The Dynamics of Prostate-specific Antigen after Definitive Radiation Therapy for Prostate Cancer

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ABSTRACT

We report the use of an exponential model for capturing the dynamics of serial measurements of prostate-specific antigen (PSA) made just before and after definitive radiation therapy of localized prostate cancer. Our study patients consisted of 164 men treated at a community hospital and without use of adjuvant hormonal therapy, and we had a mean of 5 years follow-up. We found that the model fits allowed us to condense PSA dynamic information into four parameters, including the initial pretreatment value of PSA, and three of these related significantly to subsequent outcome. The model also provided greater understanding of the prognosis of men with rising PSA after radiation therapy. Specifically, two of the model’s parameters allowed us to compare the PSA status of these men to those with hormone-refractory disease, and we discovered that at the time of “biochemical relapse,” there is a broad spectrum in expected probability of imminent death as well as in time to an adverse outcome. Thus, the model provides information that allows one to stratify men with rising PSA into a continuous spectrum from low to high risk for an adverse outcome. We believe these results show that exponential models have the potential for providing useful clinical information about men with rising PSA after definitive radiation therapy and that they could help us decide when further therapy is needed. Therefore, we recommend further study and development of these models as part of clinical research protocols involving radiation therapy of localized prostate cancer.

INTRODUCTION

Radiation therapy and radical prostatectomy comprise the two most important treatments for localized prostate cancer, and after either treatment it is customary to use serial measurements of serum PSA to decide whether there is evidence of recurrence or metastasis. The way PSA is interpreted then depends upon which of these treatments was given. Whereas radiation therapy leaves the prostate in the patient, surgery by and large does not. Thus, a rising PSA after radiation treatment can reflect recovering normal prostatic tissue, cancer, or both, and rising values of PSA have preceded other clinical evidence of treatment failure (1). Choosing between the explanations for a rising PSA is not straightforward, and the selection of a time point for biochemical relapse has been elusive. Consequently, several definitions of “biochemical relapse” have been used, and to deal with the confusion the American Society for Therapeutic Radiology and Oncology Consensus Panel recommended a definition of biochemical failure to be “three consecutive increases in PSA” (2). Nevertheless, controversy and uncertainty about the definition of biochemical relapse persists (3).

Both before and coincident with these controversies about biochemical relapse, many have found that exponential functions of time can model serial values of PSA after radiation treatment (4–12), and Table 1 summarizes six such studies. In the table, y is the serum concentration of PSA at time t, and p1–p4 are the parameters of the models. Each of these four parameters is designed to have a positive value, and each is constant with respect to time although not constant between patients. Three of the models are identical and divide the values of PSA into two components: the first for the fall in PSA with time during and immediately after treatment, and the second for a rising PSA that persists. These two components are given mathematically in the terms \( p1 \cdot \exp(-p2 \cdot t) \) and \( p3 \cdot \exp(p4 \cdot t) \). Here the \( p1 \) and \( p3 \) parameters provide the amplitude or amount of PSA attributed to each component with units of ng/ml. The exponential terms \(-p2\) and \( p3 \) control the rate of change of each component with time. These can also be called relative velocities \((rv)\), because for these separate components they are the derivative of the natural logarithm of \( y \) with respect to \( t \), or \((dy/dt)/y\), which in turn is the velocity of PSA divided by the value of PSA (13). Thus, the units for \( p2 \) and \( p3 \) are 1/time. These \( rv \) also relate to the half life and doubling time of PSA. Specifically, \( p2 \) equates to 0.69/half life for the falling component of PSA, and \( p3 \) equates to 0.69/doubling time for the rising component (14). Using examples of individual patients, some investigators have shown that exponential models fit observed data closely, but despite good fits, one group concluded that “the estimation of serum PSA kinetic parameters alone appears to have little, if any clinical usefulness” (6). We thought this issue was worth revisiting to see first how well an exponential model fit the PSA data from a population of patients treated with definitive radiation. Then, if the model fit well, we wanted to study how the model might improve our understanding about the issues of biochemical failure and recurrence of tumor after treatment. This report addresses these issues.
PATIENTS AND METHODS

This study is based on 164 men with prostate cancer and who were treated with definitive external beam radiation therapy at Moore Regional Hospital in Pinehurst, NC. All were treated with external beam delivered to the prostate, seminal vesicles, and periprostatic area through antero-posterior and lateral fields to a dose of 4500 cGy and at the rate of 180 cGy per fraction. Then the field was reduced slightly, and the remainder of the dosage was delivered at the rate of 200 cGy per fraction. None were treated with either neoadjuvant or adjuvant androgen ablation. Table 2 summarizes their characteristics, including their pretreatment PSA, T stage (15), Gleason tumor score (16), mean and range of follow-up in months, and number of serial measurements of PSA available for studying. All of the data used for this study were obtained as part of routine clinical evaluation and follow-up.

Model Used to Fit Serial Values of PSA after Treatment. The model we chose is a modification of the one introduced by Zagars et al. (6) and briefly referred to later (14).

### Table 1 Published exponential models for PSA after definitive radiation therapy

<table>
<thead>
<tr>
<th>Year</th>
<th>First author</th>
<th>No. of patients</th>
<th>Model(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1992</td>
<td>Ritter et al. (5)</td>
<td>63</td>
<td>[ y = p_1 + p_2 \exp(-p_3 t) ]</td>
</tr>
<tr>
<td>1993</td>
<td>Zagars and Pollack (6)</td>
<td>154</td>
<td>[ y = p_1 \exp(-p_2 t) + p_3 \exp(p_4 t) ]</td>
</tr>
<tr>
<td>1993</td>
<td>D’Amico and Hanks (7)</td>
<td>22</td>
<td>[ y = \exp(p_1 t) ]</td>
</tr>
<tr>
<td>1993</td>
<td>Cox et al. (10)</td>
<td>122</td>
<td>[ y = p_1 \exp(-p_2 t) + p_3 \exp(p_4 t) ]</td>
</tr>
<tr>
<td>1994</td>
<td>Pollack et al. (11)</td>
<td>100</td>
<td>[ y = p_1 \exp(-p_2 t) + p_3 \exp(p_4 t) ]</td>
</tr>
<tr>
<td>1998</td>
<td>Hanlon et al. (12)</td>
<td>153</td>
<td>[ y = p_1 \exp(-p_2 t) + p_3 \exp(p_4 t) + (t &gt; 20) ]</td>
</tr>
</tbody>
</table>

* y, the serum concentration of PSA at time t; p1–p4, the parameters of the models, each of which has a positive value and is constant with respect to time although not constant between patients.

* Zagars and Pollack (6) obtained a second model by setting p2 = 0.

* Cox et al. (10) obtained three additional models from this general one by setting p2 = p4, p3 = 0, and p4 = 0, respectively.

* For the Hanlon et al. (12) model, time (t) is in months, and I (t > 20) in the equation is defined as 0 if t is <20 months and 1 if t is ≥20 months.

### Table 2 Characteristics of patients studied

<table>
<thead>
<tr>
<th>Pretreatment PSA (ng/ml)</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean, 23.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, 0.8–315</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td></td>
</tr>
<tr>
<td>1</td>
<td>34</td>
<td>20.7</td>
</tr>
<tr>
<td>2</td>
<td>88</td>
<td>53.7</td>
</tr>
<tr>
<td>3</td>
<td>39</td>
<td>23.8</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
<td>1.2</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>3</td>
<td>11</td>
<td>6.7</td>
</tr>
<tr>
<td>4</td>
<td>11</td>
<td>6.7</td>
</tr>
<tr>
<td>5</td>
<td>27</td>
<td>16.5</td>
</tr>
<tr>
<td>6</td>
<td>62</td>
<td>37.8</td>
</tr>
<tr>
<td>7</td>
<td>31</td>
<td>18.9</td>
</tr>
<tr>
<td>8</td>
<td>12</td>
<td>7.3</td>
</tr>
<tr>
<td>9</td>
<td>3</td>
<td>1.8</td>
</tr>
<tr>
<td>10</td>
<td>1</td>
<td>0.6</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Follow-up duration (mos)</th>
<th>Number</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean, 59.6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, 25.6–114.3</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of PSA values</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean, 6.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Range, 4–15</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* Total number of patients, 164.

If y symbolizes the concentration of serum PSA and y0 symbolizes the baseline or pretreatment PSA, then the model is given as:

\[ y = a \cdot \exp(-b \cdot t) + (y_0 - a) \cdot \exp(c \cdot t) \]  
(A)

This model differs from Zagars’ model in that there are three adjustable parameters (a, b, and c) rather than four, and the model is forced to include the initial value of PSA. For example, substitution of t = 0 in Eq. A demonstrates that y will equal y0.

We chose this restriction of Zagars’ model, because the baseline PSA is so prognostically important for posttreatment outcomes (17–23). By including y0 as a nonadjustable parameter, all of the adjustments in a, b, and c are dependent on the value of y0, and to discriminate them from the parameters of Table 1, we use the symbols of a, b, and c. Using just those patients with at least four measurements of PSA after the nadir and before any hormonal treatment, we then fit the model to the data with a modification of the Gauss-Newton algorithm (24) and a program written in the C computer programming language (25). The program derived and then printed least squares estimates of a, b, and c.

**Definition of Biochemical Relapse.** Biochemical relapse was defined as a sequence of three increasing values of PSA after the nadir with the third value >1.4 ng/ml. Except for
the specification of the threshold of 1.4 ng/ml, this definition is identical to the recent consensus definition (2). Furthermore, we also included as relapsed a few with the first postnadir PSA of 9 ng/ml but who did not have a third PSA taken before subsequent hormonal treatment. After the recommendation of the consensus group, we set the time of relapse as midway between the time of nadir and the first of the rising PSA levels (2).

**PSA Hazard Score.** Recently, two studies of two Cancer and Leukemia Group B protocols for HRPC demonstrated that the level of PSA as well as the \( r_v \) of PSA were prognostic for imminent death (13, 26). The combined use of log(PSA) and \( r_v \) were initially found to be prognostic in 137 (13), and this combination was validated as prognostic with new patients in the second study (26). Although their best prognostic model used serum hemoglobin and patient weight (26), we did not have

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**Table 3** Model parameters \( a, b, c, \) and \( d \) obtained from computer fits of the serial measurements of PSA

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Mean</th>
<th>Range</th>
</tr>
</thead>
<tbody>
<tr>
<td>( a ) (ng/ml)( ^a )</td>
<td>22.8</td>
<td>0.6–315</td>
</tr>
<tr>
<td>( a/y_0 )</td>
<td>0.94</td>
<td>0.56–1.0</td>
</tr>
<tr>
<td>( b ) (1/mo)( ^b )</td>
<td>0.37</td>
<td>0.038–1.15</td>
</tr>
<tr>
<td>( (y_0 - a) ) (ng/ml)( ^d )</td>
<td>0.90</td>
<td>( 4 \times 10^{-7} )–23.7</td>
</tr>
<tr>
<td>( c ) (1/mo)( ^c )</td>
<td>0.048</td>
<td>0–0.53</td>
</tr>
</tbody>
</table>

\( ^a \) \( a \) provides the amplitude of the decreasing component of PSA after radiation therapy, i.e., the amount of PSA expected to disappear with treatment.

\( ^b \) \( a/Initial \) PSA provides the proportion of initial PSA expected to disappear with treatment.

\( ^c \) \( b \) gives the relative velocity of the decreasing component of PSA.

\( ^d \) \( (y_0 - a) \) provides the amplitude of the increasing component of PSA after radiation therapy, i.e., the initial amount of PSA not affected by treatment.

\( ^c \) \( c \) provides the relative velocity of the increasing component of PSA.

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**Fig. 2** Plot of PSA versus time of follow-up for four typical patients of the 164. Points, observed values of PSA in ng/ml; curved line, fit obtained by the exponential function of Eq. A.

**Fig. 3** Plot of observed PSA on horizontal axis versus that predicted by the exponential function after it was fit to the data (vertical axis). The line shows where perfect fit occurs. All PSA values from all patients appear on this graph.
these serial measurements in our data. Thus, we relied on a two-
variable PSA hazard score \((hs)\) that used just the \(\log(PSA)\) and
the average \(rv\). This \(hs\) was an updated one, because it was
derived from the combined data of the two Cancer and Leuke-
mia Group B studies. It is calculated at any time \(t\) as:

\[
hs(t) = 0.258*(\log(y) - 4.55) + 0.583*(rv - 0.0764) \quad (B)
\]

where \(y\) symbolizes the PSA at time \(t\) and \(rv\) symbolizes the
time average of \(rv\). (The coefficient 0.583 and mean 0.0764 differ from the magnitude of previously published values be-
cause here \(rv\) is in units of 1/mo rather than 1/day.) In general,
as the value of \(hs\) rises above zero, so too does the observed
probability of imminent death, and this is illustrated for the \(hs\) of
Eq. B in Fig. 1. Because the rising component of PSA after
treatment in the exponential model of Eq. A is given by:

\[
y(t) = (y0 - a)*\exp(c*t) \quad (C)
\]

and because the average \(rv\) for the rising component of PSA is
equivalent to \(c\), we could obtain the \(hs(t)\) from parameters \(y0, a,\)
and \(c\) as:

\[
hs(t) = 0.258*(\log(y0 - a) + c*t - 4.55) + 0.583*(c - 0.0764) \quad (D)
\]

Thus, we could use this equation to estimate a PSA-based
hazard score at any time during follow-up. Alternatively, by
solving for \(t\), we could also use this equation to estimate the time
required to reach a certain value of the hazard score.

**Statistical Methods.** To examine the relationship be-
tween model parameters and the adverse outcome of either

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**Table 4** Logistic regression model showing the association between
model parameters and adverse outcome

<table>
<thead>
<tr>
<th>Coefficient</th>
<th>SE</th>
<th>(P)</th>
</tr>
</thead>
<tbody>
<tr>
<td>(\log(a))</td>
<td>0.48</td>
<td>0.32</td>
</tr>
<tr>
<td>(b)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>(\log(y0 - a))</td>
<td>0.61</td>
<td>0.22</td>
</tr>
<tr>
<td>(c)</td>
<td>26</td>
<td>6.3</td>
</tr>
<tr>
<td>Gleason score</td>
<td></td>
<td>0.049</td>
</tr>
<tr>
<td>Tumor stage</td>
<td></td>
<td>0.78</td>
</tr>
</tbody>
</table>

\(a\) Adverse outcomes consisted of either death because of prostate
cancer or observed distant metastases in those still living at the conclu-
sion of the study period.

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**Fig. 4** Frequency distributions of
the parameters of the exponential
model after fitting to each patient’s
data. Vertical axes, numbers of pa-
tients; horizontal axes, parameter \(a\)
expressed as a fraction of initial
PSA (i.e., \(a/y0\)), parameter \(b\), log-
arithm of \((y0 - a)\), and parameter \(c\), respectively.

**Fig. 5** Frequency distribution of calculated PSA hazard score at the
time of designated relapse. The time of relapse was assigned by usual
criteria (see “Patients and Methods”) and without using information
from the exponential model. The PSA hazard score was derived from
data on HRPC (26), and its calculation for our patients used information
from the exponential model and Eq. D.
distant metastasis or death ascribed to prostate cancer, we used the logistic regression model (27, 28) and the S-PLUS software package (MathSoft, Inc., Seattle, WA). All Ps are for two-sided tests of hypothesis.

RESULTS

Overall Fit of Exponential Model to the PSA Data. Fig. 2 shows how the model fit the data of four typical patients. The points are the observed values of PSA, and the line shows the fitted model. Clearly, the model provides satisfactory fits for these four. Although space prevents us from illustrating the fits for all 164 patients, Fig. 3 shows in a single graph how the observed values of PSA compared with the fitted values for all patients and all time points. The observed values of PSA are given on the horizontal axis, and fitted values are given on the vertical axis, and the line shows where perfect agreement should occur. The closer the points are to the line, the better is the fit of the model to the data, and in our opinion, this graph demonstrates that the model of Eq. A fits the combination of observed values. This result implies that the fitting process and Eq. A are sufficient to summarize and capture the information provided by serial measurements of PSA.

Parameter Values Obtained. Table 3 summarizes the values of the parameters of the model as well as the two derived parameters a/y0 and y0 − a. In general, the value of a was closely linked to y0, the value of baseline PSA; and this can be especially seen in the derived parameter a/y0, which gives the ratio of a to y0, i.e., the proportion of initial PSA expected to eventually decline to zero. Because the average value of a/y0 was 0.94, this implies that for an average patient, 94% of initial PSA was found to eventually disappear. Stated another way, this result means that for an average patient, 94% of the initial PSA was allocated to the first exponential component of Eq. A. The table also gives the mean and ranges for parameters a, b, c, and y0 − a. Clearly, there is considerable variation among these patients in how fast PSA falls (i.e., b), how fast it eventually rises (i.e., c), and in the magnitude of the rising component (i.e., y0 − a). This is illustrated in Fig. 4, which shows the frequency distributions of a as a fraction of y0 (i.e., a/y0), b, log(y0 − a), and c. Altogether, the results underscore how much natural heterogeneity there exists among patients regarding how PSA behaves after treatment.

Association between Model Parameters and Adverse Outcome. Table 4 shows the results of a logistic regression model analysis of the association between the model parameters derived from the fits and the subsequent observation of either death attributable to prostate cancer (15 patients) or observed distant metastasis in patients still living at the end of the study period (an additional 6 patients). We chose to use the natural logarithm of parameters a and y0 − a because their units were ng/ml and because the natural logarithm of PSA has been shown to be more prognostic than the untransformed PSA (29). Whereas there was no significant association between parameter b and adverse outcome, parameters a and c and the derived (y0 − a) were significantly associated with outcome. Specifically, higher values of a, c, and (y0 − a) implied a higher likelihood of adverse outcome, and the statistical association was strongest for c, the relative velocity of the rising component of PSA. The bottom two lines indicate the relative importance of Gleason score and tumor stage in this model and show how the dynamics of PSA are more important than either Gleason score or stage.

Calculated PSA Hazard Score at Designated Time of Biochemical Relapse. Using Eq. D and parameters y0 − a and c from the fitted exponential model, we calculated the HRPC-derived PSA hazard score (hs) at the time of designated biochemical relapse. Fig. 5 shows the frequency distribution of the result, and it demonstrates a broad range of values of hs at the time of relapse. In other words, although all were said to have relapsed, their situation with regard to the hazard for imminent death was not at all similar. All of these “relapsed” patients had negative values of hs with a median of −1.1 and a range from −1.6 to −0.2, so that in comparison to men with HRPC, all of them had a low hazard of imminent death. By solving Eq. D for t, we estimated the additional time necessary to reach the mean hs for men with HRPC. This estimated time ranged from a minimum of 0.9 years to >12 years, with a median of 5 years. Thus, the dynamics of PSA as captured by this exponential model suggest that at the time of ordinarily designated biochemical relapse, there are broad spectrums in the likelihood for imminent death as well as in the expected time lapse to an adverse outcome comparable with HRPC.

DISCUSSION

The results of this study show that in a new patient data set, an exponential model can fit serial values of PSA well, and such fits suggest that we can estimate both the level and rv of PSA at specific times of follow-up. Because in general the more parameters a model uses, the better it will fit raw data, Zagar’s original four-parameter model could fit our data even better. Nevertheless, we prefer the model with three adjustable parameters because it incorporates the value of pretreatment PSA as a fixed parameter (our y0) and because log(y0) has been shown to be an important prognostic parameter for outcome after definitive radiation treatment (29). Our purpose, however, is not so much to argue the superiority of fit obtained with Eq. A as to demonstrate that its fit is sufficient to capture dynamic information found in serial measurements of PSA, and we believe that the details in Figs. 2 and 3, together with the result of a mean error between observed and fitted value of 0.069 ng/ml, establish this conclusion. What is more important than obtaining the best fit of PSA data are how such dynamic information relates to subsequent outcomes and how it increases our understanding of patients with rising PSA after treatment.

The results suggest that the magnitudes of the PSA component designated to fall (parameter a) as well as the component designated to continue to rise (parameter y0 − a) are prognostically important. In other words, although the relative velocity of the rising component (parameter c) is the most important dynamic feature of posttreatment PSA, the level or magnitudes of PSA are also important. A similar result was found in HRPC (13, 26). Whereas some have published that the doubling time of PSA after treatment is important (30, 31), our results suggest
that to optimize a PSA-based prognostic model, one must include a measure of the magnitude of PSA as well as its relative velocity. In most general terms, slow rises in PSA of significant magnitude can be as bad as fast rises of low initial magnitude. Nevertheless, to know how one patient’s PSA values relate to outcome, one must do some mathematics, i.e., one must calculate a dynamic variable such as doubling time or \( rv \) and then incorporate it into a multivariate statistical model. In our opinion, optimizing the statistical model will require more analyses on new and larger data sets, but our results hint at the form that such a model is likely to take and also suggest that both magnitude and \( rv \) of PSA are important.

Clearly, men with rising values of PSA after treatment are in general a long way from death, and this is demonstrated by the few deaths (just 15) we observed in our patients after a relatively long follow-up period. By contrast, men with HRPC are closer to death from prostate cancer, and it is therefore easier to relate the dynamics of PSA to the event of death. Thus, we find it useful to compare the dynamics of rising PSA after definitive radiation treatment to the dynamics of those closer to death. The exponential model allows us to do this and in so doing allows us to gain some understanding about the status of men with a rising PSA. For example, we have demonstrated that a popular definition of biochemical relapse identifies an outcome with considerable prognostic variation. Many men with such biochemical failures may be years away from an outcome comparable with HRPC. Others may be closer to death. By modeling the dynamics of their rise in PSA, we can appreciate where they lie in this spectrum, and our results clearly demonstrate that there is a continuum of probable outcome just as PSA level is a continuous biological measure and as are the parameters of Eq. A. Clearly, some rising values of PSA relate simply to regrowing benign prostatic tissues. Some relate to slowly regrowing tumor, and some relate to faster growing tumor of greater initial volume. By designating all of these as biochemical relapse, we oversimplify a complex biological spectrum, and in this way the calculated hazard score of Eqs. B and D bring us closer to the reality of outcome. For these reasons, we believe that the exponential modeling and its relationship to the dynamics of PSA in HRPC could become a helpful clinical tool. At the same time, we believe that better scores could be obtained with more complex multivariate models that include serial measurements of factors other than PSA.

In summary, we have found that the dynamic details about posttreatment PSA can be accurately captured with an exponential model. Such dynamics relate significantly to subsequent outcome and more accurately describe the circumstances of patients with rising values of PSA after radiation therapy than the simple designation of “biochemical failure.” We expect that further development of exponential models will yield a tool that optimizes the information that serial measurements of PSA provide. This in turn could help patients and their physicians make more informed decisions about the need for additional treatment.

REFERENCES


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