Tumor Length in Prostate Cancer

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Abstract

To evaluate the impact of tumor length and fraction of positive biopsy cores on overall survival, I used the data for 526 patients with prostate cancer. Median follow-up in patients not observed until death was more than 6 years. In a Cox model analysis that included age, serum prostate-specific antigen (PSA) level, grade, and fraction of positive cores, tumor length was the most closely associated with overall survival time ($P = 6 \times 10^{-5}$); however, the impact of tumor length was mostly for a subset of men with tumors measuring more than 20 mm. Patient age, serum PSA level, Gleason score, fraction of cores with tumor, and tumor length were all significantly codependent variables. For routine cases of prostate cancer, measuring tumor length in the needle cores may be unnecessary. Tumor length may assist studies of long-term outcomes or treatment trials in prostate cancer by reducing baseline variance better than other prognostic variables. For the few patients with unusually large amounts of tumor in biopsy specimens, tumor length may provide a concise indicator for the likelihood of an adverse outcome, especially when the values of other prognostic variables appear by themselves to be less ominous.

Since the 1990s, many have observed that the quantity of tumor in needle biopsy specimens of the prostate is important for prognosis. For example, the amount of tumor in the biopsy specimens has been positively correlated with tumor volume, with tumor stage (ie, pT stage), with nodal metastases, and with biochemical tumor failure manifest by a rising serum prostate-specific antigen (PSA) level after treatment. These 4 outcomes can be seen as the first in a sequence of 6 outcomes in prostate cancer that include metastases, hormone-refractory tumor, and the event of death (overall survival).

Although biochemical tumor failure is the outcome most commonly studied, patients with failure can still be treated with radiotherapy if their initial treatment was surgery, and they can also be treated hormonally. Furthermore, after such secondary treatments, many of the patients with biochemical failure do well and die of other causes. The central question for many men at the time of diagnosis is whether the tumor will shorten their life, and its answer will undoubtedly affect their decisions about the choice and timing of treatment.

Thus, the outcome that may be of greatest concern to these men is overall survival. Any observations made at the time of diagnosis and that can relate to the time of death should be important, and they are likely also to be useful for deciding treatment. Nevertheless, I know of just 1 group that studied the relationship between the quantity of tumor in the initial needle biopsy specimens and overall survival, and they had just 7 patients who were followed up until death.

Finally, the optimal way to measure the amount of tumor in needle biopsy specimens remains unclear. The quantity of tumor in needle cores has been expressed as number of positive cores, fraction or percentage of positive cores, overall
estimate of the percentage of tissue with tumor, total tumor length in millimeters, greatest tumor length in 1 core, greatest percentage of tumor in 1 core, and greatest percentage of high-grade tumor.35

To study some of these issues, I began, in 1997, to prospectively record 2 measures of the quantity of tumor in needle biopsy specimens of the prostate: fraction of cores with tumor and total tumor length in millimeters. In addition, I retrospectively measured these 2 variables in 55 cases in which the patients underwent biopsy earlier and whose biopsy specimens were reviewed for other purposes. Herein, I report how the fraction of cores with tumor and total tumor length relate to overall survival in 526 men diagnosed with prostate cancer and followed up until their death or for a median of more than 6 years.

Materials and Methods

Study Patients

The study patients comprised 526 men who were diagnosed with prostate cancer. All but 55 were diagnosed during the period from 1997 to 2006, and all of the diagnoses were made on needle biopsy specimens. In addition, I recorded the Gleason score, the number of cores with tumor, and the linear measurement of total tumor length in millimeters along the axis of the biopsy. For tumor length, I used the same calibrated eyepiece micrometer I use to measure tumor thickness in cutaneous melanomas, and no other lengths were recorded. In other words, throughout this article, tumor length refers to the total length of the tumor.

Of the men whose data were included in the study, 444 were patients in the Durham Veterans Affairs Medical Center (VAMC), Durham, NC, and the remaining 82 were participants in a concurrent Cancer and Leukemia Group B study for which I was a pathology reviewer. Of the 526 patients, 314 were treated with radical prostatectomy, 159 were treated primarily by external beam radiation therapy, and the remaining 53 were treated as needed by other methods, including hormonal therapy. In general, information about clinical stage was not uniformly documented in their medical records; however, I assumed that all patients treated by surgery or radiation therapy had clinically localized tumor, because the standard of practice routinely excluded these treatments for patients with evidence of metastatic tumor. Furthermore, I excluded men whose initial values of PSA exceeded 100 ng/mL (100 µg/L). I obtained survival data from hospital records or public records of deaths (eg, see www.peoplefinders.com), and the study was approved by the local VAMC Institutional Review Board. Other details about these study patients and their tumors are given in Table 1.

Table 1
Characteristics of Study Population

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>526</td>
</tr>
<tr>
<td>Mean age (range), y</td>
<td>64 (42-88)</td>
</tr>
<tr>
<td>Primary treatment</td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>314</td>
</tr>
<tr>
<td>Radiation</td>
<td>159</td>
</tr>
<tr>
<td>Other</td>
<td>53</td>
</tr>
<tr>
<td>Mean serum PSA level (range), ng/mL*</td>
<td>12.3 (0.0-99.6)</td>
</tr>
<tr>
<td>Mean total No. of biopsy cores (range)</td>
<td>7.3 (1-16)</td>
</tr>
<tr>
<td>Mean biopsy Gleason score (range)</td>
<td>6.7 (4-10)</td>
</tr>
<tr>
<td>No. of patients observed until death</td>
<td>108</td>
</tr>
<tr>
<td>Mean follow-up of patients alive at last follow-up (range), y</td>
<td>6.1 (0.5-15.2)</td>
</tr>
<tr>
<td>Mean tumor length (range), mm</td>
<td>13.4 (0.02-135.8)</td>
</tr>
</tbody>
</table>

* Prostate-specific antigen (PSA) levels are given in conventional units; to convert to Système International units (µg/L), multiply by 1.0.

Statistical Methods

To relate clinical and histologic variables to overall survival time, I used Kaplan-Meier plots, the Cox proportional hazards model, and the Weibull survival model.50 To relate continuous variables to the categories of Gleason score, I used the nonparametric Kruskal-Wallis test. All analyses were done using S-PLUS software (MathSoft, Seattle, WA), and all P values were 2-sided.

Results

Survival and Quantity of Tumor in the Biopsy Specimens

Figure 1 shows the distribution of tumor lengths in the study population. Figure 2 provides a Kaplan-Meier plot of 5-year survival probability vs the fraction of biopsy cores.

![Figure 1](image1)

![Figure 2](image2)

Tumor length.
with tumor, and the plot shows that as the fraction increased, the survival probability decreased. Cox model analysis also demonstrated that this association was significant ($P = .0004$).

**Figure 3** provides a similar Kaplan-Meier plot of 5-year survival probability, this time, however, vs tumor length in millimeters, and once again, the plot shows that as tumor length increased the survival probability decreased. Cox model analysis also demonstrated that this association was also significant and with a smaller $P$ value of $1.6 \times 10^{-8}$.

**Table 2** shows a multivariable Cox model analysis that tests for the importance of the quantity of tumor after controlling for the effects of patient age and serum PSA level. Gleason score was also examined. The results demonstrate that tumor length was significantly associated with overall survival ($P = 6 \times 10^{-5}$), and the strength of association between tumor length and survival was greater than the associations between age or PSA level and survival. After controlling for the effect of tumor length, the fraction of biopsy cores with tumor contributed no further prognostic information, nor did Gleason score, tumor length divided by the number of positive cores, or tumor length divided by the total number of cores obtained.

Finally, I used a Weibull survival model to estimate the impact of tumor length on survival probability 5 years after diagnosis. Using just the 2 significant variables of patient age and tumor length in Table 2, the Weibull model fit the data well (result not shown), and plots of the estimated 5-year survival probabilities for tumor lengths ranging from 0.5 to 130 mm for the ages of 50, 60, and 70 years appear as shown in **Figure 4**. The results demonstrate that tumor length has a modest impact on overall survival until tumor lengths exceed 20 mm (2 cm).

**Codependence Between Tumor Length and Other Variables**

In this study, I investigated 5 prognostic variables, all of which can be known at the time of diagnosis. These 5 are patient age, serum PSA level, Gleason score, fraction of cores with tumor, and tumor length, but I found that they provide at best overlapping information because they are not statistically independent of one another. For example, many have demonstrated that the serum PSA level is related to patient age (eg, see Vollmer and Grunkemeier and Vollmer).

By using the data, I found that serum PSA level was also positively and significantly related to Gleason score ($P = .001$; Kruskal-Wallis test). Whereas the median value of PSA levels for Gleason scores 4 through 6 was 7.3 ng/mL (7.3 µg/L), the median value for Gleason scores 7 through 10 was 9.2 ng/mL.
suggest that among the pretreatment variables of patient age, serum PSA level, Gleason score, and 2 measurements of tumor quantity, the total tumor length provides the most information about overall survival. Of course, these 5 variables provide overlapping prognostic information because they are not statistically independent. The question to consider then is whether measuring tumor length is worth the additional effort a pathologist must make to record this variable, especially when so few routinely measure tumor length and when few or no urologists use this measurement to decide treatment.

Despite the need for an eyepiece micrometer and the 1 or 2 minutes required to measure tumor length, this measurement has advantages over several other estimates of the amount of tumor present, such as overall percentage of tumor and the fraction of cores with tumor. For example, it is more objective. It requires no subjective estimate of the number of cores, when they frequently fracture into smaller pieces, nor does it require a subjective estimate of the percentage of total biopsy tissue that contains tumor. All one need do is to measure the length of each focus of diagnostic tumor in the units of the micrometer and along an axis parallel to the needle biopsy specimen, sum these units, and convert the sum to millimeters. If the eyepiece micrometer is already calibrated to measure tumor thickness in cutaneous melanomas, then the same algorithm can be used to measure total tumor length in millimeters for the prostate. Using an electronic calculator simplifies the task.

Weakening the argument for measuring tumor length is the observation that this variable’s importance is largely limited to a modest number of tumors. For example, more than 75% of this study’s patients had tumor lengths of less than 18 mm. Examination of Figures 3 and 4 shows that in the range of 0 to 20 mm, the expected 5-year survival should be high despite the exact tumor length. In other words, tumor length does not impact survival over typical values obtained for most men with prostate cancer. By contrast, tumor lengths of more than 20 mm affect survival more dramatically, but such tumors are not common, and they tend to have higher Gleason scores and larger fractions of positive cores.

This study demonstrates that total tumor length in biopsy specimens of the prostate is an important prognostic variable that is more closely related to overall survival than patient age, serum PSA level, Gleason score, and fraction of cores with tumor. Its measurement requires a modest extra effort for pathologists—an effort similar to measuring the Breslow thickness in cutaneous melanoma. At the same time, this variable’s prognostic impact is limited for most men with prostate cancer and comes into play mostly for a subset whose tumor lengths exceed 20 mm. Altogether, the results suggest that investigators obtaining data for large prospective studies of outcomes in prostate cancer or for clinical trials should consider measuring and recording tumor lengths on their patients.

Discussion

The most important information derived from a set of prostate biopsy specimens is the diagnosis, that is, the presence or absence of tumor. (For the moment, patterns of nondiagnostic atypia will not be addressed.) If tumor is present, then other important clinical observations made by the time of biopsy include the patient’s age, presence of comorbidities, serum PSA level, and clinical stage. To these variables, pathologists routinely add Gleason score and often an estimate of the quantity of tumor present. Now these results

(9.2 µg/L). I found that the fraction of positive cores was also positively and significantly related to Gleason score (P ~ 0; Kruskal-Wallis test). Whereas the median fraction of positive cores for Gleason scores 4 through 6 was 0.29, the median fraction for Gleason scores 7 through 10 was 0.5. Similarly, I found that tumor length was positively and significantly related to Gleason score (P ~ 0; Kruskal-Wallis test). Whereas the median tumor length for Gleason scores 4 through 6 was 2.9 mm, the median length for Gleason scores 7 through 10 was 13.1 mm. In addition, linear regression analyses demonstrated that fraction of positive cores and tumor length were significantly and positively related to serum PSA level (P ~ 0) and to one another (P ~ 0). Finally, I found that fraction of cores with tumor and tumor length were significantly and positively related to patient age (P ~ 0; linear regression). Thus, all 5 of these variables are codependent. Although the number of core biopsies varied among these patients, there was no association between tumor length and the number of cores (P > .2; linear regression).

Figure 4 Estimated probabilities of 5-year survival vs tumor length for 3 men at the respective ages of 50, 60, and 70 years. The estimates are from a Weibull model that used just age and tumor length as explanatory variables.
because this measurement is now largely ignored and because it may reduce baseline variance in such studies. For others, the routine measurement of tumor length should be optional, unless one wants to call attention to particular cases with high tumor lengths. In such cases, tumor length may be more likely to reflect shortened overall survival than other measures.

References


