Predicting Tumor Volume in Radical Prostatectomy Specimens From Patients With Prostate Cancer

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Abstract

Tumor volume has prognostic value in numerous malignant neoplasms; however, the determination of tumor volume in prostatic adenocarcinoma remains problematic. We tested the hypothesis that the diameter of the largest focus of carcinoma in whole-mount prostate sections predicts the volume of adenocarcinoma in the entire prostate. We evaluated 184 radical prostatectomy specimens by whole-mount processing of the entire prostate. The maximum diameter of the largest focus of carcinoma was measured directly on glass slides. Tumor volume in the entire prostate was calculated by the grid method. The maximum tumor diameter ranged from 0.1 to 4.1 cm (median, 1.6 cm). The total tumor volume ranged from 0.1 to 12.5 cm³ (median, 1.6 cm³). There were significant correlations between maximum tumor diameter and tumor volume (Spearman correlation coefficient = 0.84; \( P < .0001 \)), surgical margin status (\( P < .001 \)), perineural invasion (\( P < .001 \)), serum prostate-specific antigen level at diagnosis (\( P = .004 \)), Gleason score (\( P = .004 \)), and pathologic stage (\( P < .0001 \)). Maximum tumor diameter is a predictor of tumor volume and might be useful for the assessment of tumor volume in routinely processed prostatectomy specimens.

During recent decades, our understanding of the natural history of prostate carcinoma has expanded rapidly. Tumor volume has emerged as a significant and valuable prognostic factor.¹ Quantitative assessment of the extent of prostatic adenocarcinoma has been problematic because gross identification of prostatic carcinoma is subtle and may be difficult,² and the cancers often are multifocal.³,⁴ Inclusion of tumor size in radical prostatectomy specimens in surgical pathology reports has been suggested,⁵,⁶ but the exact method for reporting has not been standardized. The Association of Directors of Anatomic and Surgical Pathology recommends that the percentage of the prostate involved by carcinoma in relation to the weight of the specimen be reported for radical prostatectomy specimens.⁷

Multiple techniques have been used to assess tumor size, including visual inspection with the pathologist’s percentage estimate,⁸,⁹ the number of blocks involved by tumor,¹⁰ the diameter of the largest tumor focus,⁸,¹⁰,¹¹ the maximal area of the tumor,¹¹ grid morphometric analysis,¹² 3-dimensional estimate,¹³ and computer-assisted image analysis.¹⁴-¹⁷ The latter methods, while accurate, are time consuming and expensive. Renshaw et al¹¹ noted that the simple measurement of the maximum diameter of the largest tumor focus can stratify prostatic adenocarcinoma in radical prostatectomy specimens based on size. Maximum dimension of the largest tumor focus was particularly useful for identifying very small tumors (<0.5 cm³) or large tumors (>2 cm³).¹¹ In the present study, radical prostatectomy specimens were analyzed by whole-mount processing to determine whether the maximum diameter of the largest focus of tumor correlated with total tumor volume and other known prognostic factors.
Materials and Methods

The study group consisted of 184 consecutive patients treated by radical retropubic prostatectomy with or without bilateral pelvic lymphadenectomy between April 1999 and July 2001 at Indiana University Hospital, Indianapolis. Patients who received preoperative androgen-deprivation therapy were excluded.

Serum prostate-specific antigen (PSA) levels were measured using the Immulite PSA assay (Diagnostics Products, Los Angeles, CA). The research was approved by the Indiana University Institutional Review Board.

The radical prostatectomy specimens were examined as previously described.18-21 Prostates were weighed, measured, inked, and fixed in 10% neutral formalin. Following fixation, the apex and base were amputated and serially sectioned at 3- to 5-mm intervals in the vertical, parasagittal plane. The seminal vesicles were sectioned parallel to their junction with the prostate and entirely submitted for examination. The remaining prostate was sectioned serially, perpendicular to the long axis from the apex of the prostate to the base, and whole-mount sections were prepared.

The greatest diameter of the largest single focus of tumor was obtained by marking both ends of the tumor on the glass slide and measuring this distance with a ruler marked in millimeters. If the tumor size was less than 0.5 cm, an ocular micrometer was used. The volume of carcinoma in the entire prostate was determined by using the grid method12,18,19,22-24 and was the sum of the volumes of individual foci of tumor. In this method, the sum of each area was multiplied by the thickness of the average slice, and the sum of these volumes was multiplied by a factor of 1.25 to account for tissue shrinkage during processing.22,23 All cancers were graded according to the Gleason system.25,26 The 1997 TNM (tumor, nodes, metastasis) system was used for pathologic staging.27

Polynomial regression predicting maximum tumor diameter (mm) with tumor volume (cm3) was performed. The Spearman coefficient of rank correlation was calculated for maximum tumor diameter with all continuous variables (tumor volume, Gleason score, and preoperative PSA level). Logistic regression was used to predict tumor at surgical margins and perineural invasion with either tumor volume (cm3) or maximal tumor dimension (cm) while controlling for TNM pathologic stage. Because of the small frequencies, stages T2a and T2b were combined, and stages T3a and T3b were combined for analysis purposes. Therefore, a categorical variable for TNM stage with 2 categories was used as an independent variable in the logistic model. P values less than .05 were considered statistically significant.

Results

We examined 184 radical prostatectomy specimens from patients ranging in age from 41 to 76 years (mean, 60 years; median, 60 years). Table II summarizes the patient and tumor characteristics, stratified by the overall median maximum tumor diameter of 1.6 cm. Preoperative PSA levels ranged from 0.28 to 44.0 ng/mL (median, 6.3 ng/mL). Gleason scores ranged from 5 to 9 (median, 7). Final pathologic T classifications were pT2a (25 cases [13.6%]), pT2b (115 cases [62.5%]), pT3a (39 cases [21.2%]), and pT3b (5 cases [2.7%]). Surgical margins were positive in 51 tumors (27.7%). The maximum tumor diameter ranged from 0.1 to 4.1 cm (median, 1.6 cm). The tumor volume ranged from 0.1 to 12.5 cm3 (median, 1.6 cm3). Stratification of tumor volume is shown in Table II.

The relationship between the maximum tumor diameter and total tumor volume is shown in Figure II. There was a significant correlation between maximum tumor diameter and tumor volume (Spearman correlation coefficient = 0.84; P < .0001). The coefficient of determination, R2, for the polynomial regression model was 0.68. The median of maximum tumor diameter was 1.6 cm in the entire study group. In 12 cases, the maximum tumor diameter was 1.6 cm. Of the 103 cases with a maximum tumor diameter of 1.6 cm or less, 31 (30.1%) had a tumor volume of 0.5 cm3 or less, 53 (51.4%) had a tumor volume of 1.0 cm3 or less, 91 (88.3%) had a tumor volume of 5.0 cm3 or less, and 1 (1.0%) had a tumor volume of more than 5.0 cm3. Of the 81 cases with a maximum tumor diameter of more than 1.6 cm, 0 (0%) had a tumor volume of 0.5 cm3 or less, 2 (2%) had a tumor volume of 1.0 cm3 or less, 22 (27%) had a tumor volume of 5.0 cm3 or less, and 33 (41%) had a tumor volume of more than 5.0 cm3. Of the 81 cases with a maximum tumor diameter of more than 1.6 cm, 0 (0%) had a tumor volume of 0.5 cm3 or less, 2 (2%) had a tumor volume of 1.0 cm3 or less, 22 (27%) had a tumor volume of 5.0 cm3 or less, and 33 (41%) had a tumor volume of more than 5.0 cm3. In addition, 25 (76%) of 33 tumors with a maximum tumor diameter of less than 1.0 cm had a tumor volume of 0.5 cm3 or less. Of 52 tumors with a maximum tumor diameter more than 2.0 cm, 37 (71%) had a tumor volume of more than 3.0 cm3.
Maximum tumor diameter correlated with surgical margin status. Of the 103 cases with a maximum tumor diameter of 1.6 cm or less, 91 (88.3%) had negative surgical margins, and 12 (11.7%) had positive surgical margins. Of the 81 patients with a maximum tumor diameter of more than 1.6 cm, 42 (52%) had negative surgical margins, and 39 (48%) had positive surgical margins. Surgical margins were positive in 0 (0%) of 12 cases with a tumor volume of 0.5 cm³ or less, 2 (8%) of 26 with a tumor volume 0.5 to 1.0 cm³, 10 (15%) of 65 with a tumor volume of more than 1.0 up to 1.6 cm³, 11 (38%) of 29 with a tumor volume of more than 1.6 up to 2.0 cm³, 18 (47%) of 38 with a tumor volume of more than 2.0 up to 3.0 cm³, and 10 (71%) of 14 with a tumor volume of more than 3.0 cm³.

Maximum tumor diameter is predictive of surgical margin status ($P = .0002$) while controlling for pathologic stage. **Table 5** summarizes the results of the logistic regression model predicting surgical margin status using tumor size and controlling for stage. The Max-rescaled $R^2$ was 0.31 using maximum tumor diameter and 0.36 using tumor volume. Both tumor volume and maximum tumor diameter were highly predictive of surgical margin status.

The maximum tumor diameter correlated with PSA level at diagnosis ($r = 0.22; P = .004$) and Gleason score ($r = 0.21; P = .004$) but not with patient age ($r = –0.08; P = .30$). The maximum tumor diameter also was associated with pathologic stage ($P < .0001$) and perineural invasion ($P < .0001$; Table 3). Perineural invasion was present in 71 (88%) of the 81 cases with a maximum tumor diameter of more than 1.6 cm.

**Discussion**

Our study of 184 totally embedded, serially sectioned, whole-mount prostatectomy specimens indicates that the maximum tumor diameter of the largest focus of carcinoma correlates with tumor volume, as well as with surgical margin status, perineural invasion, preoperative PSA level, Gleason score, and pathologic stage. A maximum tumor diameter of 1.6 cm or less strongly correlates with a tumor volume of less than 3 cm³. Maximum tumor diameter was a significant predictor of larger tumor volume (>5 cm³), whereas the majority of tumors with maximum tumor diameters of less than 1 cm had tumor volumes of 1.0 cm³ or less. Tumor volume has been shown to be an important prognostic indicator for prostatic carcinoma. Bostwick et al proposed a volume-based prognostic index as an adjunct to staging for prostate cancer, with intraprostatic tumor volume stratified as less than 1 cm³, 1 to 5 cm³, and more than 5 cm³. These authors found that progression from capsular
Invasion to seminal vesicle invasion and finally metastasis was linked to increasing tumor volume. Stamey et al. showed that in 34 patients with tumor volumes less than 3.0 cm³, none had pelvic lymph node metastases, while 6 of 34 patients with tumors greater than 3.0 cm³ had metastases. In a more recent series, more than 85% of patients with tumor volumes less than 2 cm³ remained free of cancer, while in 85% of patients with tumor volumes of more than 7 cm³, the tumor progressed. McNeal and Haillot related the pattern of spread of adenocarcinoma to tumor volume, noting that peripheral zone and transition zone tumors smaller than 4 cm³ in volume remained confined to their zone of origin, but that bilateral spread is more frequent in tumors more than 4 cm³. Others have noted that tumors with volumes less than 0.5 or 1 cm³ rarely progress.

Inclusion of information about prostatic tumor size or extent in surgical pathology reports is recommended. Multiple methods have been used to measure the sizes of prostatic carcinomas. There is, however, currently no widely accepted method for quantitation of cancer volume in radical prostatectomy specimens or for the reporting of tumor size in surgical pathology reports. Given the variety of methods now used to estimate tumor size in radical prostatectomy specimens at numerous institutions, a multicenter collaborative study is needed to determine which of these methods provides the most significant prognostic information, controlling for other prognostic factors such as tumor stage, preoperative PSA concentrations, Gleason score, and surgical margin status.

Maximum tumor diameter has recently been suggested as a fast, easy, and objective method of stratifying the sizes of prostatic carcinomas in radical prostatectomy specimens. Renshaw et al. demonstrated that measurements of the maximum diameter of the largest focus of tumor, the largest single tumor area, and the sum of the areas of 2 separate tumor foci correlated with tumor volume. Maximum tumor diameter was most useful for tumor volumes less than 0.5 cm³ and greater than 2.0 cm³. In further studies, Renshaw et al. found that maximum tumor diameter was a predictor of PSA failure and, in a pilot study, demonstrated that maximum tumor diameter was as effective in this prediction as the greatest tumor area or sum of the 2 greatest areas.

Other estimates of tumor size also have been used, including percentage of carcinoma and area of the largest tumor focus. Noguchi et al. evaluated morphometric techniques for determining prostate carcinoma volume and found that tumor area was more accurate than a single maximum tumor diameter measurement. These methods, however, have disadvantages, such as requiring knowledge of specimen processing for assessment of the percentage of carcinoma and making an additional measurement for tumor area. Nevertheless, we recognize that tumor shape varies; hence, a tumor with a larger single maximum tumor diameter might be confined in the remaining 2 dimensions, still yielding a small tumor volume.

Our findings indicate a significant correlation between maximum tumor diameter and tumor volume, with a Spearman correlation coefficient of 0.84 (P < .0001). Our results of regression predicting maximum tumor diameter using tumor volume as the independent variable yielded similar results to those published by Renshaw et al., in which maximum tumor diameter = 7.769 + 5.405x – 0.386x². Renshaw et al. noted increasing correlation of

### Table 3
Correlation of Maximum Tumor Diameter and Pathologic Stage, Surgical Margins, and Perineural Invasion

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Cases</th>
<th>Maximum Tumor Diameter</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pathologic stage†</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>T2a</td>
<td>25</td>
<td>1.0</td>
<td>0.5</td>
</tr>
<tr>
<td>T2b</td>
<td>115</td>
<td>1.5</td>
<td>0.6</td>
</tr>
<tr>
<td>T3a</td>
<td>39</td>
<td>2.4</td>
<td>0.8</td>
</tr>
<tr>
<td>T3b</td>
<td>5</td>
<td>2.8</td>
<td>0.5</td>
</tr>
<tr>
<td>Surgical margins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>133</td>
<td>1.5</td>
<td>0.7</td>
</tr>
<tr>
<td>Positive</td>
<td>51</td>
<td>2.2</td>
<td>0.7</td>
</tr>
<tr>
<td>Perineural invasion</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>55</td>
<td>1.2</td>
<td>0.6</td>
</tr>
<tr>
<td>Positive</td>
<td>129</td>
<td>1.9</td>
<td>0.8</td>
</tr>
</tbody>
</table>

* Kruskal-Wallis or Wilcoxon rank sum test.
† The 1997 TNM staging system was used.

### Table 4
Relationship Between Surgical Margin Status and Tumor Size

<table>
<thead>
<tr>
<th>Variable</th>
<th>No. of Cases</th>
<th>Mean</th>
<th>SD</th>
<th>Median</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor volume (cm³)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive surgical margins</td>
<td>51</td>
<td>4.33</td>
<td>3.30</td>
<td>3.16</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Negative surgical margins</td>
<td>133</td>
<td>1.58</td>
<td>1.36</td>
<td>1.20</td>
<td></td>
</tr>
<tr>
<td>Maximum tumor diameter (cm)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Positive surgical margins</td>
<td>51</td>
<td>2.25</td>
<td>0.72</td>
<td>2.10</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>Negative surgical margins</td>
<td>133</td>
<td>1.46</td>
<td>0.72</td>
<td>1.40</td>
<td></td>
</tr>
</tbody>
</table>

* Wilcoxon rank sum test.
tumor volume with the largest single tumor area, the sum of the largest dimensions of 2 separate tumor foci, and the sum of the 2 largest areas. In addition, Carvalhal et al\textsuperscript{37} noted an 11\% increase in the chance of tumor recurrence for each 5\% increase in the percentage of carcinoma assessed through visual estimate. We did not analyze these tumor measurements in the present study.

In contrast with previous studies of the value of maximum tumor diameter, our study evaluated totally embedded, serially sectioned, whole-mount prostatectomy specimens that were processed uniformly. The majority of prostates in our study contained multifocal tumor, in accord with the findings of others.\textsuperscript{4} The use of whole-mount processing eliminates the need for multiple blocks and slides per cross-section. Thus, areas of contiguous tumor within a cross-section that could be confused as separate foci on routinely processed slides were recognized readily as a single focus in our study. This may explain the increased correlation of maximum tumor diameter with tumor volume in our study compared with findings in previous studies.

Nevertheless, whole-mount processing is not necessary to accurately measure the maximum tumor diameter. Even with routinely processed sections, one can organize them and mentally piece them together to determine whether 2 separate areas on 2 separate slides represent the same tumor nodule or distinct tumors. Maintaining cross-sectional orientation to measure a maximum tumor diameter encompassing multiple routine slides, however, would be more challenging than working with whole-mount specimens.

The excellent correlation between the maximum tumor diameter and total tumor volume in our study indicates that the tumor volume can be estimated by measuring maximum tumor diameter from routinely processed radical prostatectomy specimens in daily practice. The majority of patients with maximum tumor diameter of less than 1 cm have small volumes of carcinoma that is unlikely to progress, whereas a significant proportion of patients with tumor length of more than 1.6 cm had a tumor volume of more than 3 cm\textsuperscript{3}. While maximum tumor diameter and tumor volume correlated tightly in the smaller tumors, as the maximum tumor diameter increased, a greater variation in tumor volume was noted.

We have shown that measurement of the maximum tumor diameter of the largest focus of tumor in radical prostatectomy specimens correlates with total intraprostatic tumor volume. Maximum tumor diameter also correlates with other predictors of clinical outcome in prostate adenocarcinoma, including surgical margin status, preoperative PSA level, Gleason score, and pathologic stage. Maximum tumor diameter may be useful for estimating tumor volume in routinely processed radical prostatectomy specimens.

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![Figure 2](image.png) An increasing maximum tumor diameter was associated with a higher rate of positive surgical margins in radical prostatectomy specimens.

### Table 5
Logistic Regression Model for Predicting Positive Surgical Margins in 184 Radical Prostatectomy Specimens

<table>
<thead>
<tr>
<th>Variable</th>
<th>Estimate</th>
<th>SE</th>
<th>Odds Ratio</th>
<th>95% Confidence Interval</th>
<th>$\chi^2$</th>
<th>$P^*$</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tumor diameter\textsuperscript{†}</td>
<td>-3.192</td>
<td>0.537</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum tumor diameter (cm)</td>
<td>1.022</td>
<td>0.285</td>
<td>2.78</td>
<td>1.62-4.98</td>
<td>14.22</td>
<td>.0002</td>
</tr>
<tr>
<td>TNM stage 3 vs stage 2</td>
<td>1.242</td>
<td>0.437</td>
<td>3.46</td>
<td>1.47-8.21</td>
<td>7.97</td>
<td>.0047</td>
</tr>
<tr>
<td>Tumor volume\textsuperscript{‡}</td>
<td>-2.465</td>
<td>0.341</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Intercept</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tumor volume (cm\textsuperscript{3})</td>
<td>0.508</td>
<td>0.129</td>
<td>1.66</td>
<td>1.31-2.18</td>
<td>21.89</td>
<td>&lt;.0001</td>
</tr>
<tr>
<td>TNM stage 3 vs stage 2</td>
<td>0.808</td>
<td>0.477</td>
<td>2.24</td>
<td>0.87-5.68</td>
<td>2.78</td>
<td>.095</td>
</tr>
</tbody>
</table>

\textsuperscript{†} Overall model, $\chi^2 = 44.5$; Max-rescaled $R^2 = 0.31$. The 1997 TNM staging system was used for both models.\textsuperscript{27}

\textsuperscript{‡} Overall model, $\chi^2 = 52.1$; Max-rescaled $R^2 = 0.36$.  

\textsuperscript{*} $P < .0001$; likelihood ratio test.
References


