Integrated Systems and Technologies: *Mathematical Oncology*

Cancer Research

A Simple PSA-Based Computational Approach Predicts the Timing of Cancer Relapse in Prostatectomized Patients

Ilaria Stura, Domenico Gabriele, and Caterina Guiot

Abstract

Recurrences of prostate cancer affect approximately one quarter of patients who have undergone radical prostatectomy. Reliable factors to predict time to relapse in specific individuals are lacking. Here, we present a mathematical model that evaluates a biologically sensible parameter (α) that can be estimated by the available follow-up data, in particular by the PSA series. This parameter is robust and highly predictive for the time to relapse, also after administration of adjuvant androgen deprivation therapies. We present a practical computational method based on the collection of only four postsurgical PSA values. This study offers a simple tool to predict prostate cancer relapse. *Cancer Res; 76(17); 4941–7. ©2016 AACR.*

Major Findings

- In the mainframe of a validated tumor growth model (1), the parameter (α) is a biologically sensible indicator of the growth potentiality of the relapsed prostate cancer.
- Provided only PSA-producing prostate cancer cells may survive after radical prostatectomy (RP), α can be simply estimated on a limited series of PSA values collected after RP, and it proves to be a reliable and robust parameter for predicting the time to relapse.
- In the absence of any adjuvant therapy, the numeric value of α is inversely correlated ($P < 0.0001$) with the time to relapse.
- When adjuvant androgen deprivation therapy (ADT) is prescribed, α is still well correlated to the timing of recurrence ($P = 0.0001$), but its value is larger, probably because ADT impacts on the prostate cancer cells' metabolic pathways.
- When the tumor becomes resistant during ADT, α values become even larger, reflecting a direct effect on the cell metabolism.
- This biologically sensible mathematical model may help clinicians in optimizing their follow-up data elaboration to early predict (and possibly counteract) prostate cancer recurrence.

Introduction

Prostate cancer is known to be one of the most slowly growing tumors, which often affects elderly people who will likely die by other causes. In addition, prostate cancer can be diagnosed earlier and tumor evolution can currently be monitored by dosing the PSA in serum, which is a safe, noninvasive, and cheap procedure. In spite of the former advantages, however, prostate cancer is known to produce local and/or distal recurrences in around a quarter of the patients undergoing radical prostatectomy (RP; see ref. 4) or radical radiotherapy (RRT), and salvage therapies may become very critical for them. In recurrent prostate cancer, after a variable time following the primary therapy (RP or RRT), a so-called biochemical recurrence is observed, with a progressive rise of the PSA values above or at 0.20 ng/mL after RP (see ref. 5). Adjuvant therapy is sometimes prescribed just after RP or RRT. One of the most frequent ones is the androgen deprivation therapy (ADT). It abruptly reduces PSA values but normally fails in the long-term control of the tumor, which possibly becomes resistant to the therapy.

Predicting the probability of recurrence of prostate cancer after RP is one of the main goals of the studies and researches in the field. Roughly speaking, there are two main ways of thinking: one (static models) relates the recurrence probability and its timing to the preoperative tumor characteristics (e.g., Gleason Score, tumor stage, surgical techniques; see Table 1 for details) and so on, whereas the second one (dynamic models) investigates the post-operative tumor dynamics mainly based on the PSA growth timing. Static models are normally validated on a huge clinical database and aim at producing simple and reliable tools for addressing therapeutic decisions. Very popular nomograms have been proposed, starting from the first model of Partin and colleagues (6), the GPSM (Gleason, PSA, seminal vesicle, and margin status) proposed by Blute and colleagues (7), the nomogram of Briganti and colleagues (8), and all their updated versions.

Dynamic models focus on the estimation of PSA velocity and doubling time, evaluating the timing of tumor proliferation from serial PSA measurements (see refs. 9–11). More complex

Department of Neuroscience, University of Turin, Torino, Italy.

Corresponding Author: Ilaria Stura, Department of Neuroscience, University of Turin, Corso Raffaello 30, Torino 10125, Italy. Phone: 3939-2385-9143; Fax: 3901-1663-4848; E-mail: ilaria.stura@unito.it

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Quick Guide to Equations and Assumptions

As shown by Castorina and colleagues (2), living beings grow according to a common phenomenological universal growth law (PUN), which includes most of the models commonly used (e.g., exponential, Gompertzian,. . .).

In this article, we focus on a second-order solution of the PUN and apply it to model the PSA dosage p collected at time t, which reflects the biochemical activity of the hormone-sensitive cell population surviving after radical prostatectomy:

$$\frac{dp}{dt} = \alpha p^{\frac{3}{4}}\left[1 - \left(\frac{p}{P}\right)^{\frac{1}{4}}\right] \quad \text{(A)}$$

where p is the PSA value (in ng/mL), P is its limiting value or carrying capacity (in our case $P = 100$ ng/mL), t is the time of the measurement expressed in months after surgery, and α is the growth parameter for PSA. Note that Eq. A corresponds to the von Bertalanffy law (Eq. B), where $K = 1/P$, $m = 3/4$, and $n = 1$.

Physical data can be renormalized following simple calculations (see ref. 3 for the details), in terms of rescaled fraction $r = (p/P)^{1/4}$ and rescaled time $\tau = \alpha\, t/4P^{1/4} - ln[1\text{-}(p_0/P)^{1/4}]$, where p_0 is the initial value of the series.

Far from being mathematical tricks, the rescaled units allow us a quick comparison between our experimental data and the parameter-less universal curve $r = 1 - e^{-\tau}$, obtained by substituting r and τ in the solution of Eq. A. PSA data being very scattered and their time correlation very poor, the α parameter value was evaluated deterministically as:

$$\alpha = 4P^{1/4}\frac{\log\left(1 - \frac{p_0}{P}\right) - \log\left(1 - \frac{p}{P}\right)}{t}$$

where $(p,\ t)$ are the PSA values and the times of the measurement, respectively. Note that the physical dimensions of α are $ng^{0.25}mL^{-0.25}month^{-1}$. In principle, α is estimated by all the patient's PSA collection, but in this article, we also investigated the case of fixed values of PSA (i.e., ref. 4) to implement a practically useful algorithm. In the case of adjuvant ADT, which tends to depress the PSA value and the tumor volume, α was calculated from the set of PSA values taken after the end of the therapy.

mathematical models were also proposed (e.g., see refs. 12–15), considering the different behaviors of the various genotypes involved, at least two types of cells, hormone sensitive and hormone resistant, detected in recurrent prostate cancer.

As the prostate tumor growth is very slow, logistic and Gompertzian growth laws have been normally preferred to the simpler exponential curve. As a matter of fact, all the three mathematical models previously cited belong to a general family of growth models, as shown by the phenomenological universality (PUN) approach (1), to which the generalized von Bertalanffy (16) growth law also pertains:

$$\frac{dw}{dt} = \alpha w^m - Kw^n \quad \text{(B)}$$

which assumes that the change of body weight w is given by the difference between the processes of building up and breaking down. α and K are constants of anabolism and catabolism, respectively. The exponents m and n indicate a proportionality to some power of the body weight w.

In this article, we will use the West and colleagues' (3) formulation of Eq. B (see Quick Guide to Equations and Assumptions). Note that the Gompertzian law is more used in modelling prostate cancer, and also in this case, a correlation between the parameters and the time to relapse can be found (17). However, to estimate the growth parameters for each patient, it is not easy to manage. In fact, we developed in ref. 17 a new procedure, combining radial basis functions and a stochastic optimization method, to estimate the Gompertzian parameters. Here, we exploit the fact that the parameter of the West law can be obtained analytically, without using complex numerical methods. Moreover, beyond the mathematical formalism, West and colleagues showed that a strictly biological interpretation could be given to the equation parameters, provided the originally indeterminate power exponent value is restricted to the well-known Kleiber law

Table 1. Terminology

pGS	Histologic scoring of the definite RP sample. pGS ranges from 2 to 10, with 2 representing the most well-differentiated tumors and 10 the least-differentiated tumors. In our patient cohort, pGS ranges from 5 to 10, and 0 indicates that the value is not known.
Pathologic T stage	Designates the size and invasiveness of the tumor. The number increases with tumor size and extent of invasiveness. For example, a microscopic lesion confined to the prostate would be T1; macroscopic tumor confined to the prostate is T2; extended tumor beyond the prostate (extracapsular extension or seminal vesicles invasion) is T3; and a massive tumor that directly invades adjacent organs (such as rectum and bladder) is T4. In our patient cohort, T stage assumes the values T2 and T3. When the stage is not known, we use the acronym "NA."
pN	N0 means that the cancer has not spread to any lymph nodes, N1 means the cancer has spread to nearby lymph nodes in the pelvis.
Surgery techniques	Retropubic, laparoscopic, or robotic.
Postoperative PSA	PSA is a protein produced exclusively by prostate cells. In case of prostatectomy, the value should be near to zero. The threshold of the biochemical relapse is 0.2 ng/mL. If the first PSA value after prostatectomy is equal to or greater than 0.2 ng/mL, local recurrences or metastases are already present.
Positive margins	Tumor extending to the surgical margin (inked surface at the pathologic exam).

Abbreviations: pGS, pathologic Gleason score; pN, regional lymph nodes.

ratio 3/4 (18), which relates the body growth with the age in many animal species, $n = 1$ and $K = \alpha\ W^{-1/4}$, W being the carrying capacity. This law was already applied to tumors in both theoretical and applied mathematical models (1, 19, 20), while the choice of a different value of the exponent $K = \alpha\ W^{-1/3}$ is preferred in case of multicellular tumor spheroids and tumor cords, where cells keep their nutrients from their surface (21).

In this article, we propose to extend its application to investigate how the PSA production grows in recurrent prostate cancer, based on the fact that tumor volume is strictly related to PSA production in radically prostatectomized patients (10, 21). In particular, we focus our attention on the growth parameter (see the Quick Guide to Equations and Assumptions for further details), which reflects the proliferation of surviving prostate cancer cells after RP and may be evaluated by the resulting overall PSA production. According to West and colleagues, α is the ratio between the metabolic energy and the energy needed for duplication of a given cell type. In the case of PSA production, it is expected to increase when cells actively produce PSA and reproduce themselves. On the contrary, it is expected to decrease when cells produce small amounts of PSA and duplicate slowly. As prostate cancer cell metabolism is regulated by androgen-sensitive agents, any intervention on the hormonal drive is expected to impact on the metabolic energy and therefore on the value estimated after such therapy. The acronym ADT (androgen deprivation therapy) actually defines different pharmacologic compounds primarily aiming at inhibiting the androgen biosynthesis, blocking the enzymes responsible for testosterone and estrogen synthesis or the receptor–ligand binding (see ref. 22). By our point of view, more than assessing the difference in clinical outcome, ADT is of great importance as it is expected to modify the metabolic level of the prostate cancer cells, challenging our model to accommodate PSA data reflecting a different metabolic status.

In the Clinical data section, the available data are presented. In the Statistical analysis section, the values of the α parameter are inserted together with those of the standard clinical parameters in a statistical multiparametric analysis to estimate how each parameter impacts on the overall predictability and the timing of recurrence on retrospective data. In the Results section, the study is extended to the relapsed patients who underwent adjuvant ADT. In the Discussion section, a brief discussion is proposed, and conclusions are given in the Conclusions section.

Materials and Methods

Clinical data

Eureka1 study (23) collected data from 3,538 patients treated by a prostatectomy (radical, nerve-sparing, uni- and bilateral) as primary therapy. The majority of them (2,831) did not undergo adjuvant ADT and only 473 (17%) relapsed.

For data inclusion in this study, further screening procedures were performed on the basis of both clinical and computational requirements:

- We only accounted for patients treated with radical prostatectomy, excluding the nerve-sparing surgeries because of possible noncancerous PSA-producing prostate cells remnants.
- We excluded the patients whose first PSA after surgery was larger than 0.2 ng/mL, as either their primary tumor was not properly removed or metastases were already present.
- Finally, to calculate the α parameter (see Quick Guide to Equations and Assumptions), we considered only the relapsed patients with at least 4 PSA values reported in their follow-up.

Statistical analysis

A multivariate statistical analysis was performed with SAS (SAS Institute Software) using the time to relapse as dependent variable and the values of all the postsurgically available parameters (Gleason score, pathologic stage, type of surgery, margins, and lymph node metastasis) plus the coefficient, calculated as described in the previous subsection, as independent variables.

The multivariate analysis was repeated by progressively excluding the nonstatistically significant parameters. Moreover, the predictive value of the parameter calculated on the whole PSA series (from 4 to 17 values measured during the follow-up, i.e., from 2 to 10 years after surgery) was compared with that estimated using only the first 4 PSA values recorded after biochemical failure. Wherever possible, data were inserted into the model as continuous variables, so that the corresponding parameter estimate computed by the model was the actual slope of the straight line on which the data were fitted. The sign of the parameter estimate determined whether the dependent variable increased (+) or decreased (−) with respect to the independent one; the absolute value determined the steepness of the slope. Qualitative as well as quantitative variables that were not continuously distributed in their range were inserted as dummies.

Results

The α parameter

In this subsection, we refer to Figs. 1 and 2 (white dots and light lines). For RP patients, the statistical analysis (see the Table 2) shows that the time to relapse does not depend on any clinical information apart from the α parameter (see Fig. 1, white dots). In particular, α is highly predictive of the range of the time to relapse, with the smaller α values being predictive for a longer disease-free time. In Fig. 1, the white circles represent the values of α versus the time to relapse. The intercept (the light one) has $P < 0.001$.

Note that the value of α is not strictly related to the month of relapse but can predict the period of the relapse very well. In particular, we want to distinguish early relapses, that is, before 2 years (24 months) after RP, to late relapses, that is, after 4 years (48 months). These thresholds can be used by clinicians to plan the follow-up visits and the (adjuvant) therapies.

In our sample, we found that $0 < \alpha < 0.01$ implies $T > 48$ months with a probability of 62% and $T > 36$ months with a probability of 93.6%. The α values ranging between 0.01 and 0.02 were not a strong predictor; in fact, 61.1% of patients relapse before 36 months and 22% after 48 months. Larger values ($0.02 < \alpha < 0.04$) imply $T < 48$ months with a probability of 100% and $T < 24$ in 78.9% of cases. $\alpha > 0.04$ implies $T < 24$ months with a probability of 100%.

We then considered the patients who underwent ADT for at least 6 months, collecting the PSA values after the end of the ADT, and excluding those who relapsed before the treatment period. Also among them, we noticed a correlation between the duration of the therapy and the value; in particular, α was perfectly correlated to the time to relapse, with no exceptions, when the treatment period is longer than one year. In Fig. 2, the white circles

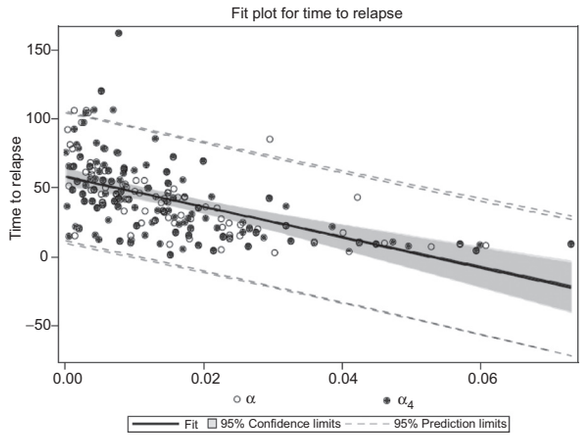

Figure 1.
No adjuvant therapies: α versus time to relapse (white dots) compared with α_4 versus time to relapse (dark dots). Both α and α_4 have a good correlation with the time to relapse. The results of the estimation of α and α_4 are comparable.

represent the values of α versus the time to relapse. The intercept (the light one) has $P < 0.001$.

In this cohort, $0 < \alpha \leq 0.01$ implies $T > 48$ months in 72.7% of cases and 100% if the adjuvant therapy is given for more than 12 months. $\alpha \geq 0.01$ implies $T < 24$ in 30% of cases, $24 < T < 48$ in 50%, and $T < 48$ months in 80%. When the adjuvant therapy is given for more than 12 months, all the patients relapsed within 24 months. As a matter of fact, in 27.1% of treated patients, relapse occurred before the end of the adjuvant ADT. Although ineffective from a clinical point of view, for these patients, a change in the metabolism of the cells is apparent, as the α values are larger than in the remaining 72.9% (0.01–0.065 instead of 0.0002–0.02).

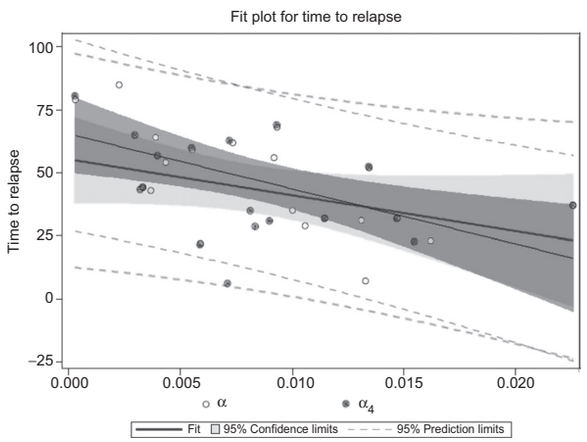

Figure 2.
ADT for at least 6 months: α versus time to relapse (white dots) compared with α_4 versus time to relapse (dark dots). Both α and α_4 have a good correlation with the time to relapse. The results of the estimation of α and α_4 are comparable.

Table 2. Output of the multivariate analysis between clinical parameters in the case of no adjuvant therapies (SAS Software)

	df	β coefficient	F value	*P* > F
Gleason score	4	1.5670	0.61	0.6566
Pathologic stage	4	4.0526	1.58	0.1856
pN	1	0.5884	0.92	0.3407
Postsurgery PSA	1	1.2551	1.95	0.1651
Positive margins	1	2.0849	3.24	0.0744
α class	5	38.6463	12.03	<0.001

NOTE: Gleason score, pathologic stage, pN, PSA after surgery, presence of positive margins, and the α class were considered as predictive variables for the time to relapse. As shown, only the α parameter is statistically correlated to the time to relapse.
Abbreviations: *df*, degrees of freedom; pN, regional lymph nodes.

Optimization of the algorithm for clinical trials: the α_4 parameter

In this subsection, we refer to Figs. 1 and 2 (dark dots and marked lines).

After showing that the α parameter is very well correlated to the time to relapse, the use in clinical practice should be encouraged by proposing simple and robust evaluation algorithms. Looking at the Quick Guide to Equations and Assumptions, α parameter is calculated using all the available data, that is, also those collected after relapse. In clinical practice, however, time to relapse should be predicted on the basis of only prerelapse data! We therefore investigated the reliability of the estimation of α using only the a limited number of PSA values collected before relapse, with a maximum of 4. We call this estimation as α_4. The α_4 value has the same behavior as α, and the two parameters can be compared as shown in Figs. 1 (no ADT cohort) and 2 (ADT cohort). The colored circles represent the values of α_4 versus the time to relapse. The intercept (the more marked one) has $P < 0.001$. In the nontreated cohort, in fact, we found that $0 < \alpha_4 < 0.01$ implies $T > 48$ months with a probability of 54% and $T > 36$ months with a probability of 82%. The α_4 between 0.01 and 0.02 is not a strong predictor as α; in fact, 55.1% of patients relapse before 36 months and 24% after 48 months. $0.02 < \alpha_4 < 0.04$ implies $T < 48$ months with a probability of 95.2% and $T < 24$ in 71.4% of cases. $\alpha_4 > 0.04$ implies $T < 24$ months with a probability of 93.3% and $T < 12$ months with a probability of 86.6%.

In the hormone-treated cohort, $0 < \alpha_4 \leq 0.01$ implies $T > 36$ months in 61.5% of cases. $\alpha_4 \geq 0.01$ implies $T < 24$ in 33.3% of cases, $24 < T < 48$ in 50%, and $T < 48$ months in 83.3%. When adjuvant therapy was given for more than 12 months, all the patients relapsed after 24 months.

Discussion

Relevant information seems to be hidden in the values of the α parameter evaluated on the PSA collection after RP, which are substantially retained also by α_4. According to ref. 3, α is originally related to the ratio between the metabolic energy required by the cell and the energy needed for duplication:

$$\alpha = \frac{B}{E}$$

where B is proportional to the metabolic rate of a single cell, and E is the metabolic energy required to create a cell. In Fig. 3, the estimated α in 4 paradigmatic patients, treated by adjuvant ADT for at least 6 months, is shown. Original data are provided

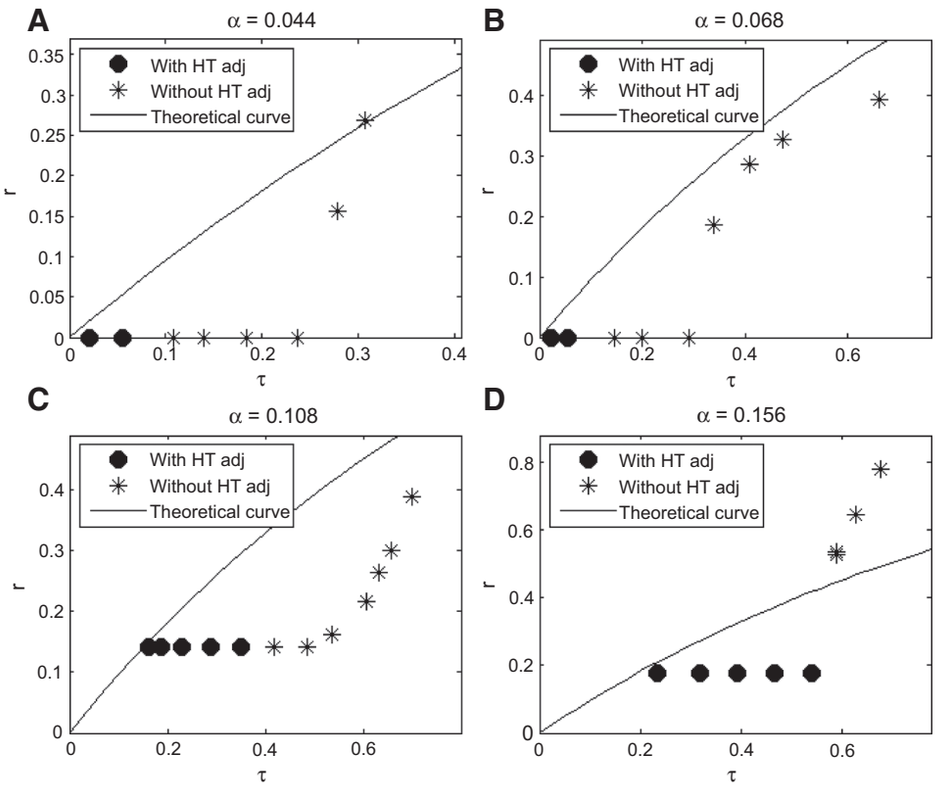

Figure 3.
Estimated in four patients (**A–D**) treated by adjuvant (adj) ADT, indicated in the legend as hormone therapy (HT), for at least 6 months. PSA values are rescaled by r and τ. Dots, PSA values during adjuvant ADT; stars, posttherapy PSA values (free growth). Black line, expected theoretical growth $r = 1 - e^{-\tau}$. Data were collected during the Eureka1 study from prostatectomized human patients.

in Table 3. PSA values are rescaled by r and τ as explained in the Quick Guide to Equations and Assumptions. Dots indicate the PSA values during adjuvant ADT, and stars indicate posttherapy PSA values (free growth). The black line represents the expected theoretical growth $r = 1 - e^{-\tau}$.

The dispersion of α is obviously related to the differences in individual growth and/or metabolic status of the recurrent tumors. It seems a reasonable fact that larger values of α correlate with faster growth, corresponding to lesser energy need for cell replication. These results suggest that some quantitative measurements of proliferation parameters, such as Ki67, would be helpful to drive clinical management.

The effect of ADT on cell metabolism is evident as well. It is well known that hormones play an important role in optimizing cell metabolism. A complete abolition of the hormonal drive is therefore reflected by a severe reduction of B during the therapy (see the dots in Fig. 3). Note that in some cases (see Fig. 3A–C), the effect remains for many months after the end of the therapy.

As soon as the normal metabolic paths are restored, however, three behaviors can be observed. The more frequent one is that the normal α value is quickly recovered and PSA data would regain their expected ranges (see stars in Fig. 3A and C). In Fig. 3B, PSAs remain under the theoretical curve: this could mean that adjuvant therapy has had a "retarding" effect on relapse. The latter behavior is shown in Fig. 3D: the tumor growth seems to be faster than expected, suggesting a sort of catch-up effect, which is common when dietary limitations are suddenly stopped. The α values, however, are smaller following ADT, possibly because the cell metabolic rate changed or part of the tumor-proliferating cells stops producing PSA following an epigenetic (adaptation) or genetic (mutation) event (24). As

Table 3. PSA data of the four patients in Fig. 3

Patient 1												
Months	6	16	31	40	53	68	80	88				
PSA	0	0	0	0	0	0	0.06	0.52				
Patient 2												
Months	4	10	27	37	54	63	76	88	123			
PSA	0	0	0	0	0	0.12	0.68	1.15	2.39			
Patient 3												
Months	1	4	9	16	23	31	39	45	53	56	59	64
PSA	0.04	0.04	0.04	0.04	0.04	0.04	0.04	0.07	0.22	0.49	0.81	2.32
Patient 4												
Months	3	10	16	22	28	32	33	35	39			
PSA	0.1	0.1	0.1	0.1	0.1	8.1	7.7	17	36.5			

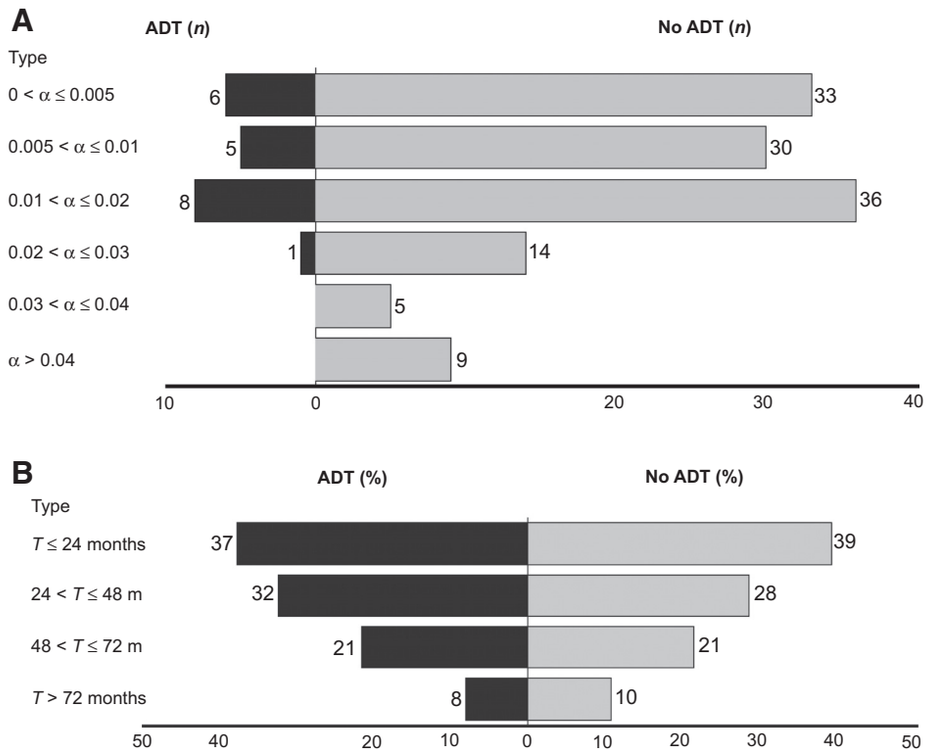

Figure 4.
Comparison between the α value with (left, dark) and without (right, light) ADT (**A**) and the time to relapse with (left, dark) and without (right, light) ADT (**B**). Bars, percentage of the patients who had a relapse in the corresponding time range.

a matter of fact, the increase of the α values in early relapsing ADT patients suggests that some mutations have occurred.

We need to understand this point better, but our hypothesis is that as therapy lowers the proliferation of cells, the tumor cannot keep on growing at the same speed, and a part of its initial energy is spent to restore its metabolic status instead of promoting growth.

The opposite behavior appears in the case of resistance to ADT: growth is faster than without therapy. The death of hormone-dependent cells favors the independent ones to mutate and proliferate, because of the sudden availability of space and nutrients. The same behavior is well described by Hanin and colleagues (25) when primary tumor removal allows a growth spurt of the metastasis. Hence, ADT increases the aggressiveness of the tumor and relapse is very fast.

An interesting comparison can be done among the values of the parameter α in case of ADT and no ADT (see Fig. 4A). The values in case of no ADT seem to be smaller, but the frequency of time to relapse (Fig. 4B) is the same in both cohorts. This means that ADT, if successful, tends to make the tumor less aggressive. However, a spread of growth is observed when it is unsuccessful. In fact, by selecting some patients who had a relapse during adjuvant ADT, we found that the parameter values were higher than in the other cases: 0.01 to 0.065 instead of 0.0002 to 0.02. It suggests that a mutation occurred, which implied a change in the metabolism of the cells.

Conclusions

The α parameter, estimated on the basis of at least 4 PSA dosages after RP, is a reliable, robust, and easily evaluable index, which is strongly related to the timing of prostate cancer recurrence in RP patients. Moreover, α is still a good predictor even when the patients were treated with adjuvant ADT.

The combination of a careful collection of PSA values and a biologically sensible computational model, possibly corroborated with tumor kinetics information, would be a valuable tool that overcomes the other traditional clinical parameters (such as pGS, pathologic staging, etc.) in predicting the timing of tumor recurrence. Future works will aim at creating a simple and friendly tool for clinicians able to automatically estimate α from the PSA series. This program should show the possible scenarios and help in planning a more effective and personalized therapy. Moreover, this calculation could be computed by a PC or laptop in a hospital, that is, the tool will be easily available. We could hence provide a biologically meaningful and practical parameter for promoting personalized medicine in this and possibly in other fields of application.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: I. Stura, D. Gabriele, C. Guiot
Development of methodology: I. Stura
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): D. Gabriele
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): I. Stura
Writing, review, and/or revision of the manuscript: I. Stura, D. Gabriele, C. Guiot
Study supervision: C. Guiot

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