Percentage of Tumor in Prostatectomy Specimens

A Study of American Veterans

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Abstract

In this study, I have estimated the percentage of tumor by visual estimate in 447 prostatectomy specimens from American Veterans Affairs patients and related this measurement to overall survival. Although percentage of tumor was significantly related to the serum prostate-specific antigen level, tumor stage, and Gleason score—that is, it was not statistically independent from these—it was more closely associated with overall survival than any of them. Altogether, 2 variables available at the time of the prostatectomy related to survival: patient age (P = .0032; Cox proportional hazards model analysis) and percentage of tumor (P = .0013; Cox model). Patient age undoubtedly reflects the combination of comorbidities and general expected length of life. Percentage of tumor, by contrast, seems to efficiently reflect any undue hazard for early death due to prostate cancer. The results suggest that percentage of tumor is a useful prognostic variable for understanding risk of early death after prostatectomy.

Although measures of tumor volume in prostatectomy specimens were once considered important by leaders in urologic pathology,1,2 such measurements have become at best controversial or even not worth doing.3,4 The problem stems from how tumor volume has been found to be unreliable associated with important outcomes such as tumor recurrence and survival after prostatectomy. For example, among 22 studies described in 21 articles,1-21 just 12 found a significant relationship between tumor volume and long-term outcomes. On the other hand, the details of these 21 reports provide further key information. For example, there are at least 2 ways tumor volume can be expressed: in cubic centimeters and as the percentage of prostate tissue with tumor. The first is an absolute measure of tumor volume, and the second is a relative measure of tumor volume, that is, relative to the entire prostate. Whereas tumor volume expressed as cubic centimeters does not depend on the size of the prostate, tumor volume expressed as a percentage does. In this way, percentage of tumor combines concepts of absolute tumor volume with intraprostatic stage.

Close examination of the same 22 studies shows that whereas just 29% demonstrated that cubic centimeters of tumor related to outcomes, 67% showed that percentage of tumor related significantly to outcomes. The outcome studied also affected the results. For example, earlier studies favored overall survival, and more recent studies have favored biochemical failure manifested by elevated levels of serum prostate-specific antigen (PSA) after prostatectomy.22 The outcome seems to matter. In the same 22 studies, just 40% demonstrated a significant association between tumor volume and biochemical failure, whereas 86% found a significant association between tumor volume and overall survival.
Although “PSA failure” has been largely accepted by committees of experts,\(^2\) it is not a proven surrogate for harder outcomes such as overall or disease-specific survival, and it is sometimes loosely connected to those outcomes.\(^2\)\(^3\)-\(^2\)\(^8\)

In consideration of these issues, I have evaluated the prostatectomy specimens of 447 American Veterans who underwent radical prostatectomy, and I have examined how the percentage of tumor and other key variables relate to their overall survival. Herein I report the results.

**Materials and Methods**

**Study Patients**

The study patients comprised 447 men who underwent radical prostatectomy for prostate cancer at the Durham, NC, Veterans Affairs Medical Center (VAMC). Although clinical stage was not recorded in the records for most of the men, all were assumed to have localized stage because all were considered candidates for prostatectomy. Furthermore, serial measurements of serum PSA were not routinely available, so that PSA velocity could not be estimated, and measures of the amount of tumor in the initial biopsy specimens were often missing. Thus, these 2 variables were not further studied.

All specimens were completely sectioned and examined histologically, and for each, the percentage of tumor was estimated by visual inspection as follows: For each slide of prostate (or tissue block), I estimated the percentage of the area occupied by tumor on just that 1 slide and then entered this into the tally of a small electronic calculator. I proceeded in this manner stepwise through the slides, and after the last slide, I used the calculator’s program to obtain an average, which I reported as the percentage of tumor. In other words, there was no estimate of the number or density of epithelial cells present in the tumor, just the percentage of tissue area occupied by tumor. In addition, I evaluated and recorded Gleason score, status of surgical margins, presence of extraprostatic tumor, and involvement of seminal vesicles. Thus, inclusion criteria for the study patients comprised the performance of prostatectomy, presence of preoperative value of serum PSA, and records of the percentage of tumor, Gleason grade, and pathologic stage in the prostatectomy specimen. I obtained survival data from hospital records or public records of deaths, and the study was approved by the local VAMC Institutional Review Board. Other details about the study patients and their tumors are given in **Table I**.

**Statistical Methods**

To relate clinical and histologic variables to overall survival time, I used Kaplan-Meier plots and the Cox proportional hazards model.\(^2\)\(^9\) To relate serum PSA level to tumor volume, I used linear regression. To relate percentage of tumor to pT3 stage, I used logistic regression,\(^3\)\(^0\) and to relate percentage of tumor to Gleason score, I used the Kruskal-Wallis nonparametric test. All analyses were done using S-PLUS software (MathSoft, Seattle, WA), and all \(P\) values were 2-sided.

**Results**

**Distribution of Percentage of Tumor**

**Figure I** shows the distribution of percentage of tumor in the study population, and it demonstrates an exponential shape. For approximately 75% of the cases, the percentage of tumor was less than 25%, and for approximately 50% of the cases, the percentage of tumor was less than 11%. Thus, most men in this study had limited replacement of the prostate by tumor.
Percentage of Tumor, Serum PSA Level, and Tumor Volume

A result from the field of morphometry suggests that on the average, the area fraction of a phenomenon in a solid is equivalent to the volume fraction of that phenomenon. The percentage of tumor comprises such an area fraction because that is how it is observed on planar tissue sections of the prostate. Thus, if prostate volume is symbolized as Vol and percentage of tumor as Pc, the volumes of benign and tumor tissues, Vb and Vc, respectively, can be approximated in a prostate as follows:

\[ V_b = \text{Vol} \times (1 - \text{Pc}/100) \]

\[ V_c = \text{Vol} \times \text{Pc}/100 \]

If the volume of the prostate is further approximated by its weight, Vb and Vc can be estimated from observations of percentage of tumor with an accuracy up to a multiple constant involving the specific gravity of the prostate, which is probably close to 1.0. Thus, for the men included in this study, the mean of Vb was estimated to be 35.4 cc (range, 4-199 cc), and the mean of Vc was estimated to be 6.5 cc (range, 0.06-107 cc). In general, serum PSA is thought to come from benign and tumor tissues, and theoretical considerations suggest that serum PSA is linearly related to Vb and Vc, although with different weighting coefficients. I tested this hypothesis by doing a linear regression analysis to relate serum PSA levels to estimates of Vb and Vc and introduced an interaction variable, Vc × Gleason score, to allow for a modifying effect of grade. The results are given in Table 2. They demonstrate that the linear model is appropriate, and the regression coefficients suggest that a tumor with a Gleason score of 6 releases approximately 15 times as much PSA per mass of tissue as benign tissue. Furthermore, the negative coefficient for the interaction term between Vc and Gleason score suggests that higher grade tumors contribute less to serum PSA per mass of tumor than lower grade tumors. Nevertheless, because Vb is usually so much larger than Vc, the results also suggest that for most men, more serum PSA comes from benign tissue than from tumor.

Percentage of Tumor, Pathologic Stage, and Gleason Score

Figure 21 shows a plot of the probability of observing the pT3 stage in the prostatectomy specimens vs percentage of tumor. Clearly, as percentage of tumor increases, so does the likelihood of observing pT3 tumor stage, and this positive association was significant (\( P \sim 0 \); logistic regression analysis). Figure 31 shows a box plot relating values of the percentage of tumor to Gleason score. Once again, the plots demonstrate that as the Gleason score increases, so does the percentage of tumor, and this positive association was also significant (\( P \sim 0 \); Kruskal-Wallis nonparametric test).

### Table 2

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>( P )</th>
</tr>
</thead>
<tbody>
<tr>
<td>( V_b )</td>
<td>0.102</td>
<td>.0000</td>
</tr>
<tr>
<td>( V_c )</td>
<td>3.55</td>
<td>.0000</td>
</tr>
<tr>
<td>( V_c \times \text{Gleason} )</td>
<td>–0.355</td>
<td>.0000</td>
</tr>
</tbody>
</table>

PSA, prostate-specific antigen.

* The serum PSA level was the dependent variable in the analysis. \( V_b \) and \( V_c \) represent, respectively, volumes of benign and tumor tissues and were estimated from the percentage of tumor and weight of prostate (see test). \( V_c \times \text{Gleason} \) is an interactive variable reflecting the effect of Gleason score but weighted by the amount of tumor.

† The negative coefficient for this interaction indicates that the positive association between tumor volume and serum PSA level is less for higher Gleason scores when compared with better differentiated tumors with lower Gleason scores. The residuals for the analysis appeared normally distributed (data not shown).

Percentage of Tumor and Overall Survival

Figure 41 shows a Kaplan-Meier plot of the probability of survival at last follow-up vs the percentage of tumor. The plot demonstrates that as the percentage of tumor rises, there is a dramatic reduction in survival probability, and a univariate Cox model analysis showed that this association was significant after controlling for the effect of censoring at last follow-up (\( P = .0016 \)). Univariate Cox model analyses also demonstrated that patient age (\( P = .0036 \)) and pT3 stage (\( P = .0051 \)) were significantly associated with overall survival but that serum PSA level (\( P = .42 \)), Gleason grade (\( P = .11 \)), estimated Vc (\( P = .12 \)), and positive surgical margins (\( P = .085 \)) were not. Table 31 shows a multivariate Cox model analysis of the combined effects of age and percentage of tumor on survival, and both were significant. When stage pT3, serum PSA level, and surgical margin status were added as variables in the

![Figure 41](https://example.com/figure41.png)

Plot of the probability of observing pT3 stage in prostatectomy specimens vs percentage of tumor. The faint line shows the relationship and was obtained from the Lowess function in S-PLUS.
multivariable Cox model, none was found to add significance ($P > .1$). Finally, to illustrate the combined effects of age and percentage of tumor on overall survival, Figure 5 shows the probability of 10-year survival predicted by a Weibull model analysis that included the explanatory variables of age and percentage of tumor. On the plot are 3 lines, one each for the ages of 50, 60, and 70 years, and altogether, they demonstrate the combined effects of age and percentage of tumor on expected survival.

Discussion

At the time of the diagnosis of prostate cancer, the central questions for many men are whether it will shorten life and whether it will cause undue pain or discomfort. Additional questions are whether to seek treatment and which treatment to seek. Thus, the impact of prostate cancer on survival—that is, overall survival—is an important issue for these men. If they choose to undergo radical prostatectomy, most will be cured of the tumor, even while experiencing complications of the surgery. For a few, however, there will remain uncertainty about whether the tumor was completely removed when their surgical margins contain tumor, when their tumor involves extraprostatic tissues or seminal vesicles, or when their serum PSA level rises above 0.2 ng/mL (0.2 µg/L) after surgery. The men then face new questions and decisions about additional treatments such as radiation or hormonal treatments, and they will once again want to know how this possible residual tumor will affect their survival.

The results in this study suggest that in this situation, percentage of tumor will be helpful because it seems to relate more closely to overall survival than does the serum PSA level, Gleason grade, or pathologic stage. The model in Table 3 suggests that 2 factors affect postoperative survival: patient age, which is a rough surrogate for comorbidities and expected

![Figure 3](image3.png) Box plot of percentage of tumor vs Gleason score in prostatectomy specimens. The horizontal lines show the median values of percentage of tumor. The solid bars show the 25th to 75th percentiles of percentage of tumor, and the brackets and thin horizontal lines show more extreme high or low values of percentage of tumor.

![Figure 4](image4.png) Kaplan-Meier plot of the probability of survival at last follow-up vs percentage of tumor in prostatectomy specimens. The faint upper and lower lines give 95% confidence intervals.

![Figure 5](image5.png) Plot of survival probability at 10 years vs percentage of tumor. The survival probability is that predicted by a Weibull model fit to the data.

![Table 3](image3.png) Cox Model Analysis of Overall Survival

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>$P$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient age</td>
<td>0.0546</td>
<td>.0032</td>
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<tr>
<td>Percentage of tumor</td>
<td>0.0153</td>
<td>.0013</td>
</tr>
</tbody>
</table>

*When stage pT3, serum prostate-specific antigen level, and surgical margin status were added as variables in a multivariable Cox model analysis, none was found to add significance ($P > .1$). Age and percentage of tumor were coded as continuous variables.
length of life, and percentage of tumor, which reflects the potential impact of the prostate cancer on subsequent survival. Although critics point out that percentage of tumor lacks statistical independence from other prognostic factors such as serum PSA level, tumor stage, and Gleason grade, such associations between measures of tumor volume and other prognostic factors are well-documented here and elsewhere and should be expected. The key issue should not concern statistical independence, but which of these measures relates best to overall survival. The results herein suggest that percentage of tumor is the best. The fact that percentage of tumor was more closely related to survival than estimated absolute tumor volume in cubic centimeters also explains some of the earlier conflicting reports about the importance of tumor volume.

Some have complained that estimating tumor volume in prostatectomy specimens is too arduous or too time-consuming or requires whole-mount processing of the specimens. In fact, estimating the percentage of tumor requires no equipment other than a routine microscope (an electronic calculator helps), no observers other than the pathologist, and neither whole-mounting technique nor complete histologic examination of the prostate. For the average case, no more than 5 minutes is required. If the prostate is too large to process completely, a systematic sampling of the gland provides a reasonable alternative. In other words, after taking the apical and bladder margins, slice the prostate sequentially across the axis of the urethra from base to bladder neck. To reduce the number of tissue blocks, process for histologic examination every other slice, 1 of 3 slices, or whatever ratio yields an acceptable number of blocks. As long as the sampling is uniform throughout the gland—that is, as long as it does not preferentially sample right over left, anterior over posterior, superior over inferior—the sampling will be systematic and unbiased and should allow the percentage of tumor to be accurately estimated.

Although the primary goal herein was to study the relationship between percentage of tumor in the prostatectomy specimen and overall survival, I also examined the way the serum PSA level depends on the combination of volumes of benign and malignant tissues in the prostate. Others have studied this issue, and most have found that serum PSA is positively associated with tumor volume and Gleason grade. Nevertheless, some have recently suggested that the serum PSA level relates only to the overall size of the prostate. In my opinion, study of the relationships between serum PSA levels and volumes of benign and malignant tissues is tricky so that the results can be misleading if the regression analysis is not optimal. For example, consideration of the kinetics and compartmental analysis of serum PSA suggests that serum PSA levels should be linearly related to these 2 volumes, Vb and Vc—that is, the relationship should not require a logarithm transformation of PSA. Yet, most prior studies have used the logarithm of serum PSA rather than the untransformed PSA, perhaps because serum PSA has a naturally skewed distribution or because it sometimes seems to be a better prognosticator when transformed. Furthermore, just 2 of these studies included measures of Vb and Vc in the regression analysis. What I have demonstrated herein is that untransformed serum PSA is significantly related to Vb and Vc. Furthermore, the residuals from the regression analysis in Table 2 showed an approximately normal distribution, and it is these residuals that must not be skewed for the analysis to be reliable. Finally, investigators finding a positive regression association between serum PSA level and Gleason score may not have studied this issue optimally because they did not control for the positive associations between tumor volume and Gleason score. Without such control, analyses can seem to show a positive relationship between Gleason score and serum PSA level simply because of the association of grade with tumor volume. But if one controls for the effect of tumor volume, as Aihara et al did and as I have done with the interaction variable in Table 2, one finds that there is an inverse relationship between serum PSA level and Gleason score.

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References