The logic of containing tumours

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An experimental system

- HCT116 human colorectal tumour cells
- Generated lines irreversibly resistant to Cdk2 inhibitor NU6102
- Mixed sensitive and resistant cells in tumour spheroids

Bacevic & Noble et al. (2017) Nature Comms
Fitness cost of resistance

In monolayer culture

- Wild type
- Resistant with/without drug

In nude mice

- Wild type
- Resistant with/without drug

Not frequency-dependent

Bacevic & Noble et al. (2017) Nature Comms
Contact inhibition and competition for space

Bacevic & Noble et al. (2017) Nature Comms

cell attempting to proliferate
cell proliferation

cost of resistance
distance from periphery

hypoaxia
drug

cell death

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Computational model of a tumour spheroid

Bacevic & Noble et al. (2017) Nature Comms
Computational model of a tumour spheroid

Bacevic & Noble et al. (2017) Nature Comms
Computational model

Dose: 0 5 10 20 50

time
Sensitive
Resistant

Control
Dose 50
Dose 20

spheroid size (mm$^3$)

days

0 0.1 0.2 0.3 0.4
4 7 10 13 16 19 22 25 28

Actual tumour spheroids

Dose: 0 5 10 20 50

time
Sensitive
Resistant

Control
Dose 50
Dose 20

spheroid size (mm$^3$)

days

0 0.1 0.2 0.3 0.4
4 7 10 13 16 19 22 25 28 31

Bacevic & Noble et al. (2017) Nature Comms
Is a cost of resistance really necessary?

**Computational model**

![Graph showing proportion of simulations with >10% resistance at day 28 for different initial distances between outermost resistant cell and tumour spheroid periphery.](image)

- **Experimentally-derived parameters**

- **Initial distance between outermost resistant cell and tumour spheroid periphery** (cell diameters)

  - **No fitness cost of resistance**
  - **No growth period before treatment**
  - **No crowding inhibition of proliferation**

*Bacevic & Noble et al. (2017) Nature Comms*
Is a cost of resistance really necessary?

Computational model

Proportion of simulations with >10% resistance

<table>
<thead>
<tr>
<th>Initial distance between outermost resistant cell and tumour spheroid periphery (cell diameters)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
</tr>
<tr>
<td>0</td>
</tr>
<tr>
<td>1</td>
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<tr>
<td>2</td>
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<tr>
<td>3</td>
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</tbody>
</table>

Experimentally-derived parameters

No fitness cost of resistance

No growth period before treatment

No crowding inhibition of proliferation

Bacevic & Noble et al. (2017) Nature Comms
Is a cost of resistance really necessary?

Computational model

![Graphs showing proportion of simulations with >10% resistance at day 28](chart)

- **Experimentally-derived parameters**
- **No fitness cost of resistance**
- **No growth period before treatment**
- **No crowding inhibition of proliferation**

Initial distance between outermost resistant cell and tumour spheroid periphery (cell diameters)

- Mean

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A general model

\[ \dot{S}(t) = S(t)g_s(S(t), R(t), C(t)) \]
\[ \dot{R}(t) = R(t)g_r(S(t), R(t)) \]

Assume

- \( g_s \) is non-increasing in \( C \)
- \( g_r \) is non-increasing in \( S \)
- \( g_r \) is independent of \( C \)
- neglect mutations

Yannick Viossat
(Ceremade, Université Paris-Dauphine)
Outcomes

**Time to progression**
- tumour exceeds its initial size, $N_0$

**Time to treatment failure**
- tumour exceeds a maximum tolerable size, $N_{tol}$

**Survival time**
- tumour reaches lethal size, $N_{crit}$
Optimality of containment

We formally prove these results hold very generally for prolonging survival:

• optimal strategy maintains tumor burden as high as possible while sensitive cells remain – *ideal containment*

• worst option is to maximize kill rate – *maximum tolerated dose*
Mathematical intuition

For a small time step $dt$:

$$R(t + dt) = R(t) + dR$$

where

$$dR \approx \dot{R}(t)dt = g_r(R(t), S(t))dt$$

So time for $R$ to grow from $R_1$ to $R_1 + dR$ is

$$dt \approx dR / g_r(R_1, S_1)$$

where $S_1$ is size of $S$ when $R = R_1$
Mathematical intuition

If we contain the tumour at initial size $N_0$ then

$$S_1 = N_0 - R_1$$

Under any other treatment, before progression we have $S_1 + R_1 \leq N_0$ and so $S_1 \leq N_0 - R_1$

By assumption, larger $S_1$ implies smaller $g_r$, which in turn implies smaller $dt$ (as $dt \propto 1/g_r$)

Hence containment minimizes growth of $R(t)$ and, since progression occurs when $R(t) = N_0$, containment maximises time to progression
Clinical gains strongly depend on competition intensity

\[ g(N) = \rho \left( N^{-1/3} - K^{-1/3} \right) \]

Gompertizian: \[ g(N) = \rho \ln(K/N) \]

logistic: \[ g(N) = \rho (1 - N/K) \]
A Gompertzian model

\[
\begin{align*}
\dot{S}(t) & = \rho \ln(K/N(t)) \left(1 - \lambda C(t)\right) S(t), \\
\dot{R}(t) & = \rho \ln(K/N(t)) R(t),
\end{align*}
\]

Adapted from Monro & Gaffney (2009)
Predicted clinical benefits (Gompertzian model)

Time to progression

Time to treatment failure

Predicted benefits as a function of initial tumor size and frequency of resistant cells.
Practical treatment strategies can be close to optimal

The constant dose and delayed constant dose treatments in Model 3.

The dashed line is the time to treatment failure under ideal containment at the initial size (subject to maximal time to progression).

Table 2: 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 the initial size for various delayed constant dose treatments (the dose is applied continuously from the first time when the maximal time to treatment failure).

Intermittent containment ($N_{\text{tol}} = 0$) between $0$ and $1$ leads to a larger time to progression than containment at $N_{\text{tol}} = 1$.

The constant dose treatments compared to containment at the initial size (subject to ideal MTD).

Times to progression, time to treatment failure, and survival time for Model 3.

The 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 the ideal MTD.

Figure 3: Time to progression for two patients whose tumors differ in treatment sensitivity (parameter $\alpha$ can be close to optimal strategies). Until $t_{\text{fail}} = 2$ between $0$ and $1$, no treatment leads to a larger time to progression than containment at $N_{\text{tol}} = 1.5$.

Viossat & Noble (in press)
Practical treatment strategies can be close to optimal

Supplementary figure 4.

Containment at $N_0$ and intermittent containment between $N_0$ and 0 in a Gompertzian growth model (Model 3 in the main text).

Dashed vertical lines indicate time to progression under containment (dashed grey) and intermittent containment (dashed black). Intermittent containment leads here to a slightly larger time to progression than containment at the upper level. However, as follows from Proposition 6, the resistant population is larger under intermittent containment (red) than under containment (pink). After progression, tumor size quickly becomes larger under intermittent containment (solid black curve) than under containment (solid grey curve). Parameter values are as in Table 1 of the main text.

Counterpart. As a consequence, the resistant population still somewhat competes with sensitive cells, and develops more slowly (Fig. 1c). The MTD treatment is thus expected to lead to a longer time to progression than its idealized version. This is especially true if treatment is relatively inefficient. In that case, by the time sensitive cells have been crushed, resistant cells are already abundant. It follows that tumor size is never very low, so that resistant cells never develop very quickly.

To quantify this phenomenon in the case of a Norton-Simon kill rate, recall that under MTD, the quantity $S_{\text{Cmax}}$ is constant. It follows that the tumor reaches its smallest size when $S = R/C_{\text{max}}$. Its size is then:

$$N = C_{\text{max}} \times S_0 R C_{\text{max}} 1,$$

with $C = C_{\text{max}}$.

Some values of this minimal size are given in Supplementary Table 9, assuming $S_0 = 10^{10}$ and $R_0 = 10^6$. It confirms that, for modest treatment effects ($C_{\text{max}} \leq 2$), the minimal tumor size under MTD is much higher than under ideal MTD (that is, than the initial resistant population).

Finally, the fact that few sensitive cells remain at the time of progression implies that, after progression, MTD and ideal MTD have similar dynamics. As a result, the difference in survival times should not be much higher than the difference in times to progression. This is what we observe in simulations (Table 2, Figs. 2d, 2f, Supplementary Figs. 7 and 6).

MTD and containment. Ideal containment at $N_0$ always leads to a higher time to progression than ideal MTD, and with a Gompertz model, typically substantially so, unless the tumor is initially very resistant. The difference in time to progression between the more realistic versions – containment at $N_0$ and MTD – is smaller. If treatment is not very efficient, MTD may even lead to a higher time to progression.
What about fitness costs of resistance?

“the theory behind adaptive therapy focuses on the phenotypic costs of the molecular mechanism(s) of resistance”


Fitness costs of resistance are unnecessary

\[
\begin{align*}
\text{sensitive cells: } \quad \dot{S}(t) &= S(t)g_s(S(t), R(t), C(t)) \\
\text{resistant cells: } \quad \dot{R}(t) &= R(t)g_r(S(t), R(t))
\end{align*}
\]

Assume

• \(g_s\) is non-increasing in \(C\)
• \(g_r\) is non-increasing in \(S\)
• \(g_r\) is independent of \(C\)
• neglect mutations
Modelling fitness costs of resistance

sensitive cells: \[ \dot{S}(t) = \rho_s \ln \left( \frac{K_s}{S(t) + \alpha R(t)} \right) (1 - \lambda C(t)) S(t), \]

resistant cells: \[ \dot{R}(t) = \rho_r \ln \left( \frac{K_r}{R(t) + \beta S(t)} \right) R(t). \]

Resistance cost may correspond to:
• generally slower growth (low \( \rho_r \))
• general inability to compete with other cells (low \( K_r \))
• specific inability to compete with sensitive cells (high \( \beta \))

\[ Viossat & Noble (in press) \]
Fitness costs of resistance are helpful (but not essential)

Figure 4: Consequences of costs of resistance in Model 3.

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 \(\beta\). This figure is based on approximate formulas that are highly accurate for the selected parameter values (see Supplementary material, Section 5.2). Supplementary Fig. 5 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 1.
Fitness costs of resistance are helpful (but not essential)
Ongoing mutations (independent of drug dose) have negligible impact.

For instance, in main text Model 3, if parameter values (other than $R_0$) are as in main text Table 1, this occurs whenever the initial fraction of resistant cells is higher than about 1% if $C_{\text{max}} = 2$ (Fig. 2d) and than about 0.1% if $C_{\text{max}} = 1.5$.

There are two explanations. First, low treatment efficiency decreases time to progression under containment. Indeed, progression then occurs as the tumor is still quite sensitive (see Fig. 2g, and Section 4.2). Second, as discussed in Section 4.4, low treatment efficiency makes MTD less problematic. Supplementary Table 9 shows that, for $C_{\text{max}} = 1.5$, the minimal tumor size under MTD is only slightly below $10^{9}$.

The average size before progression will be substantially higher than $10^{9}$, compared to $N_0 = 10^{10} + 10^6$'s. The time to progress beyond size $N_{\text{ref}}$ is expected to be greater (compare Figs. 2d and 2h). Moreover, even when MTD and containment at $N_0$ are comparable in terms of time to progression, the resistant population is always smaller under containment, leading to longer times to treatment failure and longer survival times under containment than under MTD. This is seen in simulations (Figs. 2d, 2e, 2f).

Finally, Supplementary Fig. 5 compares containment and MTD in a Gompertzian growth model, with and without mutations after treatment initiation, for two different mutation rates. It suggests that, while complicating the analysis and the obtention of explicit or semi-explicit formulas, taking into account ongoing mutations does not substantially affect outcomes (see also Supplementary Table 6).
Conclusions

Containment strategies generally improve on MTD

This is true even if resistance has no cellular fitness cost

Predicted clinical gains crucially depend on the intensity of competition between sensitive and resistant cells

Practical treatment strategies can be close to optimal

Support for further experimental and clinical trials
Patients, objectives, and tumor dynamics

We address five key questions:

• How to best implement the containment idea?
• Idealized containment at size $N > N_{\text{min}}$.
• Idealized aggressive treatment: $N = N_{\text{max}}$.
• Maximal tolerated dose (MTD).
• Various models have been proposed to intuitively than treating at the maximal tolerated dose.

Stage 1: sensitive, resistant, and total tumor size under containment, and progresses beyond until the tumor reaches size $N_{\text{crit}}$. Under idealized containment, tumor burden $N$ minimizes resistance: for any other treatment $r$, $r < N_{\text{ref}}$.

Main Objectives

A critical (lethal) tumor burden $C$ is reached when $N > C$.

Result 1 (with bounded treatment level).

• obvious effect: good for all treatments
• indirect effect: make resistant cells initially rare.

Result 2 (with bounded treatment level).

• between containment at $N_{\text{min}}$ and $N_{\text{max}}$, treatment is delayed.
• higher the tumor burden, the better. Stabilizing tumor between containment at $N_{\text{min}}$ and $N_{\text{max}}$.

Does effective containment depend on a resistance cost?

Intuition.

Both continuous low-dose and intermittent high dose containment is sound if $N_{\text{min}}$ is large.

This is true even in the absence of resistance costs.

Does effective containment depend on a resistance cost?

Inference.

• much higher gains than Logistic growth.
• $N_{\text{min}}$, treatment is delayed
• in the absence of treatment. Whether resistance typically entails a significant cost is debated. Our results show that on a resistant cost: the fact that the resistance mechanism

Conclusion.

• does not provide an advantage for intermittent high dose containment over continuous low dose containment.

Conclusions

• does not provide an advantage for intermittent high dose containment over continuous low dose containment.

References

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HC. Monro and EA. Gaffney. Modelling chemotherapy resistance in palliation with sensitive cells weakens as the sensitive population

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