Carcinoma Extent in Prostate Needle Biopsy Tissue in the Prediction of Whole Gland Tumor Volume in a Screening Population

James S. Lewis, Jr, MD,1 Robin T. Vollmer, MD,2 and Peter A. Humphrey, MD, PhD1

Key Words: Prostate; Cancer; Tumor volume; Needle biopsy; Radical prostatectomy; PSA; Prostate-specific antigen; Screening

Abstract

Increasing prostate tumor volume has been shown to correlate with numerous adverse prognostic indicators for patients with prostate carcinoma. The ability to predict tumor volume from pretreatment parameters is potentially critical in the stratification of patients for different management strategies. We assessed the capacity of preoperative variables to predict tumor volume in 100 men diagnosed with prostate cancer in a prostate-specific antigen (PSA)-based screening program. Preoperative information included total serum PSA concentration and needle biopsy tissue variables, including Gleason score, number of positive cores, linear extent of carcinoma in millimeters, greatest percentage of carcinoma (in a single core), total percentage of carcinoma (all cores), presence of perineural invasion, and percentage of high-grade carcinoma. The postoperative end point was total tumor volume in radical prostatectomy tissue, calculated by image analysis. We determined independently significant factors and generated a predictive model for whole gland tumor volume. Total tumor volume was related significantly in multivariate analysis to 3 preoperative variables: linear extent of carcinoma, exponential number of positive cores, and serum PSA. A predictive model generated based on these 3 variables accounted for only 65% of the natural deviance of the data owing to data-point scatter for individual patients, suggesting that additional variables are needed to more accurately predict tumor volume. Findings highlight the importance of reporting quantitative measures of tumor amount in prostate needle biopsy specimens; several measures of tumor extent (vs 1 measure) provide maximal information on prostate cancer size.

Prostate cancer is the most common malignant neoplasm in American men, other than superficial skin cancer, and the second leading cause of cancer death in American men.1 In 2001, it was estimated to represent 30% of all new cancer diagnoses in men and to account for 30,200 deaths.1 Clearly, prostate cancer is a significant cause of morbidity and mortality. However, currently, prostate cancer has a very unpredictable clinical course in individual patients. There is a low ratio of mortality to clinical disease incidence and a very low ratio of clinical disease and mortality to the incidence of unsuspected cancers revealed at autopsy, the great majority of which are very small (<0.1 cm³).

In 1969, it was suggested that biologic malignant potential of prostate cancer was strongly correlated with size of the primary cancer.2 Since then, increasing tumor size has been linked to increasing pretreatment serum prostate specific antigen (PSA) levels, increasing histologic grade, increasing surface area of capsular penetration, seminal vesicle invasion, positive surgical margins, lymph node metastases, and disease progression and survival after radical prostatectomy.3-7 Stamey et al8 showed a strong, independent predictive value of whole gland tumor volume for biochemical failure after treatment by radical prostatectomy. Moreover, all definitions of clinically significant vs potentially insignificant prostatic carcinoma incorporate tumor size measurements.7,9-11 Thus, it would be desirable to define tumor size preoperatively to predict which patients may have a clinically insignificant cancer and to determine which patients are likely to benefit from intervention.

There are few studies evaluating multiple histopathologic variables in prostate needle biopsy tissue to preoperatively predict whole gland tumor volume,12-20 and only 2 studies on the relationship of preoperative variables to total tumor volume in a PSA screening population have been published.13,17 In previous investigations, in a PSA-based screening population,
multiple measures of prostate needle biopsy carcinoma extent, including number of positive cores, percentage of positive cores, total percentage of carcinoma (TPC), and linear millimeters of total carcinoma, were all significantly linked to total tumor volume. We analyzed additional histopathologic variables in needle biopsy tissue, including the greatest percentage of carcinoma in a single core (GPC), perineural invasion, and percentage of carcinoma that was high-grade Gleason pattern 4 or 5 in relation to total tumor volume. We also developed a regression model of preoperative variables to predict total tumor volume. The significance of capturing more than 1 measure of tumor extent in prostate needle biopsy tissue is highlighted by our findings in the present study.

Materials and Methods

Patient Selection

One hundred patients with matched needle biopsies and completely embedded radical prostatectomy specimens from the PSA-based screening program at Washington University Medical Center (St Louis, MO) were identified retrospectively. For all patients, carcinoma was diagnosed at biopsy and clinically organ-confined disease was present, and all patients underwent radical prostatectomy between 1992 and 1996. None of these patients had a history of prostate cancer or prostate surgery, and those with a history of prostatitis were excluded. Screening serum PSA levels were determined by immunometric assay with kits (Tandem-R) obtained from Hybritech (San Diego, CA), as previously described. Patients underwent transrectal prostatic ultrasonography and ultrasound-guided prostate biopsy using an 18-gauge needle and a biopsy gun as previously described.

Pathologic Analysis of Needle Biopsy Tissue

Carcinoma in needle biopsy tissue was assessed after routine 10% formalin fixation, embedding in paraffin, serial sectioning, and H&E staining. All biopsy specimens were reviewed by one or two of us (J.S.L. and/or P.A.H.), and any discrepancies were resolved by mutual agreement. Carcinoma was characterized for the following variables: Gleason grade, number of positive cores, linear extent of carcinoma, GPC, TPC (all cores), presence of perineural invasion, and percentage of carcinoma that was high-grade Gleason pattern 4 or 5. Gleason primary and secondary grades with sum scores were assigned. Linear extent of carcinoma was measured using a single Olympus WHK 10× micrometer eyepiece with a linear array of 100 bars (Olympus Optica, Tokyo, Japan). At a magnification of 100×, 1 mm equals 100-bar intervals. Measurements were performed linearly along the long axis of all cores. With the fine hairs provided by the micrometer, minute (“skip”) areas of nontumorous prostate parenchyma as small as 0.1 mm could be excluded from measurement. Percentage of involvement of cores was estimated by visual inspection by using a 4x microscopic field as 100 and visually breaking down the cores along their long axis into divisions of 10. No allowance was made for the amount of tumor across the short axis of the cores. The GPC value represents the percentage of carcinoma in the needle core with the greatest amount of tumor involvement, whereas the TPC value represents the percentage of carcinoma in all needle cores of the diagnostic biopsy session. Increments of 10% were used in visual inspection estimates of percentage of prostatic needle biopsy tissue involved by carcinoma. The amount of high-grade carcinoma (Gleason grade 4 or 5) was estimated visually as a percentage of all carcinoma, perineural invasion was assessed as present or absent, and, finally, the number of core biopsy specimens containing carcinoma was quantified. The number of individual cores present for evaluation was determined visually at the time of gross description.

Radical Prostatectomy Image Analysis

The radical prostatectomy specimens were handled and processed in a standard manner with embedding of all prostatic tissue as previously described. Total tumor volume was quantitated using the SAMBA 4000 image analyzer and the prostate SAM software program (both from Imaging Products International, Chantilly, VA). To calculate tumor volume, regions of carcinoma on each slide were indicated with a marking pen, and surface area of carcinoma in square centimeters was determined by the computer after tracing the carcinoma regions using a digitizing pad. To obtain tumor volume in cubic centimeters for each case, the sum of all tumor areas was multiplied by section thickness (0.4 cm) and a shrinkage factor (×1.33).

Statistical Analysis

We used a general linear model to relate the continuous dependent variable of observed tumor volume (cm³) in the radical prostatectomy specimen to the preoperative variables. We examined the residuals to ensure that they were approximately normally distributed. For binary dependent variables such as perineural invasion, we used the logistic regression model. Pearson correlation coefficients on the relationships between preoperative variables and total tumor volume were generated. All analyses were done with the S-PLUS software (MathSoft, Seattle, WA).

Results

Clinical and Pathologic Features

The clinical and pathologic features of this patient population are given in Table 1. The 100 patients ranged in age
from 41 to 76 years (mean, 63.8 years). The mean ± SD tumor volume from image analysis was 1.9 ± 2.5 cm³ with 28% of cancers 0.5 cm³ or less. The average whole gland Gleason score was 6.0 for all 100 cases. For preoperative variables, the average number of positive needle biopsies was 1.7, the average linear millimeters of carcinoma in needle biopsy tissue was 3.8, the average PSA was 6.1 ng/mL, and the average needle biopsy Gleason score was 5.9. Perineural invasion was identified in 12% of needle biopsy cases. Other important points about our data set are the preponderance of preoperative PSA values between 4 and 10 ng/mL (67%) and the vast majority of cancers with a Gleason score of 5 to 7 (89%).

Scatter-Plot Profiles for Relationship of Needle Biopsy Tumor Extent and Preoperative PSA With Whole-Gland Total Tumor Volume

Univariate analysis established highly significant relationships between linear millimeters of carcinoma, number of positive cores, GPC, TPC, and preoperative PSA with tumor volume in the whole gland, but plots of individual point distributions revealed substantial scatter. Pearson correlation coefficients for these plots are as follows: 0.55 for number of positive cores ($P = .0$), 0.51 for linear millimeters of carcinoma ($P = .0$), 0.43 for TPC ($P = .0$), 0.41 for preoperative PSA ($P = .0$), and 0.29 for GPC ($P = .0037$). The depicted lines in Figures 1 through 5 represent a smoothing function, showing the overall trend in the data.

Pathologic Tumor Volume: Multivariate Correlation Analyses

Correlation of each preoperative variable separately with total tumor volume using a general linear model showed that 3 variables were related significantly to whole gland tumor volume Table 2. Total tumor length was most closely associated with tumor volume ($P = 8 \times 10^{-5}$), as was the serum PSA level ($P = 3.8 \times 10^{-5}$). The GPC seemed to add significant information ($P = .013$), but this variable had a negative coefficient, implying an inverse association with tumor volume. Furthermore, because the GPC was associated significantly with total tumor length ($P = .0$ by linear regression), with the number of positive cores ($P = .0$ by linear regression), and with the PSA level ($P = .02$ by linear regression), we believe its inclusion in the model was an example of overfitting, and, for this reason, we did not include it in the final model. Needle biopsy Gleason score, percentage of high-grade Gleason grade 4 or 5, and perineural invasion by carcinoma were not of significance in predicting tumor volume.

Pathologic Tumor Volume: Predictive Model

The results for the best model for predicting tumor volume are shown in the following equation. The variables can...
be used in this equation to predict the tumor volume as follows:

Predicted Volume (cm$^3$) = 0.216 × tumor length + 0.0216 × Exponent(No. of positive cores) + 0.137 × PSA

**Figure 6** shows the plot of the observed tumor volume vs that predicted by the model. The line shows where perfect agreement should occur, and the fact that many points are removed from the line shows the limitations of the model performance using the training set. The model has not been tested with an independent data set. More than 65% of the predicted tumor volumes fell within less than 1 cm$^3$ of the actual tumor volume.

**Discussion**

The results of our analysis demonstrate that several preoperative variables are related significantly to whole gland total tumor volume in multivariate analysis. A quantitative
measure, the total linear extent of carcinoma, measured in a standard way by ocular micrometer, exhibited the strongest association. The number of positive cores also was related highly to total tumor volume. Moreover, the use of both of these measures of needle biopsy tissue tumor extent, along with the preoperative serum PSA level, in a regression equation yielded the best model to predict tumor volume. This suggests that it may be important to report more than 1 measure of tumor extent in needle biopsy specimens.

Measures of carcinoma extent in prostate needle biopsy specimens are important since they are related to pathologic end points of radical prostatectomy tumor volume, margin status, extraprostatic extension, and lymph node status33-47 and to the clinical end point of biochemical failure after radical prostatectomy and radiation therapy.33,38,43,48,49 (We analyzed the relationship of carcinoma extent in needle biopsy tissue to pathologic stage for the 100 cases reported here, but this population number seems to be underpowered to address any potential relationship with stage. Expansion of this series to assess this stage end point is in progress.) In addition, carcinoma extent in the needle biopsy specimen can be used in nomograms and models to counsel patients in selection of therapy, based on predicted pathologic stage50 and based on prediction of the likelihood of potentially insignificant prostate cancer.10,19,51

We found that 2 measures of tumor extent in needle biopsy specimens—linear millimeters and number of positive cores—were most highly predictive of tumor volume. It should be noted, however, that a literature survey indicated that no one method is definitively superior52 (Table 3). Indeed, in the few previous studies that have examined more than 2 separate measures of needle biopsy tumor extent,12-15,19 roughly equivalent predictive power for whole gland tumor volume was found for total linear millimeters of carcinoma, fraction of positive cores, number of positive cores, and total percentage of carcinoma. Thus, an argument may be made for reporting all of these measures of tumor extent. Our data suggest that reporting more than 1 measure of tumor extent in needle biopsy tissue may provide additional information. The number of cores positive for carcinoma and total linear millimeters of carcinoma may be more quantitative and reproducible measures of tumor extent in needle biopsy specimens compared with the visual inspection estimates of the percentage of carcinoma involving prostate needle biopsy tissue.53 Measurement of total linear millimeters by ocular micrometer may, however, be more labor-intensive and time-consuming. Visual estimates of linear millimeters of carcinoma could be captured if one determines the size of a visual field of a light microscope at specific magnifications.5 Whether measurements of linear millimeters obtained via such an approach harbor the same strength of association with pathologic end points, such as tumor volume, has not been assessed.

The difficulty in accurately predicting whole gland tumor volume from pretreatment needle biopsy histopathologic

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**Table 3**

<table>
<thead>
<tr>
<th>Variable</th>
<th>Coefficient</th>
<th>SE</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total tumor length (mm)</td>
<td>0.216</td>
<td>0.066</td>
<td>~ .00</td>
</tr>
<tr>
<td>No. of positive cores</td>
<td>0.0216</td>
<td>0.005</td>
<td>8 × 10⁻⁵</td>
</tr>
<tr>
<td>Total preoperative prostate-specific antigen level</td>
<td>0.137</td>
<td>0.039</td>
<td>3.8 × 10⁻⁵</td>
</tr>
<tr>
<td>Greatest percentage of carcinoma in a single core</td>
<td>—</td>
<td>—</td>
<td>.013</td>
</tr>
<tr>
<td>Total percentage of carcinoma in all cores</td>
<td>—</td>
<td>—</td>
<td>&gt;.08</td>
</tr>
<tr>
<td>Gleason score (&lt;7 vs ≥7)</td>
<td>—</td>
<td>—</td>
<td>&gt;.9</td>
</tr>
<tr>
<td>Percentage high-grade (Gleason pattern 4 or 5)</td>
<td>—</td>
<td>—</td>
<td>&gt;.3</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td>—</td>
<td>—</td>
<td>&gt;.3</td>
</tr>
</tbody>
</table>

*The analysis was done with a general linear model. The coefficients and standard errors of the coefficients (SE) are listed for a 3-variable model that includes just the significant variables, but they are omitted for nonsignificant variables. See text regarding greatest percentage of carcinoma.*
findings and serum PSA is highlighted by inspection of the scatter of points in Figures 1 through 5 and our model construction of an equation using these 3 pretreatment variables. It is clear by examination of the wide distribution of whole gland tumor volumes for each of these 3 individual variables that 1 variable by itself is not absolutely predictive of tumor volume, despite statistical significance. For example, as can be noted in Figure 1, it is well-established that a minimal amount of tumor in needle core biopsy tissue is not predictive of a small volume of tumor in the prostate gland. Location of a significant component of the tumor in the transition zone, which was not sampled by the peripheral zone–directed sextant biopsy cores procured in our study, could be a confounding factor. To address this issue, further research is warranted. In the future, combining several measures of tumor extent in needle biopsy specimens with other preoperative variables to predict whole gland tumor volume and pathologic tumor stage should be pursued, with incorporation of new tissue and serum markers.

Our study was limited, but also unique, in that we assessed pretreatment variables in patients enrolled in a formal PSA-screening program. While these prostate cancers detected in a formal PSA-screening program and nonscreening PSA-detected (clinical stage T1c) prostate cancers tend to be smaller and of lower stage, the scatter of our pretreatment data points in plots vs tumor volume is similar to that of nonscreened patients. In addition, our study was retrospective. The practical usefulness and added

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**Table 3**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Patients</th>
<th>No. of Biopsy Cores</th>
<th>Significant Preoperative Variables Predictive of Tumor Volume</th>
</tr>
</thead>
<tbody>
<tr>
<td>Terris et al.</td>
<td>124</td>
<td>6</td>
<td>≤3 mm of cancer in needle biopsy specimen associated with small (0.5 cm³) tumors (r = 0.54), percentage of carcinoma in biopsy predicted percentage of carcinoma in radical prostatectomy with low R² = 0.22</td>
</tr>
<tr>
<td>Thomassen et al.</td>
<td>32</td>
<td>Not given</td>
<td>Percentage of carcinoma in biopsy tissue correlated with tumor volume (R = 0.79)</td>
</tr>
<tr>
<td>Häggen et al.</td>
<td>60</td>
<td>10</td>
<td>≤3 mm of carcinoma in needle biopsy specimen associated with small (≤0.5 cm³) tumors</td>
</tr>
<tr>
<td>Irwin and Trapasso</td>
<td>Not given</td>
<td>Not given</td>
<td>Percentage of carcinoma in biopsy tissue correlated with tumor volume (R = 0.79)</td>
</tr>
<tr>
<td>Terris et al.</td>
<td>124</td>
<td>6</td>
<td>Total length of cancer (mm; Pearson r = 0.55), No. of positive biopsy specimens (r = 0.54), and percentage of carcinoma (r = 0.47) roughly equivalent in prediction of volume</td>
</tr>
<tr>
<td>Loch et al.</td>
<td>65</td>
<td>6</td>
<td>Core cancer length sum in millimeters predicted volume of largest cancer (r = 0.65; P &lt; .0001)</td>
</tr>
<tr>
<td>Humphrey et al.</td>
<td>50</td>
<td>4</td>
<td>No. of positive cores (r = 0.670), percentage of positive cores (r = 0.636), percentage of carcinoma (r = 0.619), and millimeters of total carcinoma (r = 0.518) in needle biopsy tissue all significant (P &lt; .001), in descending order, to &quot;dominant&quot; tumor volume</td>
</tr>
<tr>
<td>Cupp et al.</td>
<td>130</td>
<td>6</td>
<td>Percentage of carcinoma, percentage of positive cores, and millimeters in cancer needle core tissue nearly equivalent in predicting total cancer volume</td>
</tr>
<tr>
<td>Dietrick et al.</td>
<td>110</td>
<td>6</td>
<td>&gt;3 mm of cancer predicted volume of &gt;0.5 cm³</td>
</tr>
<tr>
<td>Peller et al.</td>
<td>102</td>
<td>6</td>
<td>Increasing No. of cores positive correlated with increasing tumor volume</td>
</tr>
<tr>
<td>Egawa et al.</td>
<td>26</td>
<td>6</td>
<td>No. of positive cores (r = 0.79), sum of biopsy tumor lengths (r = 0.74), percentage of tumor (r = 0.65-0.73), sum of biopsy tumor area (r = 0.65), and maximum biopsy core length (r = 0.61) significantly related, in descending order, to &quot;dominant&quot; tumor volume</td>
</tr>
<tr>
<td>Egawa et al.</td>
<td>80</td>
<td>6-10</td>
<td>Total cancer length correlated better with tumor volume using 10 (Pearson r = 0.56) vs 6 cores (Pearson r = 0.39)</td>
</tr>
<tr>
<td>Arcangeli et al.</td>
<td>108</td>
<td>6</td>
<td>Percentage of carcinoma (Pearson r = 0.46) and percentage of positive cores (Pearson r = 0.41) correlated with total tumor volume in a screening population</td>
</tr>
<tr>
<td>Sebo et al.</td>
<td>207</td>
<td>6</td>
<td>Percentage of positive cores (Spearman r = 0.52) and percentage of carcinoma (Pearson r = 0.52) significant in univariate and multivariate analyses</td>
</tr>
<tr>
<td>Noguchi et al.</td>
<td>222</td>
<td>6</td>
<td>Total millimeters in length of cancer (Pearson r = 0.261), No. of positive biopsy specimens (Pearson r = 0.195), and percentage of positive biopsy specimens (Pearson r = 0.171) significantly related, in descending order, to largest cancer volume; only total length significant in multivariate analysis</td>
</tr>
<tr>
<td>Rubin et al.</td>
<td>101</td>
<td>Not given</td>
<td>Tumor area (cm²) showed weak (r² = 0.05) but significant (P = .02) correlation with tumor volume</td>
</tr>
<tr>
<td>Sebo et al.</td>
<td>454</td>
<td>6</td>
<td>Percentage of cores positive and percentage of surface with carcinoma significantly correlated with tumor volume</td>
</tr>
<tr>
<td>Present study</td>
<td>100</td>
<td>6</td>
<td>Total tumor length (mm; P = .001) and No. of positive cores (P = 4 × 10⁻⁵) significantly associated with total tumor volume in multivariate analysis</td>
</tr>
</tbody>
</table>

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Table 4

<table>
<thead>
<tr>
<th>Organization</th>
<th>Recommendation</th>
</tr>
</thead>
<tbody>
<tr>
<td>College of American Pathologists</td>
<td>“In core biopsies, the absolute number or percentage of cores involved, the linear extent of involvement in millimeters, and the proportion (percent) of surface area of prostatic tissue involved may be used.”</td>
</tr>
<tr>
<td>Association of Directors of Anatomic and Surgical Pathology</td>
<td>Under “Optional pathologic features that can be included if desired”: “Report the amount of tumor in millimeters along with a measurement of the length of each core(s) involved”</td>
</tr>
<tr>
<td>World Health Organization</td>
<td>“The Committee recommends that pathologists include the total percent of cancer in the total number of needle biopsy segments”</td>
</tr>
</tbody>
</table>

From the 1Lauren V. Ackerman Laboratory of Surgical Pathology, Washington University School of Medicine, St Louis, MO; and 2Laboratory Medicine, Veterans Administration and Duke University Medical Centers, Durham, NC.

References


Address reprint requests to Dr Humphrey: Dept of Pathology and Immunology, Washington University School of Medicine, 660 S Euclid Ave, Campus Box 8118, St Louis, MO 63110.


53. True LD, Wallner K. Why linear extent, not percent, of cancer should be used to measure cancer in needle biopsies [abstract]. Mod Pathol. 2002;15:184A.


