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Impact of resistance on treatment failure in metastatic prostate cancer patients

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Introduction

- Resistance strongly affects response of cancer to treatment, therefore, investigating the link between resistance and treatment failure is of utmost importance[1,2].
- Assessing the level of resistance within lesion during treatment is hardly possible with standard measuring techniques (e.g., imaging modalities or biopsies). Computational models can be used to identify hidden biological processes.
- **We aimed to evaluate the evolution of resistance and its impact on treatment response** in metastatic prostate cancer (mPC) patients with a data-driven computational model.

Model

- A deterministic population model, consisting of ordinary differential equations, was used to describe dynamics of **drug-sensitive (T_S) and drug-resistant cells (T_R)** in individual lesion[3,4,5].
  - $\frac{dT_S}{dt} = (g_S - D(t)) \cdot T_S \cdot ln\left(\frac{B}{\sum_{j=1}^{N}(T_R^j + T_S^j)}\right) - m \cdot D \cdot T_S$
  - $\frac{dT_R}{dt} = (g_R - D_0) \cdot T_R \cdot ln\left(\frac{B}{\sum_{j=1}^{N}(T_R^j + T_S^j)}\right) + m \cdot D \cdot T_S$
  - $\frac{dD}{dt} = d \cdot D \cdot \left(1 - \frac{D}{D_{MAX}}\right)$
  - $T_S(t=0) = (1 - IR) \cdot T(t=0)$
  - $T_R(t=0) = IR \cdot T\ (t=0)$

Variable	Description	Units	Assumptions
T	Total number of cells within a lesion	cells	$T = T_S + T_R$ is proportional to total lesion uptake ($_iSUV_{total}$)
T_S	Number of drug-sensitive cells	cells	Lesion initially consists of $(1 - IR) \cdot T$ drug-sensitive cells
T_R	Number of drug-resistant cells	cells	Lesion initially consists of $IR \cdot T$ drug-resistant cells
D	Dose-specific death rate	1/day	Before starting treatment, D is equivalent to D_0
t	Time	day	
Parameter	**Description**	**Units**	**Assumptions**
g_S	Proliferation rate of drug-sensitive cells	1/day	Literature[6]
g_R	Proliferation rate of drug-resistant cells	1/day	Fitted (fixed across lesions and patients)
B	Maximum possible total tumor burden within a patient	cells	Calculated from CT
D_0	Natural death rate	1/day	Literature[6]
d	Drug efficiency	/	Fitted (varying across lesions and patients[7,8])
D_{MAX}	Maximum drug-induced death rate	1/day	Fitted (fixed across lesions and patients)
m	Scaling factor linking drug concentration with mutation rate of drug-sensitive into drug-resistant cells[6]	/	Fitted (fixed across lesions and patients)
IR	Proportion of intrinsically resistant cells	/	Fitted (varying across lesions and patients)
N	Number of lesions within a patient	/	Tallied on ^{18}F-NaF PET/CT scan

Data and Methods

- mPC patients (n=7), receiving enzalutamide, were scanned with ^{18}F-NaF PET/CT at baseline (t_0), month 3 (t_3), and progression or year 2 ($t_{progress}$).
- Bone lesions were identified and segmented using statistically optimized regional thresholds (SORT)[9]. A total of **233 lesions (range: 8-52 lesions per patient)** were identified.
- Lesions were classified as **completely responding (iCR), partially responding (iPR), stable disease (iSD), or progressing disease (iPD)** based on test-retest limits of agreement of lesion-level NaF total uptake ($_iSUV_{total}$) [10].
- **Percentage of correctly classified lesions** was used to assess model performance.
- Patient-level treatment response was evaluated by calculating the **relative change in patient-level total tumor burden ($_gT$),** defined as $\sum_{j=1}^{N} {}_iSUV_{total}^j$, **and the proportion of $_gT$ consisting of resistant cells (^r_gT),** defined as $\sum_{j=1}^{N} T_R^j / {}_gT$, for various time points until the $t_{progress}$.
- **Time (t_{EX}), when lesions consist of only drug-resistant cells ($T = T_R, T_S = 0$)** and consequently stops responding to treatment, was defined. Heterogeneity in t_{EX} within a patient was evaluated as the minimum and maximum t_{EX}.
- The correlation between t_{EX} and IR was assessed.

Results

- The percentage of lesions that the model **correctly classified in treatment response categories,** due to the relative change in $_iSUV_{total}$ between NaF PET scans was (**Figure 1**):
  - t_0: t_3: 95%
  - t_0: $t\_progress$: 82%
  - t_3: $t_{progress}$: 78%
- The evolution of ^r_gT and relative change in $_gT$, according to the model prediction, is shown on **Figure 2.**
- In only **3/7 patients, $_gT$ is higher than at baseline** ($_gT$ of t_0 scan) at the time of disease progression or year 2 ($t_{progress}$), seen in **Figure 2B.**
- **Figure 2A** clearly showes that in more than 50% of the patients (4/7), **the treatment is already inefficient at $0.75 \cdot t_{progress}$.**

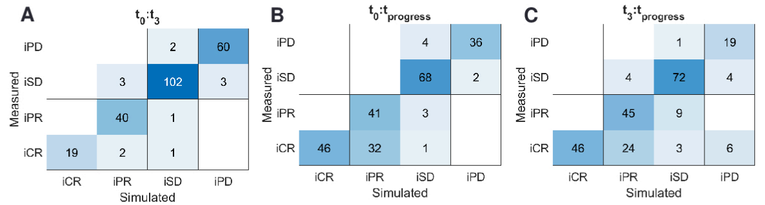

Figure 1: Model performance in classifying lesions in treatment response categories. Numbers represent the number of correctly classified lesions in each of the four treatment response categories: completely responding (iCR), partially responding (iPR), stable disease (iSD), progressing disease (iPD), based on test-retest limits of agreement for $_iSUV_{total}$. Relative change in $_iSUV_{total}$ is calculated between t_0: t_3 (A), t_0: $t_{progress}$ (B) and t_3: $t_{progress}$ (C) scans.

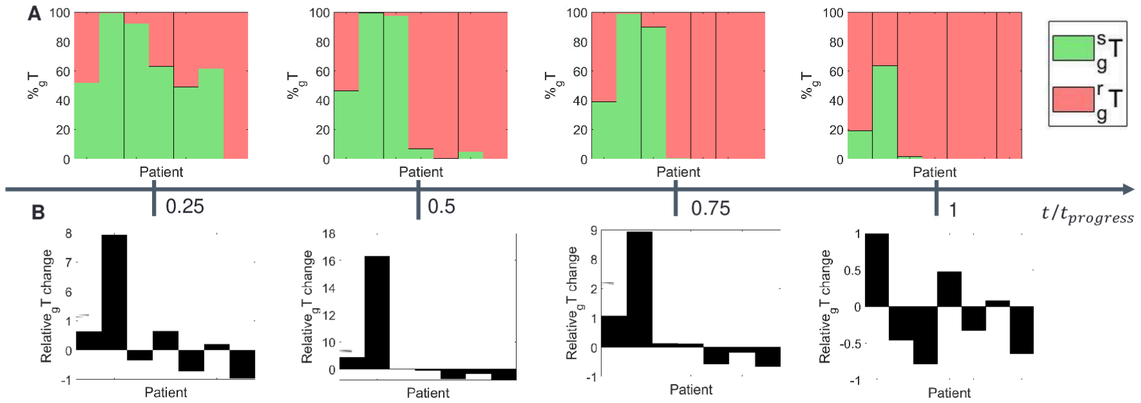

Figure 2: Modeled evolution of resistant part of patient-level total tumor burden (A) and relative change in patient-level total tumor burden (B). (A) Presented are percentages of drug-sensitive (^s_gT, green) and drug-resistant (^r_gT, red) patient-level total tumor burden ($_gT$) at four time points, equally distributed until the time of disease progression or year 2 ($t_{progress}$). (B) Relative $_gT$ change for each patient is presented. Change is calculated based on $_gT$ at t_0 scan.

- Median t_{EX} among patients was 6.1 months. Large **intra-patient heterogeneity in t_{EX}** is observed (**Table 1**), as evidenced by minimum and maximum t_{EX} within a patient.
- **t_{EX} has a positive linear correlation with IR**, with correlation coefficient 0.41(p<0.001).

Table 1: Range of the time of treatment failure (t_{EX}) of individual lesions per patient compared to the time of disease progression or two years ($t_{progress}$). Inter- and intra-patient heterogeneity in t_{EX} can be observed.

Patient	Range of t_{EX} (months)	$t_{progress}$(months)
1	0.4-9.1	9.1
2	1.0-16.5	16.5
3	0.4-24.5	24.5
4	0.9-9.3	9.3
5	0.5-15.7	16.4
6	0.4-6.8	6.8
7	0.5-8.7	23.7

Discussion and Conclusion

- Despite some patients showing favorable relative change in $_gT$ at $t_{progress}$, our results show that in 3/7 patients $_gT$ consists of only drug-resistant cells ($_gT = {}^r_gT$) even before $t_{progress}$. **This results indicate that patients may fail enzalutamide even before clinical evidence of disease progression.**
- With a strong correlation between IR and t_{EX}, we show the **importance of intrinsically resistant cells for treatment failure of individual lesions.**

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