larger clinical gains. Our findings therefore underscore the need to characterize intratumor cell-cell competition [24]. A useful indicator that could be measured experimentally is the amount by which the resistant population growth rate increases – if at all – upon elimination of sensitive cells.

Although we have investigated various extensions and variants of our basic model, we have not considered all potential clinical costs and benefits of containment. By maintaining a substantial tumor burden, containment might increase risk of metastasis, cancer-induced illness such as cachexia, or emergence of more aggressive tumor clones via mutation. On the other hand, containment has the important advantage of reduced treatment toxicity. Stabilizing tumor size might additionally lead to a more stable tumor microenvironment and better drug delivery, which would be consistent with the finding that, in preclinical trials in mice, tumor size could be stabilized using progressively lower doses [11]. Further experimental and theoretical research is needed to clarify whether the benefit of containment in terms of prolonging survival always outweighs its potential downsides. Notwithstanding these important caveats, our findings generally strengthen the case for conducting further experimental and clinical trials of tumor containment strategies.

Table 2: **Parameter values.** Except where specified, we use these parameter values to obtain numerical results.

Parameter	Meaning	Value	Model(s)
K	tumor carrying capacity	2×10^{12}	Model 1
K_s	carrying capacity of a fully susceptible tumor	2×10^{12}	Model 2
K_r	carrying capacity of a fully resistant tumor	varied	Model 2
ρ	baseline per-cell growth rate (per day)	0.005928	Model 1
ρ_r	baseline per-cell growth rate of resistant cells (per day)	0.005928	Model 2
ρ_s	baseline per-cell growth rate of sensitive cells (per day)	0.005928	Model 2
α	competition coefficient	1	Model 2
β	competition coefficient	varied	Model 2
λ	treatment sensitivity	1	Model 1 and Model 2
N_0	initial tumor size	10^{10}	Model 1 and Model 2
R_0	initial resistant cell population size	2.3×10^5	Model 1 and Model 2
N_{tol}	tumor size corresponding to treatment failure	7×10^{10}	Model 1 and Model 2
N_{crit}	lethal tumor size	5×10^{11}	Model 1 and Model 2

Methods

Various mathematical models have been proposed to evaluate the costs and benefits of therapeutic strategies to contain the growth of tumors [3,4,9,10,12,14–16,18–22] or bacterial populations [23,27]. Many of these models assume two types of cells: sensitive and fully resistant. The mathematical proofs of our main qualitative results (see Supplementary material, Section 2.1) apply to any such model where, all else being equal, increasing treatment dose decreases the sensitive population growth rate, and increasing the sensitive population size decreases the resistant population growth rate. Some results further require that increasing the resistant population size does not increase the sensitive population growth rate (thus excluding beneficial ecological interactions).

Our three main outcomes are time to progression (until the tumor exceeds its initial size, N_0), time to treatment failure (until the tumor exceeds a threshold size determined by the physician and patient, N_{tol}), and survival time (until the tumor reaches a lethal size, N_{crit}). The tumor burdens that correspond to these outcomes will be patient-specific. The size that defines treatment failure, N_{tol}, may be either higher or lower than the initial burden, N_0.

We focus on three kinds of treatment: constant dose (which includes no treatment and maximum tolerated dose as special cases), continuous containment (stabilization of tumor burden for as long as possible via a continuous, variable low dose treatment, constrained by a maximum dose C_{max}), and intermittent containment (maintaining tumor burden between upper and lower bounds via intermittent, high dose treatment, as has been applied in a clinical trial [12]). A fourth kind of strategy, delaying treatment, is studied in Supplementary material.

To reveal the logic of containment as clearly as possible, we also consider idealized versions of these treatments, with no constraint on the maximum instantaneous dose (so that the sensitive population can be reduced instantly to any desired size). These idealized treatments, though biologically unrealistic, help reveal the basic logic of containment and provide reference points largely independent of model details. In the idealized form of maximum tolerated dose treatment (ideal MTD), the sensitive population is instantly eliminated.

In the case of idealized containment at some tumor size N_{ref}, the tumor grows until N_{ref} (or is instantly reduced to N_{ref}) and is then stabilized at this level as long as the resistant population size is less than N_{ref}. In the idealized version of intermittent containment, tumor size is instantly reduced to a lower threshold N_{min} whenever it reaches an upper limit N_{max} (unless the initial resistant population size is larger than N_{min}, in which case all sensitive cells are instantly eliminated).

Our numerical simulations employ a two-type model with Gompertzian growth (Model 1) previously studied by Monro and Gaffney (2009) [15], except that, for the sake of simplicity, we neglect resistance mutations that

occur during treatment, which we find have only small effects on outcomes (Supplementary Table 6 and Section 6 of Supplementary material). We use parameter values from Monro and Gaffney (2009), which were derived from empirical data (Table 2). The initial size of the resistant subpopulation is derived through the Goldie-Coldman (1979) formula [2]: $R_0 = (1 - N_0^{-2\tau})N_0/2$, where $\tau = 10^{-6}$ is the mutation and backmutation rate of Monro and Gaffney, and N_0 the initial tumor size. Simulations were conducted in R using the deSolve package [34].

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