Findings in 12-Core Transrectal Ultrasound-Guided Prostate Needle Biopsy That Predict More Advanced Cancer at Prostatectomy

Analysis of 388 Biopsy-Prostatectomy Pairs

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Key Words: 12-Core prostate biopsy; Prostatectomy; Advanced stage

Abstract

We analyzed 5 features on 12-core transrectal ultrasound-guided prostate needle biopsy (TRUS) to predict the extent of cancer at radical prostatectomy (RP). In 388 TRUS-RP pairs, number of positive cores (NPC), percentage of each core involved (%PC), perineural invasion (PNI), Gleason score (GS), distribution of positive cores (DPC), and preoperative prostate-specific antigen (PSA) were correlated with extraprostatic extension (EPE), seminal vesicle invasion (SVI), positive surgical margin (R1), positive lymph nodes (N1), and tumor volume. All features predicted EPE and SVI. NPC, GS, %PC, and PNI strongly predicted R1 status. RP tumor volume was directly proportional to the NPC and %PC. PSA alone and with selected biopsy findings correlated with tumor volume, stage, SVI, and N1 (P < .0001). Contiguous DPC was a significant risk for EPE and SVI (P < .0001) compared with isolated positive cores. Findings at 12-core TRUS along with preoperative PSA reliably predict advanced local disease and have practical value as guides to effective planning for surgical resections.

Prostate-specific antigen (PSA) screening detects prostate cancer at lower stages with smaller tumor volume compared with cancer detected only by digital rectal examination.1 This trend has been associated with a progressive increase in a number of cores obtained at each biopsy event.2 A recent literature review by Chun et al3 concluded that the current optimal sample number for the initial prostate biopsy event should include no less than 10 cores. Repeat, extended saturation biopsy of up to 32 cores is indicated, the review continued, in younger men with negative initial biopsies and a persistent suspicion of having prostate cancer.3 For the initial biopsy, some institutions advocate 14-core needle biopsy sampling that includes 2 additional bilateral transitional zone biopsies to detect tumors in the anterior area of the prostate, along with the standard dozen biopsies to sample the rest of the gland.4,5 At our institution, most urologists currently use a 12-core transrectal ultrasound-guided prostate needle biopsy (TRUS) as the initial procedure for patients with an elevated serum PSA level and a digital rectal examination that fails to detect a “suspicious” nodule(s).

This study evaluated how well 12-core TRUS in conjunction with preoperative PSA level predicts the following 5 measures of advanced disease that can be demonstrated at radical prostatectomy: (1) extraprostatic extension (EPE), (2) tumor volume, (3) seminal vesicle invasion (SVI), (4) positive surgical margin (R1), and (5) metastasis to regional lymph nodes (N1). Previously published reports have addressed the predictive usefulness of similar biopsy features after the harvest of fewer cores per biopsy event.1,6-9 This article presents a comprehensive analysis of the features of 12-core TRUS, the most widely used initial biopsy in contemporary practice, that predict locally advanced disease at radical prostatectomy when
combined with the preoperative PSA level. Predicting more advanced disease at radical prostatectomy by biopsy findings in conjunction with preoperative PSA may influence a surgeon’s choice of approach to resection, intraoperative frozen section sampling, and extent of regional lymph node dissection.

**Materials and Methods**

With approval from our institutional review board, we reviewed prostate needle biopsy findings in consecutive patients who underwent 12-core TRUS and then radical prostatectomies at Henry Ford Hospital, Detroit, MI, from late 2004 through 2008. Cases with preoperative hormonal or radiation therapy were excluded from the study. A standard biopsy procedure sampled parasagittal midline and lateral apical, medial, and basal regions bilaterally for a total of 12 cores. The needle cores were submitted separately and individually for each biopsy site. Gleason score, percentage of the tissue involved by the tumor, and presence or absence of perineural invasion were reported for each core. We recorded a total percentage of cancer in each individual biopsy core, which was a percentage of a single focus of carcinoma or a sum of separate tumor foci percentages if sizable distance was seen between them. Preoperative PSA levels were classified into 3 categories: less than 4 ng/mL, 4 to 10 ng/mL, and more than 10 ng/mL. The biopsy data analyzed included the following: (1) number of positive cores, (2) percentage of tumor in each biopsy core, (3) presence of perineural invasion, (4) highest Gleason score, and (5) distribution of positive cores. We classified the distribution of positive cores into contiguous (ie, positive cores from adjacent sampling regions), discontiguous (ie, positive cores separated by region[s] with benign core), or mixed.

Three statistical parameters captured the information about the percentage of each core involved: the maximum percentage, the average percentage, and the coefficient of variation (CV) of tumor percentage (ie, SD over the mean) across the 12 cores for a given patient. A low CV was taken to indicate that the percentage of cores involved is more uniform. A high CV indicated greater variability in tumor involvement from one core to another.

Prostatectomy specimens were all submitted completely in macrocassettes that included both seminal vesicles. Apical and basal sections were cut perpendicular to the surgical margin and submitted entirely in conventional cassettes. Lymph nodes were also submitted entirely for histologic examination. Gleason grading of biopsy and prostatectomy tumor specimens and pathologic prostatectomy tumor staging were carried out according to the recommendations of the International Society of Urological Pathology consensus conferences held in 2005 and 2009, respectively. Invasion of the bladder neck by the tumor identified microscopically was classified as pathologic stage T3a. Tumor volume was assessed by mapping tumor in each slide, then assigning a percentage of the tumor to the slide. The percentages of tumor in all slides were summed and divided by the total number of the slides of prostate tissue to yield the overall tumor volume in percentages. The prostatectomy data included in the analysis were as follows: (1) tumor volume, (2) EPE, (3) positive surgical margin, (4) SVI, and (5) metastatic disease in the regional lymph nodes.

In the statistical analyses, continuous variables were categorized by quartiles or by median when associations with categorical variables were sought. Otherwise, the continuous scale was used. To assess the potential association between variables, statistics for contingency tables were calculated. If both variables were ordinal, the Mantel-Haenszel was used, and for 2 × 2 tables, the Fisher exact test. When both variables were continuous, the Pearson correlation coefficient was estimated as the measure of association. All calculations were performed using SAS for Windows, version 9.1 (SAS, Cary, NC), and a P value of less than .05 was considered significant.
Results

During the 4.5-year study period, among 3,379 radical prostatectomies performed at Vattikuti Urology Institute, Henry Ford Hospital, 388 biopsy-prostatectomy pairs satisfied inclusion criteria. The other 2,991 prostatectomy cases were excluded because biopsies were done in outside institutions or because biopsy procedures other than the 12-core TRUS were used. Among the 388 cases, robotic-assisted radical prostatectomy was performed in 378 (97.4%) and the remaining 10 operations (2.6%) were open retropubic prostatectomies. All surgeon-controlled robotic-assisted radical prostatectomies were performed according to the technique developed by Menon et al.16,17

The mean ± SD age of patients was 60.8 ± 7.4 years (range, 39-80 years). The mean ± SD preoperative PSA level was 6.4 ± 5.0 ng/mL (range, 0.5-50 ng/mL). The preoperative PSA fell into the following 3-part distribution: less than 4 ng/mL, 82 cases (21.1%); 4 to 10 ng/mL, 265 cases (68.3%); and more than 10 ng/mL, 41 cases (10.6%). Perineural invasion was seen on biopsy in 17.0% of all study cases (66/388). The mean ± SD prostate weight was 50.1 ± 19.6 g (range, 11-160 g). The mean ± SD percentage of tissue involved by tumor at radical prostatectomy was 16.1% ± 12.3% (range, 0%-70%). Microscopic bladder neck invasion was identified in 2 prostatectomy specimens that were staged as pT3a according to the current guidelines.13 Two cases had no residual carcinoma identified at prostatectomy. Both of these cases had one positive biopsy core involving Gleason score 3 + 3 cancer involving less than 5% of the core.

EPE (pT3a), SVI (pT3b), and Positive Surgical Margin (R1)

The number of positive cores, percentage of each core involved, perineural invasion, Gleason score, distribution of positive cores, and preoperative PSA level showed a statistically significant relationship with EPE and SVI (Table 1, Table 2, and Table 3) (Figure 1). For margins, the correlation was significant for 4 measures: the number of positive cores, highest Gleason score, percentage of tumor in each core as measured by the average \( (P = .02) \) or the CV \( (P = .0065) \), and perineural invasion (Tables 1 and 2). Predictive power of maximal core tumor percentage for margin status almost reached statistical significance \( (P = .058) \). The strengths of these associations were directly proportional with increasing level of disease severity documented at radical prostatectomy except for the CV of tumor percentage across the biopsy cores. For this measure, worse disease (EPE, SVI, and R1) was more likely when the CV was high, that is, worse disease correlated with more homogeneous tumor distribution across the biopsy cores. Distribution of positive cores at biopsy did not show significant correlation with margin status (Figure 1).

### Table 1

<table>
<thead>
<tr>
<th>No. of positive cores</th>
<th>EPE</th>
<th>SVI</th>
<th>R1</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>77</td>
<td>10 (13)</td>
<td>3 (4)</td>
</tr>
<tr>
<td>2</td>
<td>81</td>
<td>15 (19)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>3-4</td>
<td>104</td>
<td>31 (29.6)</td>
<td>8 (7.7)</td>
</tr>
<tr>
<td>5-6</td>
<td>77</td>
<td>25 (32)</td>
<td>11 (14)</td>
</tr>
<tr>
<td>7+</td>
<td>49</td>
<td>15 (31)</td>
<td>14 (29)</td>
</tr>
<tr>
<td>( P )</td>
<td>.0021</td>
<td>&lt;.0001</td>
<td>.0073</td>
</tr>
</tbody>
</table>

**Table 2**

<table>
<thead>
<tr>
<th>Presence of perineural invasion</th>
<th>No. of cases</th>
<th>EPE</th>
<th>SVI</th>
<th>R1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Absent</td>
<td>322</td>
<td>67 (20.8)</td>
<td>25 (7.8)</td>
<td>77 (23.9)</td>
</tr>
<tr>
<td>Present</td>
<td>66</td>
<td>29 (44)</td>
<td>13 (20)</td>
<td>29 (44)</td>
</tr>
</tbody>
</table>

### Table 3

<table>
<thead>
<tr>
<th>Preoperative PSA level, ng/mL</th>
<th>Tumor Volume &gt;15%</th>
<th>EPE</th>
<th>SVI</th>
<th>N1</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;4</td>
<td>16/80 (20)</td>
<td>12/80 (15)</td>
<td>2/80 (3)</td>
<td>0/62 (0)</td>
</tr>
<tr>
<td>4-10</td>
<td>93/265 (35.1)</td>
<td>75/265 (28.3)</td>
<td>20/265 (7.5)</td>
<td>5/215 (2.3)</td>
</tr>
<tr>
<td>&gt;10</td>
<td>26/41 (61)</td>
<td>9/41 (22)</td>
<td>15/41 (37)</td>
<td>5/40 (13)</td>
</tr>
</tbody>
</table>

EPE, extraprostatic extension; PSA, prostate-specific antigen; SVI, seminal vesicle invasion.

* Data are given as number (percentage) of cases.
\( \text{P} < .0002. \)
\( \text{P} = .1525. \)
\( \text{P} < .0001. \)
\( \text{P} < .0014. \)
Regarding core contiguity, the smallest likelihood for adverse outcomes was for isolated positive cores; the largest likelihood was for contiguous positive cores (Figure 1). Biopsy events that had mixed characteristics, ie, isolated and contiguous positive cores, predicted an intermediate likelihood for adverse disease at radical prostatectomy. Preoperative PSA levels also significantly \((P < .0001)\) predicted SVI (Table 3). In the prostatectomy specimens, statistically significant direct association \((P < .0001)\) was observed between pathologic tumor stage and tumor volume Table 4.

Tumor Volume

As shown in Table 5, the number of positive cores was directly proportional \((P < .0001)\) to tumor volume at radical prostatectomy. Analogous correlations were also seen between maximum \((P < .0001)\) and average \((P < .0001)\) core percentages with tumor volume at radical prostatectomy. Correspondingly, the CV of core percentage was inversely proportional to radical prostatectomy tumor volume \((P < .0001)\). The CV of core percentage was smaller as greater average and maximum core tumor percentages were seen in cases in which more positive cores were encountered. The preoperative PSA level was a significant predictor of tumor volume at radical prostatectomy (Table 5), but the combination of preoperative PSA level with the number of positive cores produced a better predictor of tumor volume at radical prostatectomy (Table 5). For a highest biopsy Gleason score of \(3 + 3\), the likelihood of high tumor volume (>15% of tissue in radical prostatectomy) was 20%. It doubled for Gleason scores of 7 to 8 and quadrupled for Gleason scores of 9 to 10.

Nodal Status

Bilateral pelvic lymph node dissection was performed in 81.7% of prostatectomies (317/388), with a 3.2% positive rate (10/317). Positive lymph nodes were more likely among cases with a high maximum percentage (>70%) or high average percentage (>14.2%) of tumor volume on biopsy cores Table 6. A preoperative PSA of more than 10 ng/mL determined a significantly increased likelihood of lymph node metastasis (Table 3). None of the patients with a preoperative PSA level of less than 4 ng/mL had lymph node metastasis. Positive lymph nodes were seen in cases with high tumor volume (mean ± SD, 27% ± 18%; range, 10%-65%); cases with lower volume tumors (mean ± SD, 17% ± 12%; range, 1%-70%) did not show lymph node metastasis. The difference between tumor volume associated with lymph node metastases reached statistical significance \((P = .015)\). Lymph node metastases were seen more frequently in cases with a high number of positive biopsy cores, but this observation was not significant (probably because of a low number of N1 cases). The majority of prostatectomy cases with positive lymph nodes (~80%) demonstrated Gleason 8+ disease, with only 2 cases with Gleason scores of 3 + 4 and 4 + 3.

In contrast, 12-core TRUS can also predict less advanced disease at prostatectomy. Cases with the least severe preoperative changes (eg, 1-2 positive biopsy cores with a Gleason score of \(3 + 3\) or \(3 + 4\), a low percentage of tumor on biopsy, discontinuous distribution of positive cores, absence of perineural invasion, and a PSA level <4 ng/mL) usually resulted in prostatectomy specimens with low-volume, organ-confined cancer; negative lymph nodes; and clear margins.
Table 6
Association of Positive Nodal Status (N1) With Maximum Percentage of Tumor and Average Percentage of Tumor per Core

<table>
<thead>
<tr>
<th>Tumor Volume</th>
<th>Cases With Positive Lymph Nodes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of each core (maximum)†</td>
<td></td>
</tr>
<tr>
<td>&lt;15</td>
<td>0/55 (0)</td>
</tr>
<tr>
<td>15-&lt;40</td>
<td>1/93 (1)</td>
</tr>
<tr>
<td>40-70</td>
<td>2/88 (2)</td>
</tr>
<tr>
<td>&gt;70</td>
<td>7/81 (9)</td>
</tr>
<tr>
<td>Percentage of each core (average)‡</td>
<td></td>
</tr>
<tr>
<td>&lt;2</td>
<td>0/54 (0)</td>
</tr>
<tr>
<td>2-&lt;6</td>
<td>0/86 (0)</td>
</tr>
<tr>
<td>6-14</td>
<td>3/84 (4)</td>
</tr>
<tr>
<td>&gt;14</td>
<td>7/93 (9)</td>
</tr>
</tbody>
</table>

* Data are given as number of cases/number of study group (percentage). The data demonstrate that risk of lymph node metastasis increases with higher percentage of tumor in any individual core and higher average percentage of tumor in all cores in 12-core transrectal ultrasound-guided prostate needle biopsy.

† P = .0025.
‡ P = .0023.

Discussion

High pathologic stage (pT3a and pT3b) and positive surgical margins are 2 proven independent risk factors for biochemical recurrence of prostate cancer in patients who undergo radical prostatectomy. An increasing number of positive cores increases the likelihood of higher stage disease and positive margins (Table 1). For 12-core TRUS, the likelihoods that these features will be found at prostatectomy are lowest for 1 or 2 positive cores and highest for 7 or more positive cores. The likelihood lies between these 2 extremes when 3 to 6 biopsy cores are positive.

The percentage of tumor across cores, as measured by 3 statistics (maximum percentage, average percentage, and CV of tumor across the cores), also predicts EPE, SVI, and positive margin status. This is particularly true for the maximum and average percentage statistics. We suggest the maximum percentage as the most convenient index to predict locally advanced disease because it is readily available in the reports and, unlike the average percentage, does not require additional calculations. For CV, a correlative downward trend was observed; the association of lower CV with higher predictive ability highlights the relation in which less tumor volume variability across the cores in a given case indicates that worse disease will be documented at radical prostatectomy.

The associations between tumor burden at biopsy and stage and margin status of prostatectomy have been reported in previous series that deployed fewer biopsy events and a smaller number of cores obtained per event. Compared with the correlation provided by sampling techniques that collected few samples, the sampling protocol used in this study, 12-core TRUS, allowed better correlation between the number and percentage of positive biopsy cores and pathologic tumor stage. A historical factor that confounds this comparison is the temporal sequence in which the 12-core TRUS was introduced after PSA screening while the older 6-core TRUS had been introduced in the pre-PSA screening era. The sampling techniques were thus applied to patient populations with different pretest probabilities of advanced local disease. As discussed earlier, the number of positive cores at biopsy is also a significant predictor of tumor volume at radical prostatectomy. In this context, the number of positive cores is the common risk factor for pathologic stage and tumor volume. This variable predicts the correlation seen between these features in resection specimens (Table 4).

Other studies have found that a high biopsy Gleason score predicts adverse outcomes at radical prostatectomy. In this study, the Gleason score remained a powerful predictor as reflected by stage and margin status at radical prostatectomy. When Gleason scores rise from 3 + 3 = 6 to 8+, the incidence of positive resection margins and pT3a doubles and triples, respectively. The frequency of SVI also increased, by more than 10 times, from a Gleason score of 6 to a score of 8+.

Perineural invasion demonstrated in biopsy cores significantly increases the likelihood of EPE, SVI, and positive margins (Table 2). Such correlation between perineural invasion on biopsy and finding EPE at resection has been well documented previously. In 2 studies, the strength of this association decreased in parallel with the detection of lower stage, lower volume tumors, and an overall decrease in disease with EPE at prostatectomy. Our study suggests that increased biopsy sampling counters this trend. The association of the perineural invasion on biopsy with positive surgical margins has been more controversial.

In this study, cases with perineural invasion on biopsy had a rate of positive surgical margins almost twice the rate in cases without this biopsy finding.

Finding adjacent positive cores on biopsy emerged from our correlations as a convenient, powerful predictor of locally advanced disease at radical prostatectomy. The smallest probabilities for EPE and SVI were seen with isolated positive cores, usually in cases with 1 to 3 positive cores. Intermediate likelihoods were found in cases in which contiguous and isolated positive cores were identified. The highest predictive probability was found in cases in which all positive cores were contiguous (Figure 1). This study seems to us to be the first report in the literature that has shown that contiguous distribution of positive biopsy cores predicts advanced local extension of cancer at radical prostatectomy. Despite the noted correlation between the distribution of positive cores with EPE and SVI, there was no statistically significant predictive power for a positive margin status. One would logically expect a higher incidence of positive surgical margin in cases with more frequent EPE (and we observed such a trend, Figure 1). However, our series has not reached a statistically significant
association between these findings because there was a subset of patients in whom a positive surgical margin was not seen in the area of EPE.

Surgeons may be able to use the finding of contiguous positive cores to anticipate the finding of extensive local disease at prostatectomy. Subsequent studies can now investigate whether laterality of contiguous positive cores can also predict the side of EPE and SVI. Such lateralizing preoperative information could also guide sampling for intraoperative frozen section consultation in efforts to avoid positive margins at radical resections. Also of interest is the question of whether the usefulness of demonstrating contiguousity of positive cores extends to biopsy events with fewer core samples. Decreasing the number of cores may increase distances between samples. These increased intercore distances, in turn, can increase uncertainty as to whether contiguous positive cores indicate multiple focal prostate cancers vs 1 large prostate tumor.

In this study, we were also able to associate biopsy findings and PSA level with pathologic stage and tumor volume in prostatectomy specimens. These specific connections add detail and precision to the strong fundamental association between the number of positive cores and tumor volume at radical prostatectomy.\textsuperscript{18,9,20-22} In particular, the number of positive cores and the maximum and average biopsy core percentage predict pathologic stage and tumor volume at radical prostatectomy. In relation to the correlation between percentage of tumor at biopsy cores with tumor volume at prostatectomy, we demonstrated a significant inverse predictive relationship between the CV of core tumor percentage and tumor volume at radical prostatectomy. High-volume tumors are usually made up of large dominant tumor nodule(s) that produce more uniform distributions of cancer throughout involved glands. This more even distribution of cancer leads biopsy cores obtained from different areas of the gland to have less variation in tumor percentage.

Finally, the ability of the number of positive cores to predict prostatectomy tumor volume may be improved by correlation with preoperative PSA levels. As shown in Table 5, there is a significant variation in predicted tumor volume for each number of positive biopsy cores when stratified PSA levels are included in the analysis. Roughly a 2 times increase in prostatectomy tumor volume for each number of positive biopsy cores was seen from the PSA category of less than 4 ng/mL to the category of more than 10 ng/mL. Together, stratified PSA level and number of positive biopsy cores make up a more detailed predictor of tumor volume than either of these measures alone (Table 5).

Despite recent advances in imaging techniques, pelvic lymph node dissection remains the most accurate staging procedure for the detection of lymph node metastasis.\textsuperscript{27} Preoperative planning decisions must balance staging benefits with the potential complications associated with pelvic lymphadenectomy.\textsuperscript{35} Recent reports have proposed criteria to identify patients requiring pelvic lymph node dissection.\textsuperscript{27,36,37} In addition to supporting the association of positive lymph node status with high Gleason score,\textsuperscript{38,39} our study linked high tumor volume with regional lymph node metastatic disease. However, probably because of the low number of cases with lymph node metastases, the association of the number of positive biopsy cores with lymph node metastasis was not statistically significant. McNeal\textsuperscript{40} reported the association of frequency of lymph node metastasis with greater tumor volume and higher percentage of high-grade cancer (Gleason scores 4 and 5). In our study, positive lymph node status correlated with a high Gleason biopsy score, high maximum and high average biopsy tumor percentages (Table 6), and high prostatectomy tumor volume. Briganti et al\textsuperscript{36} analyzed corresponding prostate biopsy specimens with 278 consecutive prostatectomy specimens that included lymph node dissection. These authors concluded that the percentage of positive cores and biopsy Gleason score are the 2 most informative predictors of positive lymph node status. Together they created a preoperative nomogram. This nomogram had an 83% accuracy for predicting lymph node status. The Briganti nomogram was recently validated by Heidenreich et al,\textsuperscript{41} who examined 499 biopsy-prostatectomy pairs and concluded that the percentage of positive cores was the most reliable predictor of lymph node metastases.

The 12-core TRUS is a powerful method of predicting locally advanced disease, including lymph node status at radical prostatectomy. The number of positive biopsy cores, highest biopsy Gleason score, percentage of tumor in each biopsy core, and perineural invasion in biopsy specimens are all strong predicting factors for EPE (pT3a), SVI (pT3b), positive surgical margin (R1), and metastatic disease in the regional lymph nodes (N1). As expected, a preoperative PSA level of more than 10 ng/mL significantly increases the likelihood of high tumor volume, pT3 stage, and lymph node metastasis. Together, stratified PSA level and number of positive cores produce a predictor of aggressive behavior more powerful than either of the 2 measures alone. Contiguity of positive cores may be an additional powerful and convenient predictor of local cancer extent and surgical margin status. Such predictors have practical value as guides to effective planning for surgical resections.

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