A theoretical analysis of tumour containment

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Abstract

Recent studies have shown that a strategy aiming for containment, not elimination, can control tumour 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 tumour 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 tumour burden more effectively than applying the maximum tolerated dose. We show that containment may substantially outperform more aggressive treatment strategies even if resistance incurs no cellular fitness cost. 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, while also clarifying conditions under which containment might fail to outperform standard of care.

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 could be suboptimal due to treatment toxicity and selection for resistance [3, 4]. A better strategy might be to use the *minimal* effective dose that contains the tumour subject to ensuring sufficient quality of life [10, 13, 27].

The logic of aiming for containment rather than elimination is based on evolutionary principles. At the beginning of therapy, a tumour 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 [5–7]. By maintaining a large population of treatment-sensitive tumour 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 [8–10], a preclinical trial [11], and a small clinical trial in metastatic castrate-resistant prostate cancer [4]. Other clinical trials are active or recruiting [12]. Yet, the underlying evolutionary theory remains only imprecisely characterized in the cancer context. With the exception of Martin *et al.* (1992) [13], previous mathematical and simulation studies [4,8–10,14–22] have focussed on particular model formulations, specific therapeutic protocols, and typically untested assumptions about tumour 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 tumour 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

This paper proves formal results for general models (Models 1 and 2, described in Methods). These models have two kinds of tumour cells: sensitive and fully resistant, with subpopulation sizes $S(t)$ and $R(t)$, respectively.

The total tumour size is $N(t) = S(t) + R(t)$. Mutations occurring after treatment initiation are neglected, for reasons we will explain. Results are illustrated for a Gompertzian model [13, 14]:

$$\begin{aligned} \dot{S}(t) &= \rho \ln(K/N(t))\,(1 - \lambda C(t))S(t), \\ \dot{R}(t) &= \rho \ln(K/N(t))\,R(t), \end{aligned} \qquad \text{(Model 3)}$$

where $C(t)$ is the drug-dose, λ is a sensitivity parameter, K is the tumour carrying capacity (the hypothetical size at which the tumour would cease to grow), and ρ is the baseline per-cell growth rate. Parameters are described in Methods, Table 2, and values are mostly taken from a previous study [14].

We compare the effect of various treatments including:

• *Containment at the initial tumour size*: stabilizes the tumour at its initial size as long as possible, subject to a maximum tolerated dose constraint $C(t) \leq C_{max}$ (or as long as some sensitive cells remain in an idealized case, called *ideal containment*).

• *Containment at a larger size* N^*: lets the tumour grow till size N^* before stabilizing it.

• *Intermittent containment*: does not treat until $N = N_{max}$, then treats at C_{max} until $N = N_{min}$, and iterates as long as possible [4].

• *Maximum Tolerated Dose (MTD)*: $C(t) = C_{max}$ throughout.

• *Ideal MTD*: eliminates sensitive cells at treatment initiation.

These treatments are illustrated in Fig. 1. The outcomes considered are:

• *Time to progression:* the time until the tumour exceeds its initial size, N_0.

• *Time to treatment failure:* until the tumour exceeds a threshold size N_{tol}, which we call the maximal tolerable size.

• *Survival time:* until the tumour reaches an hypothetical lethal size, N_{crit}.

Details are given in Methods.

When is containment optimal?

The optimal treatment strategy depends on the clinical objective. If the emphasis is on rapidly reducing tumour burden then maximum tolerated dose (MTD) is clearly superior to containment. However, if the aim is to maximize time to progression, 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 tumour 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 Information for a review of previous studies).

If the objective is to maximize time to progression then, under the above assumptions, the best possible treatment is the containment strategy that precisely maintains the original tumour burden for as long as some sensitive cells remain, which we called ideal containment. Moreover, among treatment strategies that eventually eliminate the sensitive population, the worst option is to eliminate sensitive cells from the start, that is, the ideal MTD treatment. Instead of maximizing time to progression, an alternative objective is to maximize the time until tumour burden exceeds a certain threshold. In this case, the optimal treatment maintains the tumour at precisely this threshold size. Formally, let $t_{idContN^*}$ and t_{alt} denote the times at which tumour size exceeds N^* under ideal containment at size $N^* > N$ and under an arbitrary alternative treatment, respectively. Then $t_{idContN^*} \geq t_{alt}$ (Supplementary Information, Proposition 3). Besides standard regularity assumptions, this result requires only that the population of sensitive cells is maximized by not treating and the resistant cell growth-rate function is non-increasing in S. The result is independent of our other assumptions.

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; that is, under containment. Conversely, competition is least effective when the sensitive population is smallest; that is, under MTD.

Which containment strategy works best depends on the objective (Figs. 1f and 1h). Time to progression is maximized by ideal containment at the initial size; time to treatment failure, by ideal containment at the maximal tolerable size. In theory, survival time would be maximized by ideal containment just below the lethal tumour size. Attempting this would however be extremely dangerous, both due to adverse effect on patient's quality of life and because too optimistic a guess of the lethal burden would lead to quick patient's death.

Clinical gains strongly depend on competition intensity

The superiority of ideal containment is qualitatively very robust and holds for both frequency-dependent and density-dependent models. Quantitatively, however, clinical benefits strongly depend on the intensity of competition. In frequency-dependent models [8, 9], a key parameter is the relative fitness of resistant cells when rare [8]. Similarly, in density-dependent models [4, 13, 14, 17, 23], a key quantity is by how much the growth rate of resistant cells increases when sensitive cells are eliminated. In the widely-used Gompertzian model of tumour growth, the per-cell growth rate decreases relatively rapidly with increasing tumour 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, possibly much smaller clinical gains [13]. Those that describe stronger competition, such as the von Bertalanffy growth model [24], predict larger gains (Fig. 2c, Extended Data Fig. 2; Supplementary Information, Section 4.1.1. Important differences between model predictions underscore the need to advance understanding of the ecological interactions that govern intra-tumour dynamics [25], which remain only poorly characterized.

Other important biological parameters

Simple mathematical expressions may be derived to quantify the effects of containment and MTD strategies in various density-dependent scenarios, and in some frequency-dependent ones (see Supplementary Information, Section 3). This enables us to examine the impact of varying any parameter on time to progression, time to treatment failure, and survival time. Recall that these three outcomes are defined, respectively, as the times until the tumour becomes larger than N_0 (the size at treatment initiation), N_{tol} (a hypothetical maximum tolerable size) and N_{crit} (the hypothetical lethal tumour 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 tumour [1], or some other effect).

For Model 3, 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 (or *fold change in progression time* [26]) 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 tumour size compared to the carrying capacity, N_0/K.

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 tumour 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 tumour size. This increases both absolute and relative benefits of containment at the initial size. Fig. 2a illustrates some of these effects for Model 3. The impact of a large initial tumour size on relative benefits of containment at the maximal tolerable size is more complex (Fig. 2b; Supplementary Information, Section 4.1.2).

Practical treatment strategies can be close to optimal

In the above mathematical analysis, we assumed no restriction on maximum dose, which permits the ideal containment strategy of maintaining the tumour precisely at a target size until it becomes fully resistant. In reality, toxicity constraints typically impose a maximum instantaneous dose C_{max}. Figs. 1a, 1b, 1c, 1d and 1e compare tumour dynamics and doses under ideal containment and under containment strategies. In the latter case, the stabilization phase is shorter because it finishes before all sensitive cells have been removed. This results in shorter times to progression or treatment failure (Figs. 2d, 2e, 2g, 2h).

For Model 2 (see Methods) with specific cellular kill rate functions, the stabilization time may be quantified with explicit formulas (Supplementary Information, Section 3). For Model 3 for instance, provided that the tumour is initially sufficiently sensitive to be stabilized by a dose no higher than C_{max}, the time at which tumour size exceeds the stabilization size N_{stab} under containment is

$$t_{N_{stab}}(Cont) = \frac{1}{\rho}\left(\ln\left[\frac{\ln(K/N_0)}{\ln(K/N_{stab})}\right] + \frac{\ln(N_0/R_0)}{\ln(K/N_{stab})} - \frac{\ln\left(\lambda C_{max}/[\lambda C_{max}-1]\right)}{\ln(K/N_{stab})}\right).$$

Omitting the last term in the bracket gives the corresponding time $t_{N_{stab}}(idCont)$ under idealized containment. Provided that resistant cells are initially rare (long stabilization phase) and the treatment is sufficiently effective (few sensitive cells remain when containment fails), non-idealized containment performs almost as well as ideal containment (Fig. 2g). Moreover, after the stabilization phase, both tumour size and resistant population size grow more slowly under containment than under ideal containment. This is because the tumour is still partially sensitive and hence responds to treatment while remaining sensitive cells slow the growth of resistant cells. Due to the latter effect, the resistant population is never higher under containment than under ideal containment. The number of resistant cells is actually never higher under containment at size N_{stab} than under any treatment that treats at C_{max} when $N > N_{stab}$ (Supplementary Information, Proposition 4). Thus, provided that sensitive cells become eventually rare, survival time should be at least as long under containment as under any such treatment, including MTD and ideal containment. This is confirmed by simulations (Figs. 1a, 1d, Figs. 2f, 2i). Differences between ideal and non-ideal containment outcomes are further discussed in Supplementary Information, Section 4.2.

An additional consideration is that a continuous containment strategy requires continuous monitoring of tumour 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 treatment has yet to be settled. Both strategies worked well in mice [11]. Although Zhang *et al.* (2017) [4] obtained highly promising clinical results from intermittent high dose treatment, a continuous low dose treatment might 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 tumour burden implies slower growth of resistance. Therefore, containment between upper and lower bounds N_{max} and N_{min} is intermediate between containment at the upper threshold and containment at the lower threshold. This holds both in terms of resistant population sizes and, in idealized cases, in terms of the time at which tumour size exceeds N_{max} (Supplementary Information, Section 2.3, Propositions 5 and 6). Thus, containment seems superior to intermittent containment, but the difference between the two types of protocol is small provided that N_{min} is a large fraction of N_{max} (compare Figs. 1g and 1h; see explicit formulas in Supplementary Information, Section 3.1.5 and Extended Data Fig. 1, and Section 3.3, Supplementary Table 4, as well as numerical results in Table 1 and Supplementary Table 5; see also Section 4.3 and Extended Data Fig. 4).

Constant dose. To maximize time to progression in Model 3, the optimal constant dose is slightly higher than $C = 1/\lambda$ (which corresponds to $C = 1$ in Fig. 3a). The constant dose $C = 1/\lambda$ stabilizes the sensitive population size, whereas containment uses the evolving dose $C = N/\lambda S = 1/\lambda + R/\lambda S$ to stabilize tumour size. According to our definition, the former approach leads to immediate progression because it allows the overall tumour size to increase from the start of treatment. However, provided that resistant cells are initially rare, the dose $C = 1/\lambda$ maintains tumour size close to the initial size for nearly as long as under containment (Figs. 3a, 3c). 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 tumour size reaches N_{tol} and then applying dose $C = 1/\lambda$ has similar outcomes as containment at the maximum tolerable size (Figs. 3b, 3e). Table 1 gives examples of times to progression, times to treatment failure, and survival times for various constant doses and other treatments. Constant dose treatments may lead to higher survival time than containment at the initial size (Fig. 3a, Extended Data Fig. 7) but to the cost of quicker progression, and they always lead to lower survival time than containment at sufficiently higher sizes.

Adaptive treatments may be close to optimal for all patients. Since delaying treatment until $N = N^*$ and then treating at an appropriate constant dose is predicted to yield similar outcomes as containment at N^*, why should we not opt for this apparently simpler treatment rather than containment? A problem is that the parameters that determine the best constant 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 Figs. 3c, 3d, 3e). 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 (Figs. 3c, 3d, 3e; Supplementary Information, Section 4.7). By contrast, a containment strategy 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 tumour 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 could 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 [4]) has the important additional benefit of adapting doses to the evolution of the tumour and to patient-specific parameters, without knowing these parameters in advance [3].

Table 1: **Time to progression, time to treatment failure, and survival time for Model 3.** 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. Note that intermittent containment between N_0 and $N_{min} = 0.8N_0$ leads to a larger time to progression than containment at N_0, but to a lower time to treatment failure and survival time. This is discussed in Supplementary Information, Section 4.3.

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
Intermittent containment ($C_{max} = 2$) between $0.5N_0$ and N_0	317	398	547
Intermittent containment ($C_{max} = 2$) between $0.8N_0$ and N_0	325	411	561
Ideal intermittent containment between $0.5N_0$ and N_0	320	397	546
Ideal intermittent containment between $0.8N_0$ and N_0	333	410	559

Fitness costs of resistance are unnecessary

A recent review article [27] noted that "the theory behind adaptive therapy focuses on the phenotypic costs of the molecular mechanism(s) of resistance." Indeed, proponents of cancer adaptive therapy have emphasized resistance mechanisms – such as up-regulation of membrane extrusion pumps – that are energetically costly, so that resistant cells are less fit than sensitive cells in the absence of treatment [27–29]. A related hypothesis is that, under intermittent containment, the *frequency* of resistant cells decreases during the gaps between doses, due to the cost of resistance. For a sufficiently high cost, tumour composition might then remain almost unchanged after each on-off treatment cycle, enabling potentially indefinite tumour containment.

This intuition is not entirely correct. For tumour composition to remain the same after an on-off treatment cycle, the *number* of resistant cells should decrease during the gap between doses, and not only their frequency (at least if the number of resistant cells increases during treatment phases). Previously proposed mathematical models typically do not satisfy this condition [4, 13, 14, 17].

Most importantly, in our preceding results we have not assumed any costs of resistance. Nevertheless, we have shown that containment may substantially outperform more aggressive treatment strategies. The key assumption is not that resistance entails a fitness cost, but rather that additional sensitive cells reduce the growth rate of resistant cells.

Fitness costs of resistance can amplify clinical gains from containment

Given that resistance costs are not *necessary* for containment to improve on MTD, the next question is whether they are *useful*. That is, do costs of resistance increase clinical gains from containment? Generally the answer is yes, but the size of the effect depends on the type of resistance cost. The most beneficial resistance costs are those that grow in the presence of sensitive cells. Consider the following model:

$$\begin{aligned} \dot{S}(t) &= \rho_s \ln\left(\frac{K_s}{S(t) + \alpha R(t)}\right)(1 - \lambda C(t))S(t), \\ \dot{R}(t) &= \rho_r \ln\left(\frac{K_r}{R(t) + \beta S(t)}\right) R(t). \end{aligned} \tag{Model 4}$$

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 tumour 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 3.

In Model 4, 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 of these costs improve outcomes for all treatments, but how do they affect comparisons between treatments? A first effect is that resistance costs slow down the emergence of resistant cells *before* treatment initiation, leading to a smaller initial resistant population. If a cure is impossible, and assuming (as we argue in Supplementary Information, Section 6.3) that mutations after treatment initiation can be neglected, this effect tends to increase the benefit of containment more than of MTD (Fig. 2; see also [14, 26]).

A second effect is that resistance costs also slow the growth of resistance *after* treatment initiation. Whether this is more beneficial to outcomes of containment or MTD depends on the type of cost. Given the same initial conditions, survival times under idealized treatments are inversely proportional to ρ_r. Thus, halving ρ_r doubles time to progression under ideal containment, but also under ideal MTD: the relative benefit is unchanged. This is because the impact of lowering ρ_r is independent of the number of sensitive cells. In a model that accounts for mutations from sensitive to resistant, lowering ρ_r may even decrease the relative benefit of containment [17].

In contrast, lowering K_r or increasing β increases relative benefits, because it harms resistant cells proportionally more in the presence of sensitive cells. In particular, a sufficient increase in the competition coefficient β can indefinitely prolong survival under containment (see next section) while having no effect on the outcomes of ideal MTD. Some of these effects are illustrated in Fig. 4 (see also [17, 30]). Since different types of resistance cost have such different impacts, it is important to study not only whether costs are typically present in tumours, but also how these costs arise and how they can be modeled.

When can the tumour be contained forever?

In Model 4, unless a fully sensitive or fully resistant tumour 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 tumour 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 tumour 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 Fig. 4a; green and yellow regions of Fig. 4b). These results are derived in Supplementary Information, 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 [31], 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 tumours 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 tumour 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 in a general setting. It follows that model details are qualitatively irrelevant, provided that resistant cells are highly resistant and that increasing the number of sensitive cells always decreases the resistant population growth rate.

However, identifying conditions under which containment strategies are expected to perform well also emphasizes that the case for containment is weaker when these conditions are not met. If resistant cells do not compete with sensitive cells, or if tumour growth is superexponential [32], then containment is likely to do worse than MTD (Supplementary Information, Section 6.1). Also if resistant cells are only partially resistant then the logic changes: resistant cells can then be attacked not only via competition with sensitive cells, but also by the treatment. Switching to MTD before the failure of low dose treatment may then be superior to a pure containment strategy, even for idealized treatments (Supplementary Information, Section 6.2). When to switch and whether the difference in outcomes is substantial remains an important topic for further investigation. Finally, although we have checked that random genetic mutations from sensitive to resistant occurring after treatment initiation do not substantially affect our results (Supplementary Information, Section 6.3; Extended Data Fig. 5), we have not investigated treatment-induced mutations [33, 34], accumulation of driver mutations, nor models involving quiescent cancer stem cells.

On the other hand, in our framework, the time until tumour size exceeds any particular threshold is maximized by maintaining tumour size precisely at this threshold for as long as there remain sensitive cells, even if resistance has no cellular fitness cost. This suggests that tumour containment experiments and trials should

not be restricted to cases where a resistance cost is assumed to exist. Our results also underline a trade-off between maximizing time to progression and maximizing the time at which tumour size becomes higher than some larger threshold. Since clinical evidence supporting containment strategies remains limited, it seems safer to test containing tumours at their initial size, or some relatively low size. If results are convincing, more ambitious strategies aiming at increasing intra-tumour competition by letting the tumour grow to its maximal tolerable size before containing it could be attempted. This maximal tolerable size would not have to be known in advance, but could be discovered during treatment, based on patient's quality of life.

To implement containment strategies, the nature of the resistance mechanism, the frequency of resistant cells, or other patient specific parameters need not be known, but a tumour burden indicator seems required. In our models, when resistant cells are initially rare, applying a dose close to the initial stabilizing dose throughout typically leads to results similar to containment at the initial size. In practice however, tumour growth is much more irregular. Thus, finding a dose, or schedule, that initially results in tumour stabilization is not enough: regular monitoring and dose adjustment are required. In Supplementary Information, Section 7, we propose a new protocol that takes into account how far tumour size is from its target and how much it recently increased or decreased.

Importantly, although the ideal form of containment is impractical, our simulations and theoretical arguments predict that more feasible containment strategies will also improve substantially on maximum tolerated dose (MTD) treatment. These more practical approaches include adaptive therapy [10], 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 tumour containment to date [4] – may be suboptimal, because it causes tumour 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, such as spatial structure [16, 35].

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 tumours that obey the Gompertzian growth law, clinical gains are predicted to be substantial, at least when resistant cells are initially rare and the initial tumour size is not very small (at least 0.1% of carrying capacity). Less conventional tumour growth models predict either smaller or larger clinical gains. Our findings therefore underscore the need to characterize intratumour competition [25]. 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 tumour burden, containment might increase risk of metastasis, cancer-induced illness such as cachexia, or emergence of more aggressive tumour clones via mutation [36]. On the other hand, containment has the important advantage of reduced treatment toxicity. Stabilizing tumour size might additionally lead to a more stable tumour microenvironment and better drug delivery, which would be consistent with the finding that, in preclinical trials in mice, tumour 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 tumour containment strategies.

Methods

Models

For qualitative results, we consider a general model with two types of tumour cells, sensitive and fully resistant, with subpopulation sizes $S(t)$ and $R(t)$, respectively. The total tumour population size is denoted by $N(t) = S(t) + R(t)$, with initial value $N_0 = S_0 + R_0$. Tumour dynamics are described by:

$$\begin{cases} \dot{S}(t) = g_s(S(t), R(t), C(t))S(t) & ; \quad S(0) = S_0 \geq 0 \\ \dot{R}(t) = g_r(S(t), R(t))R(t) & ; \quad R(0) = R_0 > 0 \end{cases} \qquad \text{(Model 1)}$$

where $\dot{S}$, $\dot{R}$ denote derivatives, and g_s and g_r are per-cell growth-rate functions; the quantity $C(t)$ is the drug dose at time t (which is assumed to equate with treatment level, neglecting details of pharmacokinetics and pharmacodynamics).

In quantitative analyses, we consider more particular density-dependent models of the form

$$\begin{aligned} \dot{S}(t) &= g_s(N(t), C(t))S(t) \\ \dot{R}(t) &= g_r(N(t))R(t), \end{aligned} \qquad \text{(Model 2)}$$

Table 2: **Parameter values.** Except when otherwise specified, numerical results use the following parameter values. Model 4 is introduced later on. 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 [14], and N_0 the initial tumour size. The value of N_{tol} is arbitrary (in log-scale, this is almost the average of N_0 and N_{crit}). The value of C_{max} is for consistency with clinical trial results reported by Zhang *et al.* (2017) [4]. On average, the cumulative dose given in that trial was 47% of the MTD, which is consistent with values of C_{max} between 2 and 2.5 assuming the initial tumour is highly sensitive (and higher values otherwise). Since $\lambda C_{max} = 2$, it takes as much time for a fully sensitive tumour size to double in the absence of treatment as to be halved under MTD, and the dose $C = C_{max}/2$ would precisely stabilize a fully sensitive tumour.

Parameter	**Meaning**	**Value**	**Model(s)**
K	tumour carrying capacity	2×10^{12}	Model 3
K_s	carrying capacity of a fully susceptible tumour	2×10^{12}	Model 4
K_r	carrying capacity of a fully resistant tumour	varied	Model 4
ρ, ρ_r, ρ_s	baseline per-cell growth rate (per day)	0.005928	Models 3 and 4
α	competition coefficient	1	Model 4
β	competition coefficient	varied	Model 4
λ	treatment sensitivity	1	Models 3 and 4
C_{max}	maximal instantaneous tolerated dose	2	Models 3 and 4
N_0	initial tumour size	10^{10}	Models 3 and 4
R_0	initial resistant cell population size	2.3×10^5	Models 3 and 4
N_{tol}	tumour size corresponding to treatment failure	7×10^{10}	Models 3 and 4
N_{crit}	lethal tumour size	5×10^{11}	Models 3 and 4

with g_r non-increasing and $g_s(N, 0) = g_r(N)$ (that is, in the absence of treatment, sensitive and resistant cells grow at the same rate). These models permit us to obtain explicit formulas for the time at which tumour size exceeds a given threshold under various treatments.

For numerical simulations, we use the Gompertzian growth model studied by Monro and Gaffney (2009) [14] (see also Martin *et al.* (1992) [13]) and introduced as Model 3 at the beginning of the Results section.

$$\begin{aligned} \dot{S}(t) &= \rho \ln(K/N(t))\,(1 - \lambda C(t))S(t), \\ \dot{R}(t) &= \rho \ln(K/N(t))\,R(t), \end{aligned} \qquad \text{(Model 3)}$$

Recall that λ is a sensitivity parameter, K is the tumour carrying capacity (the hypothetical size at which the tumour would cease to grow), and ρ is the baseline per-cell growth rate. We focus on this model in our numerical simulations to facilitate comparison with previous analysis [14], and because Gompertzian growth has been shown to describe tumour growth better than alternative models such as logistic growth [37, 38]. Where not explicitly varied, the values of ρ, K, N_0 and R_0 are the same as in Monro and Gaffney [14] (Table 2), except that we neglect mutations and backmutations after treatment initiation. We also consider a variant of Model 3 to study the impact of various types of resistance cost (Model 4 in the section "Fitness costs of resistance can amplify clinical gains from containment").

Assumptions

We make four key assumptions regarding Model 1.

First, the growth rate of sensitive cells is positive in the absence of treatment and decreases as treatment dose is increased (g_s is non-increasing in C).

Second, resistant cells are fully resistant (g_r does not depend on C).

Third, all else being equal, the larger the subpopulation of sensitive cells, the lower the growth-rate of resistant cells (g_r is non-increasing in S). This is a standard assumption in the adaptive therapy literature (see Supplementary Information, Section 1), which might result from density-dependence (the larger the tumour, the larger its doubling time [13, 14, 26], as in the Gompertzian Model 3), frequency-dependence (the rarer resistant cells, the larger their doubling time [8, 9]), a combination of those two factors [4, 8, 15, 17, 18, 21], or some other form of inhibition of resistant cells by sensitive cells. It is important to note that this assumption does not imply a fitness cost of resistance; we permit the possibility that resistant cells are as fit or even fitter than sensitive cells in the absence of treatment.

Fourth, mutations between the sensitive and resistant phenotypes that occur after treatment initiation may be neglected. This assumption is justified in Supplementary Information, Section 6.3, in Supplementary Table 6, and in Extended Data Fig. 5.

On top of standard regularity assumptions on growth-rate functions, this is enough for our key results. Some results also require that increasing the resistant population does not increase the growth-rate of sensitive cells

(g_s is non-increasing in R), excluding cooperative interactions. This assumption is not satisfied in models with a Norton-Simon kill rate, e.g., Model 3, but for most of our results, it may be replaced by the assumption that the number of sensitive cells is maximized by not treating. This holds in Model 3, and any instance of Model 2 (see Supplementary Information, Section 2.4).

Finally, the instantaneous dose $C(t)$ is assumed no higher than a maximal tolerated dose C_{max}, but this assumption is relaxed in our idealized treatments (see below).

Treatments

The three main treatment strategies we consider are the following:

• *Maximal Tolerated Dose (MTD)*: $C(t) = C_{max}$ throughout.

• *Containment at the initial tumour size* N_0: this treatment continuously adjusts the dose to maintain total tumour size at $N(t) = N_0$ as long as possible with a dose $C(t) \leq C_{max}$, then treats at C_{max} once $N > N_0$ (unless the tumour size returns to N_0, in which case it is again stabilized at N_0 for as long as possible, and so on). Mathematically, the stabilizing dose is found by solving the equation $\dot{N}(t) = 0$. In the Gompertzian Model 3, this leads to $C(t) = N(t)/\lambda S(t)$. The dose administered is the minimum of this stabilizing dose and of C_{max}. In practice, containment would only be approximative, and the appropriate dose would be found by regular monitoring of the patient and dose adjustments. This would not require to differentiate between sensitive and resistant cells. Possible protocols are discussed in Supplementary Information, Section 7.

• *Containment at some other threshold size* N^*: this treatment does not treat until tumour size reaches N^* (if $N^* \geq N_0$), or treats at the maximal tolerated dose until tumour size is reduced to N^* (if $N^* < N_0$), and then contains the tumour at this threshold as above.

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 (so that $S(t) = 0$ for all $t > 0$). This is called "aggressive treatment" or "elimination of sensitive cells" by Hansen *et al.* (2017, 2019) [17] [39] and Hansen and Read (2020) [26]. We may think of this as a treatment inducing an infinite cellular kill rate. *Ideal containment at the initial tumour size* maintains the tumour at its initial size as long as some sensitive cells remain. The tumour is then fully resistant, hence its later growth independent of the treatment. *Ideal containment at some other threshold* N^* lets the tumour grow to N^* (or instantly reduces tumour size to N^*, if $N^* < N_0$), then stabilizes tumour size at this threshold as long as some sensitive cells remain. Containment in the sense of Hansen *et al.* (2017) [17], from which we borrow this vocabulary, corresponds to our ideal containment treatment, except that we do not allow for an instantaneous increase in tumour size.

Containment and MTD treatments are illustrated in Fig. 1. We also consider other possibilities such as *constant dose or delayed constant dose treatments*, studied by Monro and Gaffney (2009) [14]; *intermittent containment* (Fig. 1g), where tumour size is maintained between a high and a low threshold, as in Zhang *et al* (2017) [4]; and forms of *metronomic therapy*, where treatment is turned on and off at predefined times.

Outcomes

Our three main outcomes are:

• *Time to progression:* defined here as the time until the tumour exceeds its initial size, N_0. The RECIST criterion is that progression occurs when tumour size is 20% larger than at treatment initiation. This 20% buffer makes sense in medical practice, due to imperfect monitoring of the tumour and imperfect forecast of treatment's effect. In our mathematical models however, this buffer is not needed, and would only obscure the analysis, so we use a more basic definition.

• *Time to treatment failure:* until the tumour exceeds a threshold size determined by the physician and patient, N_{tol}, which we call the maximal tolerable size. This may be thought of as the maximal tumour size at which the tumour is not quickly life threatening, based on physician's expertise, and does not result in too severe side effects for the patient. Due to this second requirement, the maximal tolerable size would only be revealed during treatment. To fix ideas, we assume that it is higher than the initial tumour burden, N_0. The case where it is lower is studied in Supplementary Information.

• *Survival time:* until the tumour reaches an hypothetical lethal size, N_{crit}, after which the patients is assumed to die quickly. This lethal tumour burden is also patient specific.

Mathematical tools and intuition

Formal mathematical proofs of our results on Model 1 can be found in Supplementary Information, Section 2. They are based on a differential equation tool called the comparison principle (a variant of Gronwall's lemma), but the basic intuition is simple (see also [17]): between time t and $t+dt$ (where dt is a small time increment), the resistant population increases from $R(t)$ to $R(t+dt) \simeq R(t) + R'(t)dt$, hence by a quantity

$$dR \simeq R'(t)dt = g_r(R(t), S(t))R(t)\, dt.$$

So, if we fix a resistant population size R_1 and a small size increment dR, the time it takes for the resistant population size to grow from R_1 to $R_1 + dR$ is roughly:

$$dt \simeq dR/R_1 g_r(R_1, S_1), \tag{2}$$

where S_1 is the sensitive population size when $R = R_1$. Assuming $R_0 \leq R_1 \leq N_0$, under ideal containment at the initial size, $S_1 + R_1 = N_0$, so $S_1 = N_0 - R_1$. Before progression, under any other treatment, $S_1 \leq N_0 - R_1$. By assumption, the larger the sensitive population, the lower the resistant population growth rate, hence the higher the duration dt in (2); it follows that the time it takes for the resistant population to grow from R_1 to $R_1 + dR$ is maximized by ideal containment (and minimized by ideal MTD, since then $S_1 = 0$). Iterating this argument shows that the resistant population $R_{idcont}(t)$ under ideal containment at the initial size will be smaller than the resistant population $R(t)$ under any alternative treatment, at least as long as none of these treatments led to progression. Since under ideal containment at the initial size, progression occurs when $R_{idcont}(t) = N_0$, this implies that progression occurs later than under any other treatment. Other results require more sophisticated arguments, but the intuition is similar.

Impact of the stabilization size

If follows from Section 2 in Supplementary Information that containment at higher sizes than the initial size leads to larger clinical gains in terms of survival time, at least when comparing ideal containment to ideal MTD (but typically also for more realistic treatments). The general intuition is that letting the tumour grow increases competition between sensitive and resistant cells, hence slows down even more the growth of resistant cells than stabilizing the tumour at its initial size. This intuition may be made more precise in Model 2.

Indeed, the clinical gain of ideal containment at size $N^* \geq N_0$, compared to no treatment, is then the duration of the stabilization phase. Moreover, due to the absence of cost of resistance, the proportion of resistant cells at the beginning of the stabilization phase is always R_0/N_0, independently of the stabilization size. The clinical gain of ideal containment is thus the time it takes for the resistant population to be multiplied by a factor N_0/R_0 (from R_0/N_0 to 1) while tumour size is maintained at N^*. But the larger N^*, the smaller the growth-rate of resistant cells when $N = N^*$, hence the larger the gains from ideal containment.

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Author contributions

Y.V. and R.N. conceived the study and wrote the manuscript. Y.V. designed and performed mathematical analyses, and conducted the literature review. R.N. designed and performed numerical modelling.

Data availability

No data sets were generated or analysed during the current study.

Code availability

Simulations were conducted in R using the deSolve package. [40]. The code for simulations is available at https://github.com/robjohnnoble/LogicOfContainingTumours.

Competing interests

The authors declare no competing interests.

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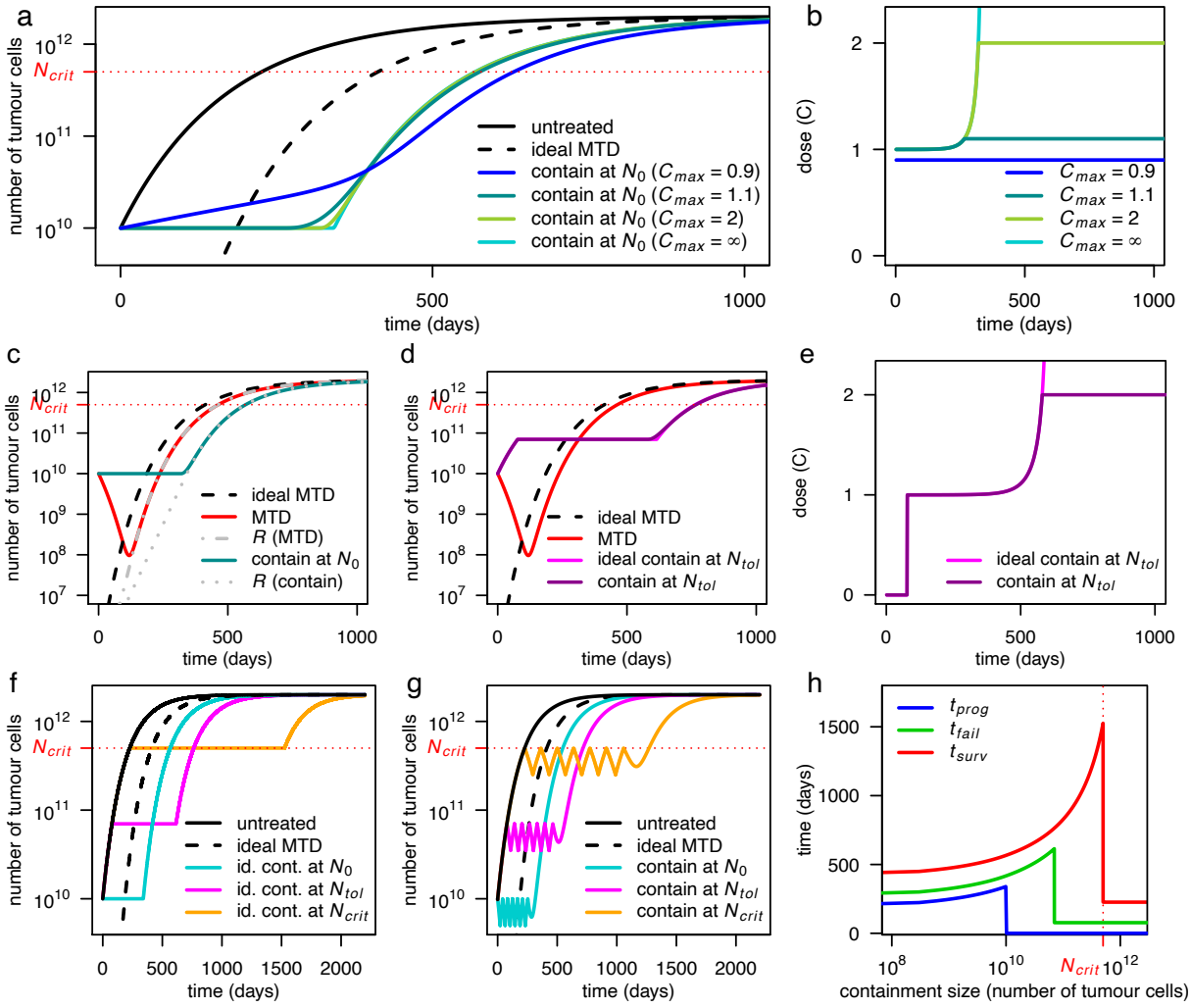

Figure 1: **Illustration of containment and MTD treatments in Model 3.** **a**, Tumour size under no treatment (black), ideal MTD (dashed), and containment at the initial size for various values of the maximum tolerated dose C_{max}. The case $C_{max} = \infty$ (light blue) corresponds to ideal containment. The patient is assumed to die shortly after tumour size becomes greater than N_{crit}. **b**, Drug dose under the containment treatments of panel a. If $C_{max} < 1$, the tumour cannot be stabilized and containment boils down to MTD. **c**, Tumour size under MTD, ideal MTD, and containment at the initial size, and resistant population size under MTD and containment. The effect of varying R_0 is illustrated in Extended Data Fig. 3.**d**, Tumour size under MTD, containment at the maximum tolerable size and their idealized counterparts. The effect of varying C_{max} is illustrated in Extended Data Fig. 6.**e**, Drug dose under containment and ideal containment at the maximum tolerable size, as represented in panel d. **f**, Tumour size under no treatment, ideal MTD, and ideal containment at three different tumour sizes. **g**, Tumour size under no treatment, ideal MTD, and intermittent containment between N_{max} and $N_{min} = N_{max}/2$ for three different values of N_{max}. **h**, 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 tumour exceeds a certain size is maximized by ideal containment at that size. Exact formulas for idealized treatments are in Supplementary Information, Section 3.

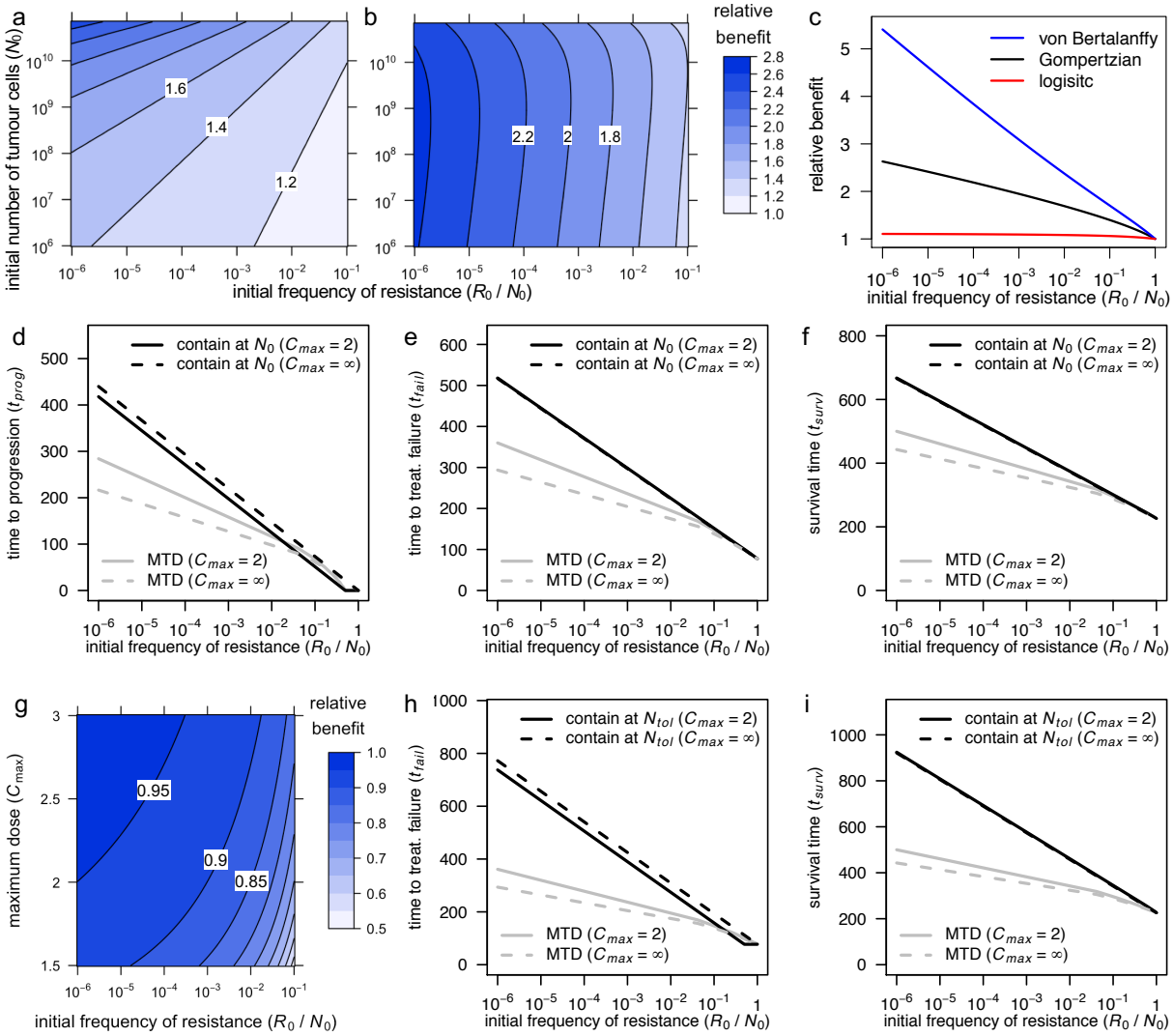

Figure 2: **Comparison of clinical benefits of containment and MTD treatments in Model 3.** **a**, Relative benefit, in terms of time to progression, for ideal containment at size N_0 versus ideal MTD (that is, ratio $t_{prog}(idContN_0)/t_{prog}(idMTD)$), as a function of initial tumour size and frequency of resistant cells. **b**, Relative benefit, in terms of time to treatment failure, for ideal containment at size N_{tol} versus ideal MTD (that is, ratio $t_{fail}(idContN_{tol})/t_{fail}(idMTD)$), as a function of initial tumour size and frequency of resistant cells. **c**, Relative benefit, in terms of time to treatment failure, for ideal containment at size N_{tol} versus ideal MTD, for a Gompertzian growth model (black curve; Model 3), a logistic growth model (red) and a von Bertalanffy growth model (blue). Parameter values for the Gompertzian growth model are as in Table 2. Parameter values of the other models are chosen so that untreated tumour growth curves are similar for tumour sizes between N_0 and N_{crit} (the lethal size). See Extended Data Fig. 2 for details. **d**, **e**, **f**, Time to progression (panel d), to treatment failure (panel e), and survival time (panel f) versus initial frequency of resistance. Outcomes are shown for MTD treatment and containment at N_0, both in the ideal case ($C_{max} = \infty$) and subject to $C_{max} = 2$. **g**, 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 Information, Section 3.3). Contour lines are at intervals of 0.05. **h**, **i**, Time to treatment failure (panel h), and survival time (panel i) versus initial frequency of resistance. Outcomes are shown for MTD treatment and containment at N_{tol}, both in the ideal case ($C_{max} = \infty$) and subject to $C_{max} = 2$.

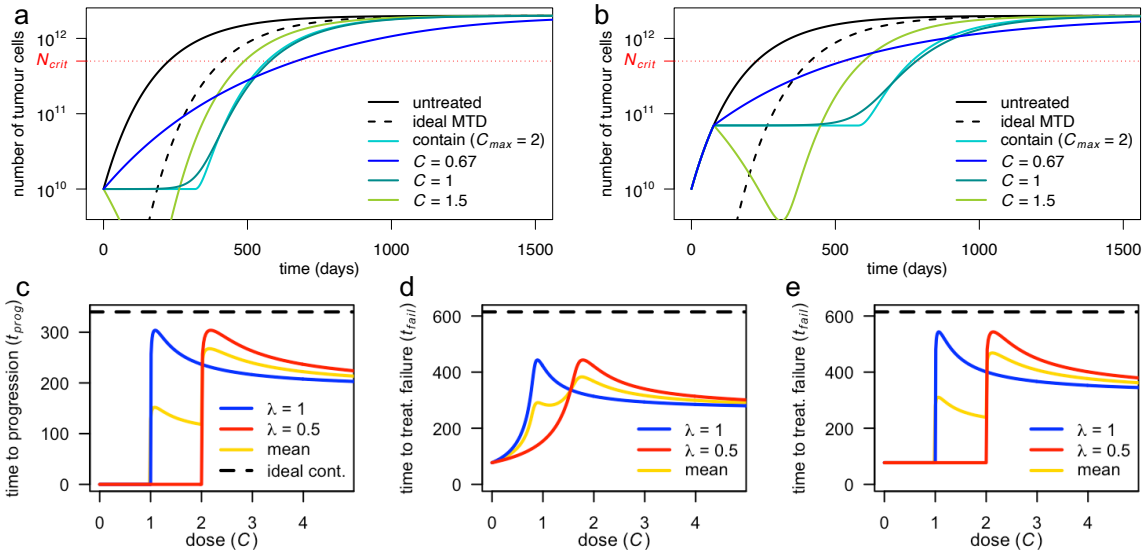

Figure 3: **Constant dose and delayed constant dose treatments in Model 3.** **a**, Tumour size for various constant dose treatments compared to containment at the initial size (subject to $C_{max} = 2$) and ideal MTD. **b**, Tumour size for various delayed constant dose treatments (the dose is applied continuously from the first time when $N = N_{tol}$) compared to containment at N_{tol} (subject to $C_{max} = 2$) and ideal MTD. Until $N = N_{tol}$, all curves are the same, except ideal MTD. **c**, Times to progression for two patients whose tumours differ in treatment sensitivity (parameter λ) under constant dose treatments, as a function of the dose. The yellow line is the mean of the two patient outcomes and the dashed line is the time to treatment failure under ideal containment at N_0 (which is the same for both patients, and the maximal time to progression). **d**, Times to treatment failure for two patients whose tumours differ in treatment sensitivity under constant dose treatments, as a function of the dose. The yellow line is the mean of the two patient outcomes and the dashed line is the time to treatment failure under ideal containment at N_{tol} (which is the same for both patients, and the maximal time to treatment failure). **e**, Times to treatment failure for two patients whose tumours differ in treatment sensitivity under delayed constant dose treatment (the dose starts to be applied when $N = N_{tol}$ for the first time). The yellow line is the mean of the two patient outcomes and the dashed line is the time to treatment failure under ideal containment at N_{tol} (which is the same for both patients, and the maximal time to treatment failure).

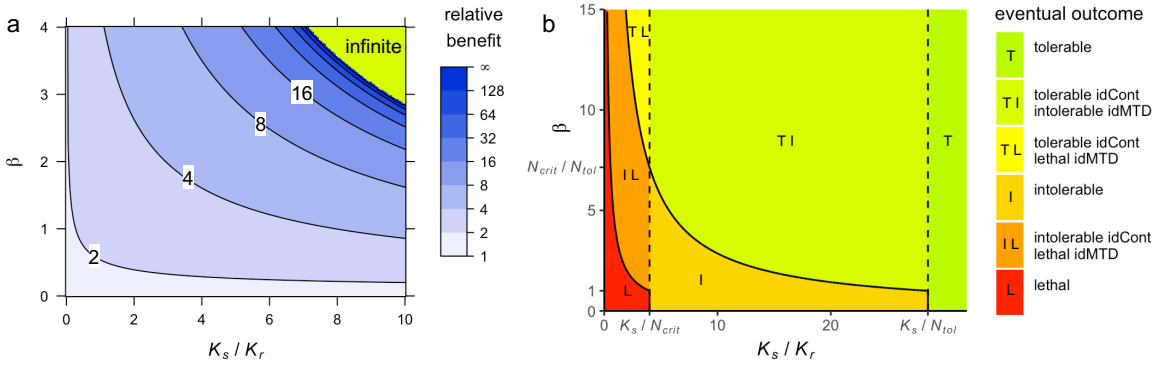

Figure 4: **Consequences of costs of resistance in Model 4.** **a**, Relative benefit, in terms of time to treatment failure, for ideal containment (at size N_{tol}) versus ideal MTD, for varied values of K_r and β. This figure is based on approximate formulas that are highly accurate for the selected parameter values (see Supplementary Information, Section 5.2). Extended Data Fig. 8 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 Information, 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.