Relating Prostate Specific-Antigen leakage with vascular tumor growth in a mathematical model of prostate cancer response to androgen deprivation

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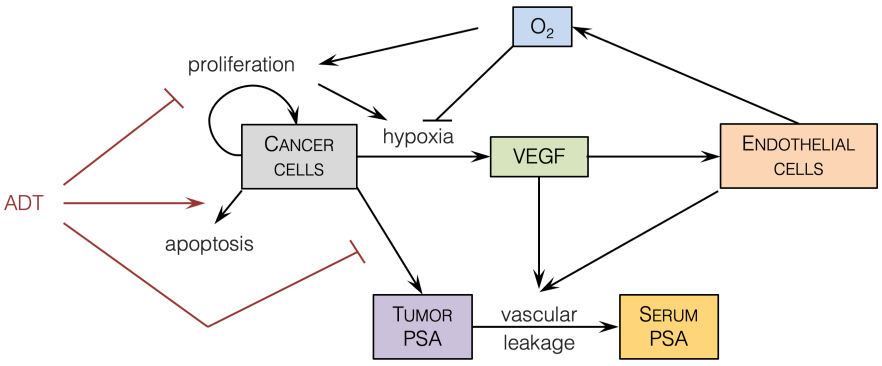
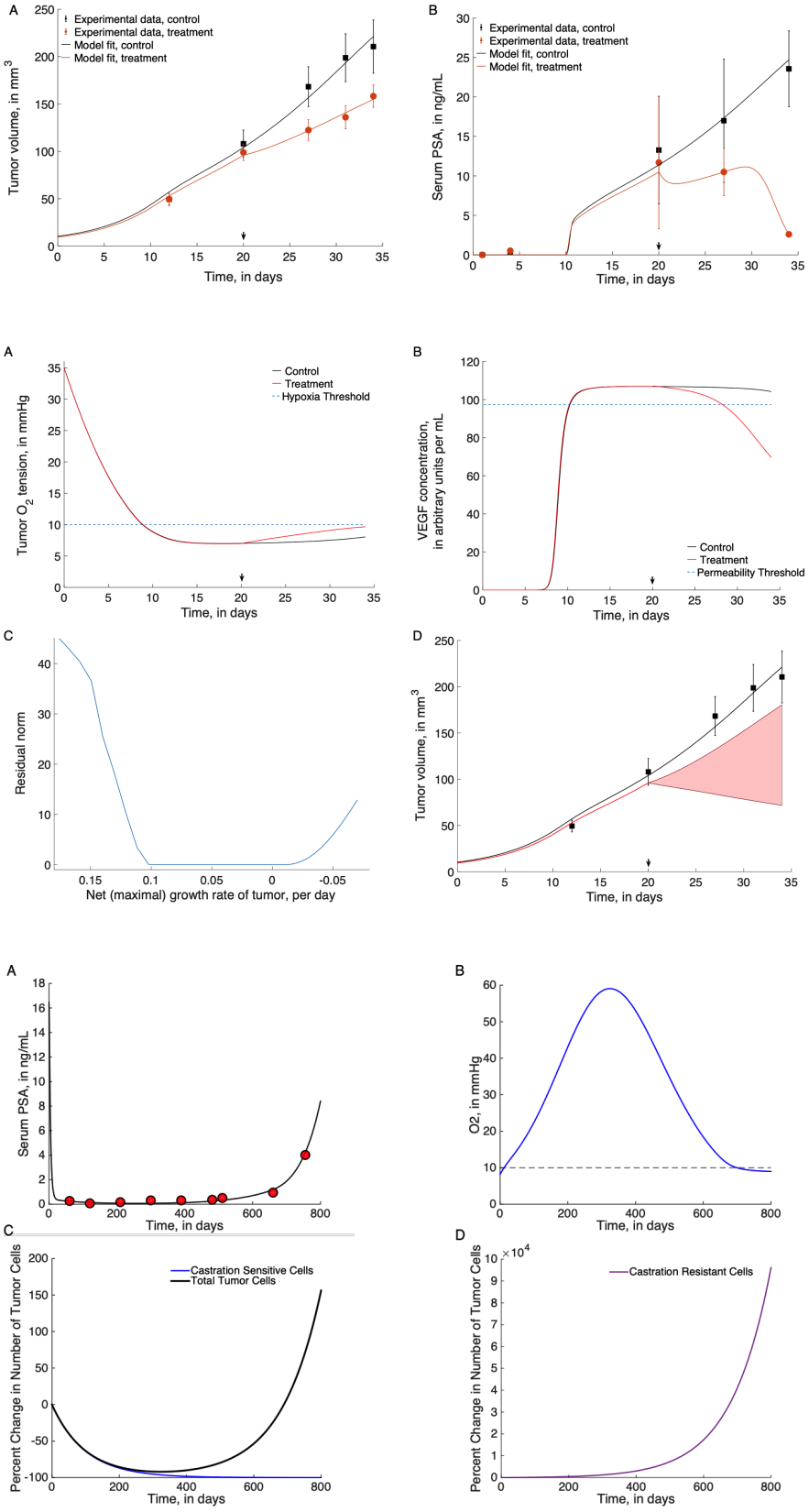
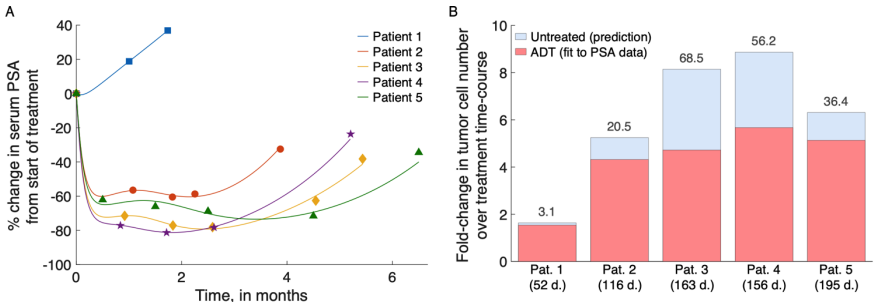
Abstract

Introduction: The use of prostate-specific antigen (PSA) as a prognostic indicator for prostate cancer (PCa) patients is controversial, especially since it has been shown to correlate poorly with tumor burden. The poor quality of PSA as a biomarker could be explained by current guidelines not accounting for the mechanism by which it enters circulation. Given that mature blood vessels are relatively impermeable to it, we hypothesize that immature and leaky blood vessels, formed under angiogenic cues in a hypoxic tumor, facilitate PSA extravasation into circulation. Methods: To explore our hypotheses, we develop a non-linear dynamical systems model describing the vascular growth of PCa, that explicitly links PSA leakage into circulation with changes in intra-tumoral oxygen tension and vessel permeability. The model is calibrated versus serum PSA and tumor burden time-courses from a mouse xenograft model of castration resistant PCa response to androgen deprivation. Results: The model recapitulates the experimentally observed – and counter-intuitive – phenomenon of increasing tumor burden despite decreasing serum PSA levels. The validated model is then extended to the human scale by incorporating patient-specific parameters and fitting individual PSA time-courses from patients with biochemically failing PCa. Our results highlight the limitations of using time to PSA failure as a clinical indicator of androgen deprivation efficacy. We propose an alternative indicator, namely a treatment efficacy index, for patients with castration resistant disease, to identify who would benefit most from enhanced androgen deprivation. Conclusions: A critical challenge in prostate cancer therapeutics is quantifying the relationship between serum PSA and tumor burden. Our results underscore the potential of mathematical modeling in understanding the limitations of serum PSA as a prognostic indicator. Finally, we provide a means of augmenting PSA time-courses in the diagnostic process, with changes in intra-tumoral vascularity and vascular architecture .







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Methods: To explore our hypotheses, we develop a nonlinear dynamical systems model describing the vascular growth of PCa, that explicitly links PSA leakage into circulation with changes in intra-tumoral oxygen tension and vessel permeability. The model is calibrated versus serum PSA and tumor burden time-courses from a mouse xenograft model of castration resistant PCa response to androgen deprivation.

Results: The model recapitulates the experimentally observed – and counter-intuitive – phenomenon of increasing tumor burden despite decreasing serum PSA levels. The validated model is then extended to the human scale by incorporating patient-specific parameters and fitting individual PSA time-courses from patients with biochemically failing PCa. Our results highlight the limitations of using time to PSA failure as a clinical indicator of androgen deprivation efficacy. We propose an alternative indicator, namely a treatment efficacy index, for patients with castration resistant disease, to identify who would benefit most from enhanced androgen deprivation.

Conclusions: A critical challenge in prostate cancer therapeutics is quantifying the relationship between serum PSA and tumor burden. Our results underscore the potential of mathematical modeling in understanding the limitations of serum PSA as a prognostic indicator. Finally, we provide a means of augmenting PSA time-courses in the diagnostic process, with changes in intra-tumoral vascularity and vascular architecture .

Introduction

Prostate cancer (PCa) is the second most common type of cancer affecting men in the United States, and a leading cause of cancer related deaths among men [1]. Due to its initial dependence on androgens for growth and survival, advanced PCa is treated with androgen deprivation therapy (ADT) – a process wherein the bioavailability of androgens to cancer cells is blocked by the constant or periodic application of a combination of chemical castration agents [2].

PCa cells produce prostate specific-antigen (PSA), thus PCa is associated with increased levels of blood serum PSA. Further, men with a higher PSA at the time of therapy initiation have been shown to have an increased risk of recurrence. Therefore, serum PSA levels are used as a prognostic indicator for response to treatment and development of metastases [3–5]. However, large-scale population studies [6, 7] found that these protocols have resulted in the diagnosis and treatment of many cases of indolent (non-aggressive) disease, while offering little mortality benefit. In 2001, Swanson et al. [8] concluded using mathematical modeling, that serum PSA is expected to correlate poorly with tumor burden due to delays between tumor growth and PSA production.

One factor affecting the poor prognostic potential of PSA could be that the diagnostic process does not account for the mechanisms by which it enters the blood stream. PSA is a 34 kDa macromolecule and mature blood vessels are relatively impermeable to it. Consequently, in a healthy prostate, PSA remains tightly confined to the gland, and only a minute proportion leaks into the circulatory system [9]. It has been postulated that to enter systemic circulation, PSA must overcome a number of barriers, including prostatic basement membrane, intervening stroma and capillary basement membrane. This in turn requires a disruption in prostate ductal lumen architecture, and alterations in vascular morphology [10]. Therefore, to better understand the relationship between serum PSA and tumor volume, we

need to account for the changes in tumor vasculature, especially in response to any treatment administered.

In general, growing tumors need a constant supply of nutrients; this is achieved by the formation of new vasculature under a process called angiogenesis [11]. Briefly, as the tumor becomes too large for existing vasculature to meet its nutritional demands, cancer cells secrete angiogenic factors, the primary one being vascular endothelial growth factor (VEGF). VEGF induces sprout tip formation in nearby vasculature, which then migrate up its concentration gradient, laying down new vessels in their wake [12]. In addition to inducing angiogenesis, VEGF also causes increased permeability of vessels [13]. Consequently, we hypothesize that a major mechanism of PSA extravasation into circulation is via immature and leaky blood vessels, formed under angiogenic cues from the developing tumor.

From the above discussion it follows that for patients receiving ADT, associating varying levels of serum PSA with changes in tumor burden needs to be interpreted in the context of changes in tumor vasculature. In fact, serum PSA may, under certain conditions, be uncorrelated with tumor burden. This has been observed in multiple mouse xenograft experiments [14, 15], wherein serum PSA showed a steady decline under ADT even though tumor volume continued to increase. Our aim here is to gain a mechanistic understanding of the biological processes that underpin these experimental observations. To this end, we develop a mathematical model describing the molecular and cellular processes leading to PSA production in PCa and it extravasation into circulation.

Indeed, several mathematical models linking changes in serum PSA with those in tumor burden in response to therapy, have been proposed [16–25]. These have made important contributions to our understanding of how PCa progresses to a castration resistant phenotype under ADT. Even so, common to all these approaches is an implicit or explicit assumption that increasing serum PSA correlates with a growing tumor, and vice versa. Our model relaxes this assumption by explicitly incorporating vascular remodeling in a growing tumor, or on that is undergoing ADT. We then simulate PSA leakage into circulation at a tissue/organ level, by explicitly accounting for the evolution of blood vessel permeability in response to such a dynamic tumor microenvironment.

Materials and Methods

Model Development

Our model of the vascular growth of PCa xenografts is cast as a system of coupled nonlinear ordinary differential equations (ODEs), that describe the temporal dynamics of the following key variables: $N(t)$, the number of tumor cells (in millions); $E(t)$, the number of endothelial cells assumed to line functional blood vessels (in millions); $V(t)$ and $P_t(t)$, the amounts of VEGF (in arbitrary units) and PSA (in ng) in the tumor, respectively; $P_s(t)$, serum PSA concentration (in ng/mL); and $L(t)$, the degree of vascular permeability (dimensionless). We also account for changes in: O_2, intratumoral oxygen tension (in mmHg); N_v, the total tumor volume (in mm^3); and V_c, intratumoral VEGF concentration (in arbitrary units/mL). We remark that VEGF concentration within a tumor is estimated to be on the order of pg/ml [26]; however, in the absence of time-course data with which to calibrate our model, we take it to be measured in arbitrary units. A model schematic is shown in figure 1.

Briefly, cancer cell proliferation is mediated by androgens [2] and the availability of nutri-

ents such as oxygen [27], supplied by tumor vasculature. For simplicity, we do not explicitly incorporate microvessel density in our model. Rather, following Jain and Jackson [28], functional blood vessels are approximated by keeping track of the endothelial cells lining them. An increase in tumor cell number relative to endothelial cell number creates a hypoxic environment, resulting in the expression of VEGF by the tumor cells [29, 30]. This is taken up by endothelial cells lining proximal blood vessels, resulting in sprouting angiogenesis [12], and a concomitant increase in oxygen tension. PCa cells also produce and secrete PSA under androgen signaling [3]. Crucially, VEGF induces a rapid increase in vascular permeability [13] that, per our hypothesis, is necessary for PSA to freely extravasate into circulation. The effects of ADT on these dynamics are: reduced tumor cell proliferation; elevated tumor cell apoptosis; and a decrease in PSA expression. Together, the following system of ODEs is taken to represent these dynamics.

$$\text{Tumor Cells}: \quad \frac{dN}{dt} = \underbrace{\epsilon_N \alpha_N N \left(1 - \frac{N_v}{K}\right)\left(\frac{1}{1+e^{-\beta_N(O_2-\nu_N)}}\right)}_{\text{proliferation}} - \underbrace{\delta_N N}_{\text{apoptosis}}, \quad (1)$$

$$\text{VEGF}: \quad \frac{dV}{dt} = \underbrace{\alpha_V \left(\frac{1}{1+e^{\beta_V(O_2-\nu_V)}}\right) N}_{\text{production by tumor cells}} - \underbrace{\delta_V V}_{\text{degradation}}, \quad (2)$$

$$\text{Endothelial Cells}: \quad \frac{dE}{dt} = \underbrace{\alpha_E E V_c}_{\text{proliferation}}, \text{ where } V_c = \frac{V}{N_v \times 10^{-3}} \quad (3)$$

$$\text{Tumor volume}: \quad N_v = vol_E E + vol_N N, \quad (4)$$

$$\text{Tumoral PSA}: \quad \frac{dP_t}{dt} = \underbrace{\epsilon_P \alpha_P N}_{\substack{\text{production by} \\ \text{tumor cells}}} - \underbrace{\delta_{Pt} P_t}_{\text{degradation}} - \underbrace{\lambda E \hat{L} P_t}_{\substack{\text{leakage into} \\ \text{circulation}}}, \quad (5)$$

$$\text{Serum PSA}: \quad \frac{dP_s}{dt} = \underbrace{\frac{\lambda E \hat{L} P_t}{vol_B}}_{\substack{\text{leakage} \\ \text{from tumor}}} - \underbrace{\delta_{Ps} P_s}_{\text{clrearance}}, \quad (6)$$

$$\text{Permeability}: \quad \frac{d\hat{L}}{dt} = \underbrace{\frac{\delta_L}{1+e^{-\beta_L(V_c-\nu_L)}}}_{\text{increase}} - \underbrace{\delta_L \hat{L}}_{\text{decrease}}, \quad (7)$$

$$\text{Tumoral } O_2: \quad O_2 = 100\omega F, \text{ where } F = \frac{vol_E E}{N_v}. \quad (8)$$

A complete description of model derivation, together with underlying assumptions, is provided in section S1 of the Supplementary Information.

Experimental Data

In experiments reported in [14], Cheng et al. investigated the effect of androgen withdrawal on castration-resistant PCa xenografts. Briefly, BALB/c athymic male mice were inoculated with CWR22Rv1 cells, an androgen-responsive but androgen independent prostate cancer cell line. These cells weakly respond to ADT, and express PSA. 4×10^6 cancer cells were

injected subcutaneously into all of the mice, and once the xenografts were established, the mice were either left untreated or underwent castration 20 days post inoculation. Tumor volume and serum PSA were measured periodically for both groups (see figure 2).

Clinical Data

In a phase 3 clinical trial designed to optimize ADT scheduling in patients with late stage PCa and rising serum PSA levels, Schulman et al. [31] reported a serum PSA time-course averaged across all patients on continuous ADT. These data were used to calibrate our model extension for investigating the emergence of castration resistance in human patients.

Serum PSA time-courses from five individual patients with castration-resistant disease, who were undergoing enhanced ADT, were obtained from [32, 33]. Treatment efficacy was determined by serum PSA concentration, with a decline below 50% of its value at the start of therapy indicative of success, and a subsequent rise above this value – or an insufficient decline in the first instance – indicative of failure [33]. These data were used to calibrate our model extension for investigating how informative time to PSA progression is in diagnosing castration resistance emergence.

Parameter Estimation

Where possible, parameter values were taken from the literature. The remaining parameters were estimated by minimizing the sum of squares between model predictions and empirical measurements (as reported in [14]) of serum PSA and tumor volume time-courses. The experimental data, together with best fits, are shown in figure 2. Further details of this process, including a list of parameter estimates, can be found in section S1 of the Supplementary Information.

Results and Discussion

PSA leakage into circulation is determined by tumor vasculature characteristics

Model simulations predict that serum PSA time-courses do not necessarily follow tumor volume time-courses. For instance, serum PSA is not predicted to increase until around day 10 post xenograft implantation, even though the tumor has grown steadily prior to this period. The corresponding predicted intra-tumoral oxygen tension and VEGF concentration time-courses, plotted in figures 3A and B, respectively, reveal the reason why. In the initial stages of xenograft growth, the tumor is well oxygenated due to proximity with murine blood vessels. However, as the tumor increases in size, it becomes hypoxic at which time tumor cells begin to secrete VEGF, causing an increase in vascular endothelial cell number and vascular permeability.

The application of ADT at day 20 results in a sharp, transient decrease in serum PSA (figure 2B, red curve). This initial decrease is a model artefact since we assume that the application of ADT causes tumor cells to instantaneously reduce PSA production, from a maximum rate of α_P to $\epsilon_P \alpha_P$, where $0 < \epsilon_P < 1$ represents the effect of therapy (see equation (4)). The subsequent and sustained decline in serum PSA is caused by a decrease in vessel permeability. Briefly, ADT down-regulates tumor cells proliferation (figure 2A, red curve), resulting in the re-establishment of a more normoxic environment (figure 3A,

red curve). Consequently, VEGF production decreases (figure 3B, red curve), causing a decline in vascular permeability around day 30, thereby preventing PSA extravasation into circulation.

We remark that in a clinical setting, tumor volume time-courses would not be observable. The response of the cancer to ADT would be inferred, in large part, from serum PSA time-course data. We simulate this 'real-world' scenario by re-estimating model parameters and only fitting the treatment serum PSA time-course data. The parameters being varied are: the net rate of tumor growth under ADT ($\epsilon_N \alpha_N - \delta_N$); the threshold of VEGF concentration at which vessel become 'leaky' (ν_L); the sensitivity of vessel permeability to this threshold (β_L); and the effect of ADT on the rate of PSA secretion by tumor cells (ϵ_P). The residual sum of squares (RSS) between model fits and PSA data is plotted as a function of the net tumor growth rate in figure 3C. As can be seen, equally good fits (flat portion of RSS curve) to the PSA data are achieved for a broad range of tumor growth rates, including tumors that continue to grow under ADT, and those that shrink (figure 3D, shaded region). These simulations suggest that serum PSA data are not fully informative of ADT-induced changes in tumor vascularity and oxygenation, and their down-stream effects on vascular permeability and PSA extravasation. Therefore, caution should be exercised in inferring the response of PCa to treatment from PSA dynamics alone.

Emergence of castration resistance in human patients

Advanced PCa is primarily treated with ADT; however, many patients eventually progress to a hormonally refractive state [2]. Of particular interest are patients receiving ADT, for whom rising PSA levels are the primary means of diagnosing the emergence of castration-resistant PCa. For instance, non-metastatic castration resistant PCa patients, in whom CT-scans and bone scans are unable to detect metastatic disease, would fall in this category, [34]. In such cases, a critical question is: When did castration-resistance really emerge?

In order to determine how informative serum PSA is in answering this question, we adapt our model to simulate the treatment of PCa in humans. In particular, it has been hypothesized that castration resistant cells are already present in ADT naïve tumors, and selection pressures created by androgen deprivation result in these cells dominating the tumor [2]. Therefore, we include this phenotype as a second cancer cell variable in our model. A complete set of equations, and details of the model scale-up are provided in section S2 of the Supplementary Information.

We are particularly interested in the following two key time points: (1) t_{PSA}, the time of PSA failure; and (2) t_{lag}, the lag time defined below. t_{PSA} is when a formal diagnosis of castration resistance is made in the clinic based on increasing serum PSA. However, by this point of time, the cancer is already castration resistant. Therefore, t_{lag} is defined as the difference between t_{PSA} and time to castration resistance emergence, which is assumed to occur when the total number of tumor cells begins to increase once again after any initial decrease induced by ADT.

Model Calibration: Figure 4A shows the best fit to the (averaged) serum PSA time-course data under ADT taken from [31]. Shown also are predicted time-courses of oxygen tension (figure 4B), and percentage change in tumor cell numbers (figure 4C, total and castration sensitive cells, and figure 4D, castration resistant cells). We remark that, from PSA data alone, it is not possible to estimate the initial tumor burden. Rather, the relative change in

tumor cell numbers can be deduced. Further details of model parameterization are provided in section S2 of the Supplementary Information.

Results: Since the patients responded positively to ADT initially, we assume that castration resistant cells constitute only a small fraction ($\sim 0.5\%$) of the tumor at the time of ADT initiation. This is reflected in an initial sharp decline in tumor cell number (figure 4C), resulting in a normoxic environment (figure 4B), causing decreased VEGF concentration and vascular permeability. This, coupled with the fact that the production of PSA in castration sensitive cells is down-regulated under ADT [35], causes a sharp fall in serum PSA. Castration resistant cells, however, continue to expand (figure 4D) and eventually take over the tumor. Serum PSA levels increase once again when the tumor environment becomes hypoxic (figure 4B) and cancer cells start to secrete VEGF. In this study, PSA progression was defined as three consecutive increasing PSA values > 4 ng/ml, taken at least 2 weeks apart, which occurred at 710 days post ADT-initiation. However, the tumor started re-growing at around day 300, so that $t_{lag} \approx 400$ days. That is, the tumor was predicted to be castration resistant more than a year before PSA progression was diagnosed.

Of course, from our earlier discussion, we must exercise caution in inferring tumor behavior from serum PSA read-outs alone. As mentioned above, the tumor burden and fraction of castration resistant cells at the start of ADT are unidentifiable from these data. We therefore conducted a global parameter sensitivity analysis using the Extended Fourier Amplitude Sensitivity test (eFAST) as described in [36], the results of which are included in section S2 of the Supplementary Information. We summarize the key points here.

The parameters with the greatest effect on t_{PSA} are the rates of endothelial cell proliferation (α_E), castration resistant tumor cell proliferation (α_R), and, to a lesser extent, the concentration of VEGF at which vessels become 'leaky' (ν_L) and the sensitivity to this threshold (β_L) (p-value < 0.01). Surprisingly, the rate of PSA expression by castration resistant cells (γ_P) and the fraction of the tumor these cells initially occupy are not critical determinants of t_{PSA}. On the other hand, the single biggest determinant of t_{lag} is α_E, with α_R, ν_L, β_L and γ_P affecting it to a much lesser extent (p-value < 0.01). Thus, our model suggests that tumor angiogenesis is a vital connection between serum PSA and tumor behavior under ADT.

Having identified the biggest determinants of t_{lag}, we varied these parameters over biologically realistic ranges, to reveal that t_{lag} assumed values between 100 and 600 days. Thus, even in a 'best' case scenario, the tumor had progressed to a castration resistant state several months prior to a diagnosis of PSA progression.

Treating castration resistant PCa with ADT and a Treatment Efficacy Index

Castration resistance does not necessarily imply androgen independence. New drugs have been developed that are stronger inhibitors of androgen signaling within the cell [33]. We next investigate how informative serum PSA time-courses are at an *individual* patient level, when castration resistant PCa is treated with ADT.

Model Calibration: The model equations remain largely unchanged from the previous subsection. Best fits to clinical data taken from [32, 33] are shown in Figure 5A. We remark that since these patients have hormonally refractive disease, we only consider a single cancer cell phenotype, namely, castration resistant.

Results: Even though enhanced ADT may not reverse castration resistant PCa growth, it may still confer therapeutic benefit by slowing down cancer growth. Clinically, t_{PSA} remains

an important determinant of ADT failure, with larger values indicating better responses to treatment. We may also define an alternative measure, I_{ADT}, of the success of treatment as: the inverse of the degree of tumor growth inhibition achieved under ADT, as compared to control (see equation (8)). Of course, I_{ADT} is impossible to measure clinically, but our calibrated model, with patient-specific parameters, provides an ideal framework with which to predict its value. For this, we simulated tumor growth with and without treatment for each patient, and compared the fold-change in tumor cell numbers at the end of the treatment period. The results are shown in the bar graph in Figure 5B, with the gray-blue portion of the bars highlighting the predicted degree of inhibition achieved under ADT, and the numbers under the x-axis indicating t_{PSA}. Patient 3 is predicted to have the greatest degree of tumor growth inhibition under ADT, whilst Patient 5 has the longest time to PSA failure. Therefore each measure of ADT success is, in and of itself, inconclusive. We instead propose a *treatment efficacy index* (e_i) for patients with castration resistant disease treated with enhanced ADT, defined as follows.

$$e_i = (I_{ADT} - 1) * t_{PSA}, \;\; I_{ADT} = \frac{\text{fold-change in tumor cell number without treatment}}{\text{fold-change in tumor cell number with treatment}} \quad (9)$$

The larger the value of e_i the more effective ADT. Each patient's e_i is indicated above the bar corresponding to them in Figure 5B. As can be seen, Patients 3 and 4 had the strongest response to treatment, whilst Patient 1 had the weakest response. Even though Patient 5 stayed on treatment the longest, the predicted reduction in tumor growth under ADT was modest, and it is possible that such a patient may have benefited from an alternative course of treatment.

Conclusions

Serum PSA is a ubiquitous prognostic indicator of PCa response to ADT [3, 34]. However, PSA remains a poor biomarker of disease [6] and tumor burden [8]. We hypothesize this is because current diagnosing guidelines do not account for the mechanism by which it enters the blood stream. In particular, immature and leaky blood vessels, formed under angiogenic cues from a growing tumor, could be a primary mechanism allowing for the extravasation of PSA into circulation. To test these hypotheses, we developed a mathematical model of vascular PCa growth. Our model captured PSA leakage into circulation at mechanistic level, by explicitly accounting for the effects of intra-tumoral oxygen tension and VEGF concentration on the permeability of tumor blood vessels. We calibrated our model versus available mouse xenograft data. We then scaled up to the human patient level, in order to determine how informative serum PSA time-courses really are in inferring patient response to ADT.

Our model simulations indicate that tumor vasculature and its morphological properties are a vital link between serum PSA dynamics and tumor response to ADT, and illustrate potential pitfalls in making inferences about tumor burden from serum PSA readouts alone. For instance, a variety of PCa responses to ADT, including tumors that continue to grow, could produce the same serum PSA time course. Further, in patients undergoing ADT, tumors could have progressed to a castration resistant state well before the clinically used time of PSA progression or failure (t_{PSA}). Patients, in whom the lag between these two times is predicted to be especially large, could potentially benefit from alternative treat-

ment strategies such as chemohormonal co-therapy [37]. We also showed that correlating the success of ADT with larger t_{PSA} values can be misleading. A retrospective analysis of PSA time-course data from five individual patients with castration resistant PCa undergoing advanced ADT revealed that the treatment may only induce a modest degree of tumor growth inhibition. Even so, serum PSA may exhibit a sustained and significant decline due to the complex interplay between tumor oxygenation and vascular permeability. We instead proposed a treatment efficacy index that takes into account both, t_{PSA}, and the (predicted) tumor growth inhibition due to ADT. The model can therefore distinguish castration resistant PCa patients who benefit the most from advanced ADT from those that might benefit from alternative treatments. However, at present, this remains a retrospective tool.

The model of vascular PCa growth and PSA leakage presented here is really a first stepping stone towards a more comprehensive quantitative description of how serum PSA dynamics correlate with tumor growth or inhibition under ADT. In our future work, we will relax some of the simplifying assumptions made here. For instance, we ignore androgen mediated-VEGF production [38], which would be down-regulated under ADT. We also do not account for the process of vessel maturation within tumors, which might affect PSA extravasation since mature vessels are relatively impermeable to it. Finally, in order for our findings to have translational value, extensive calibration and validation of the model would be needed, including using human patient data. Nonetheless, the model developed here offers useful insight into the mechanisms governing the leakage of PSA into circulation. Continued efforts in this direction have the potential to improve the reliability of PSA as a prognostic biomarker in prostate cancer patients.

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