The accuracy of pathological data for the prediction of insignificant prostate cancer

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INTRODUCTION

The detection of patients with nonpalpable prostate cancer has increased since the advent of prostate-specific antigen (PSA) screening. Modified prostatic biopsy schemes have also contributed to higher detection rates (1). Many of these earlier, smaller cancers are low volume (< 0.5 cm³), low grade and clinically insignificant tumors. Approximately one third of patients with stage T1c cancer have potentially clinically insignificant tumors, and approximately 5% of radical prostatectomy (RP) patients have small cancers that are difficult to identify histologically (2).

Epstein et al. initially created a set of four criteria to predict insignificant prostate cancer prior to definitive therapy: PSA density 0.1–0.15, low or intermediate cancer grade, core involvement of less than 3 mm, and involvement of only one needle biopsy core. These criteria identified...
79% of tumors with a volume $\leq 0.5 \text{ cm}^3$ that were organ confined and did not qualify as high-grade lesions at the time of RP (3).

However, the Epstein criteria, which were later updated (4), are insufficient, and 20% of patients who fulfill these criteria may have unfavorable pathological cancer characteristics at RP (5). The validity of these criteria has been questioned. Jeldres et al. demonstrated that the Epstein criteria may not be applicable to European men because prostate cancer was underestimated in 24% of these patients (1).

The aim of this study was to assess the prediction of insignificant prostate cancer based on the biopsy findings of patients who underwent RP and exhibited insignificant cancer. The biopsy features from these subjects were evaluated, and patients whose biopsies had similar parameters were selected. The biopsies were correlated with the respective RP specimens to identify the lesion characteristics and the clinical significance of the tumor.

MATERIALS AND METHODS

A total of 592 patients underwent transrectal ultrasound-guided (TRUS) prostate biopsy followed by radical prostatectomy for prostate cancer from January 2001 to December 2010. A single surgeon (MS) treated all patients and a single uropathologist (KRML) examined all biopsies and surgical specimens. The surgical specimens were fixed in 10% buffered formalin, the entire surgical margin was stained with India ink, the left and right lobes were separated, 3 mm transverse serial sections were taken from each lobe, and the entire gland was submitted for histologic examination. Sections of the bladder neck, prostatic apex, seminal vesicles, and pelvic lymph nodes were also submitted to exam. The Gleason score (GS) was used for histologic grading (6). The tumor volume was evaluated as described by Humphrey et al. (7). Briefly, a grid was placed below the slides, on which the area involved by the tumor had been previously sketched out. The percentage of tumor on a slide was determined by dividing the number of squares involved by tumor by the number of squares occupied by the whole section on the slide. Tumor volume was defined as the mean percentage of tumor in the prostate gland (the percentage of tumor on each slide divided by the number of slides from the prostate gland). Extraprostatic involvement was defined as tumor infiltration of the adipose tissue, the neurovascular plexus, or the parenchyma of the seminal vesicles. The TNM 2010 system was used for tumor staging and patients were classified as pT2 when tumor was confined to the organ and pT3 when EPE or seminal vesicles were infiltrated by tumor. PM was considered when tumor glands were inked with India ink.

Twenty-two (3.7%) of the 592 patients exhibited insignificant tumor in their RP, which was defined as an organ-confined adenocarcinoma, Gleason score (GS) $\leq 6$ with no tertiary high grade Gleason pattern, and a tumor volume $\leq 0.5 \text{ cm}^3$ (Figure-1). The biopsies from these patients were analyzed, and twenty cases (91%) presented the following features: adenocarcinoma (GS) $\leq 6$, one to three positive cores that consisted of less than 50% tumor and a total percentage of positive fragments $\leq 10\%$. These features, which are similar to the Epstein criteria regarding pathological findings and are referred during the paper as “our criteria”, served as the parameters for the selection of patients with potentially insignificant prostate cancer. In order to evaluate the importance of pathological findings in defining these tumors, our criteria were purposely created based solely on the biopsy features and did not include PSA or any imaging method. These criteria were used to review the biopsy and radical prostatectomy results and define the sensitivity, specificity, and positive and negative predictive value of these parameters for the identification of insignificant prostate carcinoma in our population.

RESULTS

Twenty-two (3.7%) of the 592 patients exhibited clinically insignificant prostate cancer in their RP with a mean GS of 5.9 (range 5 to 6) and a tumor volume less than 0.5 cm$^3$ that was organ-confined. Twenty patients (91%) also had potentially insignificant prostate cancer in their biopsies. These biopsy features, which served as
our criteria mentioned above, exhibited a mean GS of 5.9 and mean positive cores of 6%. This group was considered real positive (Table-1). The remaining 2 patients (9%) had GS of 7 in the biopsy, 3 cores positive for tumor, a higher percentage of a single core (40% and 70%) and 4% and 6% positive cores (in 13 and 14 cores, respectively). We consider this group as false negative, since we would not expect them to have insignificant tumor in the RP. The RPs of additional patients who exhibited similar prostate biopsy characteristics of the real positive group were re-examined. A total of 149 patients (26%) had biopsies that met our criteria and were characterized as probable IPC.

The mean GS was also 5.9, the mean percentage of tumor in a single core was 23.3%, and the mean percentage of cores that were positive for tumor was 5.4% (range 1.5 to 10%), which represented one to two positive cores in a mean of 15 biopsies. However, their RPs revealed clinically significant carcinomas, including patients with pT3 disease (4.7%) as well as patients with intermediate and high grade tumor (56 patients with GS 7 and 16 with GS > 7). This group was considered false positive, which means they could have been considered as having IPC based on their biopsy features, despite having tumor with adverse pathological characteristics. The real negative group

* 22 patients had clinically insignificant prostate cancer; however, 2 patients had unfavorable features in their biopsy.
Table 1 - Comparison between biopsy and RP of the patients regarding clinical significance of the tumor.

<table>
<thead>
<tr>
<th>Number of patients (%)</th>
<th>Biopsy</th>
<th>Radical Prostatectomy 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>20 (3.4%)</td>
<td>insignificant</td>
<td>insignificant</td>
</tr>
<tr>
<td>149 (25.2%)</td>
<td>insignificant</td>
<td>significant</td>
</tr>
<tr>
<td>2 (0.34%)</td>
<td>significant</td>
<td>insignificant</td>
</tr>
<tr>
<td>421 (71.11%)</td>
<td>significant</td>
<td>significant</td>
</tr>
</tbody>
</table>

1 Gold Standard

was composed of 421 men whose biopsy and RP revealed significant prostate cancer. All patient data are detailed in Table-2.

The sensitivity of our criteria for the identification of clinically insignificant prostate cancer in RP was 91% with 74% specificity. The positive predictive value was only 12%, and the negative predictive value was 99.5%. Therefore, if our criteria were used to predict significant cancer, the probability of a patient exhibiting significant cancer would be almost certain at level of accuracy of 91.4%.

**DISCUSSION**

Several studies have questioned the efficacy of diagnosing limited cancer by needle biopsy, and the possibility of predicting tumor extent at RP based on biopsies. The applicability and validity of the criteria and nomograms that are commonly used to predict insignificant prostate cancer have also been discussed. The current study designed a set of novel criteria that were based on our own data and restricted to morphological aspects without the consideration of clinical stage or tumor markers. Although clinical findings, such as PSA level and PSA density, were not used, the features of the biopsies from patients with insignificant tumors at RP were similar to the biopsy criteria in the literature, such as a GS $\leq 6$ and limited tumor extent on biopsy. The current study does not propose criteria or models for the prediction of insignificant tumor. Conversely, this study clarified the use of precise morphological findings of prostate biopsy in the identification of insignificant prostate cancer.

Our data for the prediction of organ-confined tumors are consistent with the literature. Bastian et al. updated the Epstein criteria, which are the most widely used criteria for the prediction of clinically insignificant prostate cancer, and demonstrated concordance with pathologically organ-confined disease and a favorable grade (GS 6) in 83.9% of patients (4). Although 91.6% of these patients had organ-confined disease, 7.6% had a GS of 7 or higher.

The validity of the Epstein criteria has been questioned in European men. In a study that evaluated 366 patients who fulfilled the contemporary Epstein criteria demonstrated a similar rate of organ-confined disease (91.7%). But the percent of patients with a GS of 7 was substantially higher; 24% of patients had a GS of 7 at RP, which yielded lower overall accuracy (76% vs. 84%) (1). Unfortunately, these authors did not mention the number of patients with clinically insignificant tumor at RP. According to our criteria, 95.3% of the tumors were organ-confined, but 48.3% were GS $\geq 7$ (37.6% patients were GS 7 and 10.7% were GS 8 or 9), which is substantially higher than the reported rate in previous studies.

Jeldres et al. argued that the differences between biopsy and radical prostatectomy with respect to GS contributed to the observed error rate of the Epstein criteria (1). A potential upgrading of the GS occurs in 24.3% to 28.2% of patients (8,9). The grade assignment is also harder to predict because of the small amount of tumor that is analyzed on biopsy. High-grade prostate cancer is the most important predictor of prognosis (10).
Table 2 - Demographics and data from prostate biopsies and radical prostatectomies from 592 patients whose biopsy and surgical specimens were examined in our laboratory from January 2001 to December 2010.

<table>
<thead>
<tr>
<th>Insignificant biopsy and insignificant RP (N = 20)</th>
<th>Biopsy</th>
<th>Radical Prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>#cores</td>
<td>GS</td>
</tr>
<tr>
<td>Mean</td>
<td>60.4</td>
<td>16.6</td>
</tr>
<tr>
<td>Median</td>
<td>59.5</td>
<td>16.5</td>
</tr>
<tr>
<td>Min</td>
<td>39</td>
<td>7.5</td>
</tr>
<tr>
<td>Max</td>
<td>74</td>
<td>24</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Insignificant biopsy and significant RP (N = 149)</th>
<th>Biopsy</th>
<th>Radical Prostatectomy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>#cores</td>
<td>GS</td>
</tr>
<tr>
<td>Mean</td>
<td>59.5</td>
<td>15</td>
</tr>
<tr>
<td>Median</td>
<td>60</td>
<td>14</td>
</tr>
<tr>
<td>Min</td>
<td>39</td>
<td>6</td>
</tr>
<tr>
<td>Max</td>
<td>76</td>
<td>30</td>
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### Significant biopsy and insignificant RP (N = 2)

<table>
<thead>
<tr>
<th>Age</th>
<th>#cores</th>
<th>GS</th>
<th>#positive cores</th>
<th>%cores</th>
<th>Greatest%</th>
<th>PNI%</th>
<th>GS</th>
<th>Tumor volume (cm$^3$)</th>
<th>pT2(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>57</td>
<td>13.5</td>
<td>7</td>
<td>3</td>
<td>5.4</td>
<td>55</td>
<td>0</td>
<td>6</td>
<td>0.4</td>
</tr>
</tbody>
</table>

### Significant biopsy and significant RP (N = 421)

<table>
<thead>
<tr>
<th>Age</th>
<th>#cores</th>
<th>GS</th>
<th>#positive cores</th>
<th>%cores</th>
<th>Greatest%</th>
<th>PNI%</th>
<th>GS</th>
<th>Tumor volume (cm$^3$)</th>
<th>pT2(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean</td>
<td>61.3</td>
<td>14.3</td>
<td>7.1</td>
<td>5.1</td>
<td>8.5</td>
<td>66.3</td>
<td>22.6%</td>
<td>7.2</td>
<td>6.08</td>
</tr>
<tr>
<td>Median</td>
<td>61</td>
<td>14</td>
<td>7</td>
<td>4</td>
<td>7.5</td>
<td>70</td>
<td>7</td>
<td>5</td>
<td>5.00</td>
</tr>
<tr>
<td>Min</td>
<td>41</td>
<td>6</td>
<td>5</td>
<td>1</td>
<td>1.2</td>
<td>2</td>
<td>4</td>
<td>0.33</td>
<td></td>
</tr>
<tr>
<td>Max</td>
<td>79</td>
<td>30</td>
<td>10</td>
<td>18</td>
<td>33.3</td>
<td>100</td>
<td>10</td>
<td>29.0</td>
<td></td>
</tr>
</tbody>
</table>
even when the tumor is organ confined, and it is the most informative predictor of biochemical recurrence (11).

Epstein et al. created their criteria to predict insignificant tumor in patients with stage T1c, and it accurately predicted 73% of insignificant tumor (3). The current study predicted only 12% of the clinically insignificant tumors, but our samples were not limited to stage T1c patients. Despite this low positive predictive value, the negative predictive value was 99%, which indicated that ninety-nine percent of the tumors that were identified as significant and required active therapy were indeed significant tumors. This result addresses the concern of overdiagnosis, which occurs at a rate of approximately 56% (12,13).

The retrospective assessment of biopsies from patients with insignificant or significant tumors at RP revealed that all of the parameters that are usually used to estimate tumor extent, such as the number of positive cores, maximal involvement of a single core, and the percentage of positive cores, were similar in both groups. These results suggest an absence of rules for insignificant tumor behavior on needle biopsy.

Numerous difficulties exist in the use of prostatic needle biopsies to predict limited cancer at RP, and even the smallest cancer focus on a needle biopsy does not guarantee a clinically insignificant tumor. Small amounts of carcinoma (total linear extent less than 3 mm) do not predict insignificant tumors (14,15). Patients who are diagnosed based on a single focus less than 3 mm (GS ≤ 6) have only a 30% chance of harboring an insignificant tumor (16). Samaratunga et al. examined 58 patients with a single minute focus of a GS 6 on biopsy, and only 10 patients (17%) had insignificant tumor at RP (17). Forty-eight patients had significant tumor, 8 patients had extraprostatic extension and 32% of the patients had a GS > 6. These authors concluded that a minute focus of prostate cancer on a needle biopsy is not indicative of insignificant carcinoma in most cases. Interestingly, this study was performed without PSA screening. However, these authors demonstrated that a larger prostate size was significantly correlated with potentially insignificant cancer. These patients likely presented earlier for PSA testing because of symptoms, and an elevated PSA level due to the benign enlargement might lead to biopsies at an earlier stage. Cupp et al. demonstrated only an 8% risk of insignificant cancer using tumor volume at biopsy (14), which is similar to our results. The percentage of tumor extension in millimeters relative to the total extension of all of the cores was 5% and a GS less than 7.

In contrast, Allan et al. evaluated 54 PSA-screened patients with limited adenocarcinoma (< 0.5 mm) on biopsy; the majority of these patients exhibited potentially insignificant cancer, but only one-third warranted definitive therapy (2). Potentially clinically insignificant tumors were present in 67% of the patients in this study, and 44% of these patients had small tumors at RP (less than 0.1 cc). These authors also reported that a PSA density cutoff of 0.15 or less was correlated with clinically insignificant tumor, and the association of these criteria with limited cancer on biopsy predicted patients with insignificant tumors with a greater than 80% accuracy.

The Epstein criteria are not perfectly accurate, but no alternatives for prediction of clinically insignificant prostate cancer are available (1). Kattan et al. derived several nomograms for the prediction of pathologically confirmed insignificant prostate cancer with an accuracy of 64 to 79% (18). However, this series included 13 to 20% of Gleason patterns of 2 as part of the GS, which is much lower than the GS consensus from 2005. Nakanishi et al. improved the accuracy of the existing tools to 73%, especially in patients with a single positive core at biopsy (19).

Chun et al. developed a nomogram to predict the probability of insignificant prostate cancer in a cohort of 1132 men and revealed a predictive accuracy of 90% (5). However, a strikingly important proportion of patients who were qualified with a high probability of insignificant tumor using the Chun et al. nomogram (63%) and the Kattan et al. nomogram (45%) harbored aggressive prostate cancer at RP. Chun et al. concluded that the nomogram studies were similar to the original Epstein et al. criteria in their ability to predict pathologically confirmed insignificant prostate cancer. Clinicians may expect a 80% accuracy when organ-confined prostate cancer is predicted.
or a 76 to 79% accuracy when pathologically confirmed insignificant prostate cancer is predicted.

Do these data suggest that a significant number of patients might be left undertreated? Is active surveillance a dangerous choice that could jeopardize the curability of prostate cancer in some men? The answer to these questions appears to be no.

A review of active surveillance revealed that the majority of patients stay on active surveillance, and once a patient requires active treatment, that patient presents with curable prostate cancer (12). The detection of prostate cancer progression in a patient who is selected for active surveillance remains a continuing challenge, and the PSA level remains important during the decision process. The progression of Gleason grade and the increased percentage of cancers per core are also indicators for the cessation of active surveillance.

Duffield et al. have also studied the RP findings of patients in whom active surveillance has failed (13). These authors relied solely on subsequent biopsy pathology to determine progression, and more extensive disease was observed in surveillance biopsies during the first 2 years of follow-up in the majority of cases.

Despite their high accuracy rates, currently available models for the prediction of insignificant prostate cancer are incorrect in 10 to 20% of cases. The addition of novel markers is required, and current imaging techniques, such as multiparametric magnetic resonance, may have a potential role.

Tumor location is problematic for sampling adequately. Anterior tumors are difficult to assess and sample clinically, and the amount of these tumors in biopsies is lower than the amount of tumor from equivalently sized posterior tumors (20,21). These tumors appeared smaller on biopsy, but they were also undersampled. Takashima et al. analyzed the anatomical patterns of disease distribution in nonpalpable tumors and demonstrated that these tumors were localized predominantly in the anterior half of the prostate at the apical to midprostate level (21). These authors suggested that additional cores from the anterior apical site could enhance the detection rate of prostate cancer. Miyake et al. evaluated the significance of additional cores in the dorsal apex and demonstrated a significant increase (9.3%) in the cancer detection rate, particularly for early stage disease (22).

In conclusion, we have shown that the biopsy data exclusively are accurate to diagnose IPC, and pathologist should suggest this possibility in their reports helping urologists, oncologists and radiotherapists to choose the better treatment for each patient.

CONFLICT OF INTEREST

None declared.

REFERENCES


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