The Relative Importance of Anatomic and PSA Factors to Outcomes After Radical Prostatectomy for Prostate Cancer

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Key Words: Prostate-specific antigen; Prostatectomy; Cancer; Grade; Tumor volume; Stage; Survival

Abstract

We report on how anatomic pathology observations and prostate-specific antigen (PSA) observations made before and just after radical prostatectomy relate to subsequent outcomes in men with prostate cancer. Our study patients consisted of more than 200 men who underwent radical prostatectomy and who had a mean follow-up of more than 6 years. We found that there were 2 categories of failures after surgery—one consisting of an eventual elevated PSA level and the other consisting of an early death from progressive tumor—and that these 2 failures related differently to PSA and anatomic pathology observations made at the time of prostatectomy. Whereas preoperative and postoperative levels of PSA related most closely to PSA failure, Gleason grade 5 and the percentage carcinoma related most closely to early death. Our results suggest how men could be sorted into 3 prognostic categories after surgery: one with high hazard for early death, a second with low hazard for early death but with high probability for eventual elevated PSA level, and a third with overall good prognosis.

Preoperative information, including prostate-specific antigen (PSA) level, histologic tumor grade, and clinical stage, provide limited predictive information about the success of radical prostatectomy for complete cure of prostate cancer. 1-4 Whereas after surgery most are cured of their tumor, some are not 5-10 and may require adjuvant radiotherapy or hormonal therapy. 11-13 Those who are not cured consist of 2 groups: one with aggressive tumors likely to cause early death and a second with a rising PSA level but without a high hazard for early death. In this setting, there has been keen interest in prognostic factors and prognostic models that could be used to predict these outcomes after surgery, as well as to define treatment failure. Clearly, such outcomes relate to the pathologic stage and grade found in the resected prostates. 14-16 Other important factors include tumor involvement of extracapsular connective tissue, surgical margins, seminal vesicles, and regional lymph nodes, as well as high histologic grade. 17

Preoperative PSA levels contribute prognostic information, because higher levels of PSA imply greater tumor volume and greater chance of tumor recurrence after surgery. 17-27 Finally, many have reported that the level and dynamics of postoperative PSA relate to subsequent outcome. 1,6,13,18,28-33 The PSA level clearly rises before other signs of recurrent tumor, 5,19 and several have reported that dynamic measures such as the time to first elevation of the PSA level, PSA velocity, PSA doubling time, and PSA level at 1 year relate significantly to adverse outcome. 13,30-33 For example, the longer the time to elevation of the PSA level and the longer the doubling time, the longer will be the time to metastasis. 13,31 The higher the PSA velocity and the higher the level of PSA at 1 year, the more likely the patient will have
metastatic recurrence vs local recurrence. The higher the value of the log slope of PSA, the shorter the time to clinical recurrence. The log slope of PSA is the same parameter as the relative velocity of PSA. Nevertheless, obtaining such dynamic measurements requires serial values of PSA, and 1 year or more after surgery may be longer than one wishes to wait before the first consideration of adjuvant therapy.

Surgery that removes almost all of the prostate and its tumor should reduce the PSA level to undetectable levels sooner than 1 year. This is because the drop in the PSA level after surgery follows an exponential equation:

$$\text{Equation 1}$$

$$\text{PSA} = \text{PSA}_0 \times \exp(-kt)$$

where preoperative PSA is symbolized as $\text{PSA}_0$, $t$ represents time, and $k$ is the kinetic constant controlling the loss of PSA from the body. The value of $k$ also equals 0.69/half-life of PSA. Because the magnitude of $k$ is approximately 0.26, this equation implies that a PSA value as high as 40 ng/mL should be 0.02 ng/mL in 30 days; that is, for most patients the PSA level should be undetectable in as little as 1 month after surgery. For this reason and because many will postpone further therapy until at least 1 month after surgery, we thought it reasonable to explore the relative importance of the first postoperative measurement of the PSA level as a potential prognostic factor to be combined with preoperative PSA and anatomic pathology information obtained from the prostatectomy specimen. We specifically wanted to study how these factors related to the separate outcomes of an eventual postoperative elevated PSA level and death attributed to prostate cancer.

### Materials and Methods

The patients studied included 216 men with localized prostate cancer who underwent radical prostatectomy at Duke University Medical Center, Durham, NC, or the Durham Veterans Affairs Medical Center. The cases were selected with respect to just 2 factors: an evaluation of the prostatectomy specimen by a dedicated uropathologist and long-term follow-up. The pathologic observations for the 106 cases from Duke were made by one of us (P.A.H.), and the corresponding observations for the 110 Veterans Affairs cases were made by another (R.T.V.). The clinical stage for all was considered to be T1 or T2, N0, and M0. We graded the cases according to the Gleason method.

We expressed the quantity of tumor as percentage carcinoma, that is, the percentage of prostate tissue with tumor. For each patient, the first postoperative value of PSA was included as a prognostic variable. The timing of this postoperative sample varied, but most occurred between 1 and 3 months after surgery. We studied 2 endpoints after prostatectomy: (1) the presence of a significantly elevated PSA level (ie, >0.5 ng/mL) at the last follow-up and before adjuvant hormonal therapy and (2) time to death. Patients who died without experiencing an elevated postoperative PSA level were considered censored at their time of death.

### Statistical Methods

We used the logistic regression model to examine the relationship between the eventual elevation of the PSA level and the prognostic factors of preoperative PSA, postoperative PSA, grade, pathologic stage, and tumor volume. We used the Cox proportional hazards model to examine the relationship between time to death and these same variables. All analyses were done with S-PLUS software (MathSoft, Seattle, WA), and all $P$ values were for 2-sided tests of hypothesis.

### Results

Table 1 summarizes the main variables used in this study, and the Gleason score and other pathologic parameters refer to just those obtained from the prostatectomy specimens. Table 2 shows the variables found by multivariate logistic regression analysis to relate significantly to an eventual elevation of the PSA level. After accounting for elevation or nonelevation of the PSA level soon after surgery, log(preoperative PSA) was the factor most significantly associated with elevation of PSA at last follow-up, and this result demonstrates that higher levels of preoperative PSA implied greater observed probability of eventual biochemical failure after surgery. Whereas without this analysis one could logically assume that elevation of the first postoperative PSA level would imply a high probability

### Table 1

<table>
<thead>
<tr>
<th>Characteristics of Study Population (N = 216)</th>
<th>Median*</th>
<th>Range*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>67</td>
<td>44-83</td>
</tr>
<tr>
<td>Gleason score</td>
<td>7</td>
<td>3-9</td>
</tr>
<tr>
<td>Initial PSA level</td>
<td>8.8</td>
<td>0.2-283.0</td>
</tr>
<tr>
<td>Percentage tumor</td>
<td>15</td>
<td>0.1-89.0</td>
</tr>
<tr>
<td>Surgical margins</td>
<td>No. negative, 89</td>
<td>No. positive, 127</td>
</tr>
<tr>
<td>Seminal vesicles</td>
<td>No. negative, 159</td>
<td>No. positive, 53</td>
</tr>
<tr>
<td>Extracapsular tumor</td>
<td>No. negative, 124</td>
<td>No. positive, 92</td>
</tr>
<tr>
<td>Postoperative PSA level</td>
<td>0.1</td>
<td>0-15.9</td>
</tr>
<tr>
<td>Follow-up time (mo)</td>
<td>70</td>
<td>&lt;1-148</td>
</tr>
</tbody>
</table>

* PSA, prostate-specific antigen.
* Unless designated otherwise.
* Seminal vesicles were not present in 4 specimens.
of biochemical failure by last follow-up, what the analysis of Table 2 demonstrates is that the first postoperative PSA level provided significant but limited information about subsequent biochemical failure and that the level of preoperative PSA provided important, additional prognostic information. Undoubtedly, these results were due to patients with a postoperative PSA level less than 0.5 ng/mL but who experienced eventual biochemical failure, which in turn related closely to the preoperative level of PSA. In this analysis, anatomic pathology variables provided limited information. Involvement of margins and the presence of Gleason grade 5 were the only significant pathologic variables, and each had a P value of .03 for the association with eventual biochemical failure. None of the remaining pathologic variables—tumor volume, tumor in extracapsular tissue or in seminal vesicles, or presence of Gleason grade 4—added to the model of Table 2, and their P values exceeded 0.1 after accounting for the 4 more significant variables in Table 2.

The coefficients in Table 2 permitted us to estimate the probability of an eventual elevated PSA level (Ppsa) as follows Equation 2:

\[
\text{Ppsa} = \frac{1}{1 + \exp(-E)}
\]

where E is given as Equation 3:

\[
E = -3.76 + \left[ 0.696 \log(\text{Preoperative PSA}) \right] + 1.66 \cdot \text{Postoperative PSA} + 1.10 \cdot \text{Margin} + 1.62 \cdot \text{G5}
\]

The variable postoperative PSA is 0 unless the postoperative PSA level is 0.5 ng/mL or more, and then it equals 1. Margin is 0 unless the margins are positive, and then it equals 1. G5 is 0 unless there is a Gleason grade of 5 (either major or minor component), and then it equals 1.

Table 2 shows the results of a Cox proportional hazards analysis of survival time after surgery and the covariate variables found to be prognostic. In contrast with the results of Table 2, the preoperative and postoperative levels of PSA were not important for this outcome (P > .5), and just 2 anatomic pathology variables were important: tumor volume measured as percentage carcinoma and the presence of Gleason grade 5. Both variables were significantly associated with shortened survival time (P < .01), and with these 2 variables present, none of the remaining pathologic variables significantly related to survival time (P > .4). The coefficients of Table 3 permitted us to estimate a hazard score as follows Equation 4:

\[
\text{Hazard Score} = 0.029 \cdot \text{Percentage Carcinoma} + 1.17 \cdot \text{G5}
\]

Although this hazard score is a direct result of the Cox analysis, Figure 1 illustrates its importance. Figure 1 provides a Kaplan-Meier plot of survival probability vs time in months from prostatectomy. The upper curve is for those with hazard scores less than 1.5, and the lower curve is for those with hazard scores of 1.5 or more. Although both groups seem to enjoy a good survival for 4 years, approximately half of those in the second group died with progressive tumor over the next 3.5-year period.

### Discussion

Our results suggest that in patients treated with radical prostatectomy, PSA-derived prognostic information and anatomic pathology–derived information relate to different outcomes for prostate cancer. Preoperative and postoperative values of PSA relate more closely to a PSA outcome than to death, and tumor volume and high grade relate more closely to death than to PSA. The disparity between a PSA outcome and death of tumor has been noted before. For example, elevated values of PSA after treatment of localized prostate cancer have most often not implied early death due to tumor.6,45,46 Patients designated as “biochemical failures”...
form a heterogeneous group with respect to more adverse outcomes, but dynamic aspects of posttreatment PSA can reduce the heterogeneity, because men who die with advanced disease have faster increases in the PSA level.\textsuperscript{30-35,45} All such results suggest that we take care when defining outcomes after radical prostatectomy. Clearly, the endpoint of biochemical failure requires less follow-up and provides fewer censored patients than using the endpoint of death of advanced prostate cancer, and, in fact, after prostatectomy most men die of causes other than prostate cancer. Thus, given the demands for earlier results, many favor the endpoint of biochemical failure over death. Now, our analysis suggests that selecting a PSA endpoint favors models with PSA-related prognostic factors. Using time to death as the endpoint, on the other hand, seems to favor anatomic factors.

The association we found between Gleason grade 5 and death has often been noted before, and, in fact, the designation of comedo necrosis as the highest Gleason grade was due to an analysis of survival time.\textsuperscript{37} More recently, Pan and colleagues\textsuperscript{47} observed that even small, tertiary components of Gleason grade 5 imply a poor outcome, and our results support their conclusions, because by using Gleason pattern 5 as a dummy variable, we found that the presence of Gleason grade 5 was related significantly to survival regardless of how much was present. By contrast, the presence or absence of Gleason grade 4 was not important. Both studies emphasize just how important it can be for surgical pathologists to recognize small foci of Gleason grade 5 both preoperatively and postoperatively. In our experience, the greatest difficulty comes with the comedo necrotic pattern, because at low magnification this morphologic feature can mimic the variant of Gleason grade 3 with cribriform morphologic features but without comedo necrosis.

The importance of percentage carcinoma for death but not for biochemical failure probably relates to how some have found tumor volume to be prognostic, while others have not.\textsuperscript{38,40,48-54} Most finding tumor volume important used endpoints other than biochemical failure,\textsuperscript{38,48-51} whereas, most not finding tumor volume prognostic used an endpoint consisting either solely of PSA failure or an endpoint in which increase of the PSA level was probably the earliest failure event.\textsuperscript{52-54} Furthermore, percentage carcinoma is different from cubic centimeters of tumor, so that a priori one cannot generalize results from using cubic centimeters to the results from using percentage carcinoma. For example, a 2-cc tumor will have a higher percentage carcinoma in a small prostate gland than the same 2-cc tumor in a larger prostate. Thus, percentage carcinoma tells us the proportion of prostate space taken over by tumor, and for this reason it is a topologic parameter rather than a direct measure of tumor volume. With a meta-analysis of 22 studies, we noted previously that percentage carcinoma was significantly more likely to be prognostic in multivariate analyses of outcome than cubic centimeters of tumor.\textsuperscript{59} Consequently, the importance one finds for tumor volume will depend on which measure is used and what outcome is studied. Because we have repeatedly found percentage carcinoma to be important, we encourage pathologists to record percentage carcinoma routinely in prostatectomy specimens. To do so requires less than 5 minutes and no more than routinely stained slides. Furthermore, measuring percentage carcinoma does not require a computer-connected image analyzer or a grid square, although one must either embed the entire prostate for histologic examination or follow a systematic sampling schema, such as every other slice.

Although we are unlikely to stop observing other anatomic pathology features such as the full Gleason score or tumor involving surgical margins, extracapsular tissues, or seminal vesicles, the importance of these observations seems small compared with the presence of Gleason grade 5, percentage carcinoma, preoperative PSA level, and postoperative PSA level. Perhaps some of these variables will become important with studies of larger numbers of patients and with longer follow-up. Furthermore, we cannot comment on the importance of perineural tumor, because it was not included routinely in our database.

The importance of Gleason grade 5 and percentage carcinoma to death from prostate cancer despite prostatectomy suggests that further studies be undertaken to determine whether we can use preoperative information to predict...
who will have a high postoperative hazard score. Specifically, we need accurate ways to predict the presence of Gleason grade 5 and percentage carcinoma in the prostatectomy specimen. Although it is well known that Gleason grades performed on biopsy specimens are often lower than the grades found in the prostatectomy specimen, increasing the number of needle biopsies could increase the accuracy of preoperative grading. In addition, quantitative measurements of the amount of tumor in core biopsy specimens may help us estimate the percentage carcinoma in the prostatectomy. For example, in a preliminary and unpublished study of the specimens of 100 patients, we found that the length of tumor measured in core biopsy specimens was associated positively with the percentage carcinoma in the prostatectomy specimen ($P = 1.4 \times 10^{-8}$). The greater the tumor length in the core biopsy specimens, the greater was the percentage carcinoma found in the prostatectomy. We will study this more formally and encourage others to use an eyepiece micrometer to measure tumor length in the core biopsy specimens. Unlike an estimate of the percentage of tumor tissue in the core biopsy specimens, the micrometer-measured length in millimeters is an objective measure, and it takes no more time to perform than does the Breslow thickness in melanoma. Furthermore, because we also have found that serum PSA levels and the fraction of positive cores added information about predicting percentage carcinoma, we believe that a combination of several preoperative variables will provide better estimates of percentage carcinoma than any single measure.

Finally, our results are based on a long follow-up of a moderate number of men after prostatectomy, and they require validation. They suggest, however, that shortly after prostatectomy, men can be sorted into the 3 categories illustrated in Table 4. First, there are a few patients with tumors of such high grade and high volume that they will not be cured by prostatectomy. By Equation 4, many of them will have hazard scores that exceed 1.5. This group is a natural one to target for prospective studies of immediate adjuvant therapy. The remaining patients who have lower hazard scores should experience a longer survival, but the group will include some who eventually have a rising PSA level. Our results suggest that the estimated probability Ppsa given by Equations 2 and 3 could help sort this remaining group into 2 further subsets: those with higher Ppsa and those with lower Ppsa. Those who have the higher probability should be followed up closely to learn about the level and dynamics of their PSA values. Those with lower probability need to be followed up less intensely, at least until the PSA begins rising, when they would require the same attention as the second group. These 3 categories comprise a hypothesis that is raised by our results and one that we believe deserves further study should our results be validated.

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### References


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### Table 4

Patient Categories Suggested by Results

<table>
<thead>
<tr>
<th>Hazard Score *</th>
<th>Ppsa †</th>
<th>Adjuvant Treatment</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>High (eg, 1.5 or more)</td>
<td>—</td>
<td>Yes</td>
<td>Frequent</td>
</tr>
<tr>
<td>Low</td>
<td>High (eg, &gt;0.5)</td>
<td>Variable</td>
<td>Frequent</td>
</tr>
<tr>
<td>Low</td>
<td>Low (eg, ≤0.5)</td>
<td>No</td>
<td>Infrequent</td>
</tr>
</tbody>
</table>

* Hazard score according to equation 4 (see text).
† Ppsa, the probability of an eventual elevated prostate-specific antigen level, according to equations 2 and 3 (see text).


