Multiple Repeat Prostate Biopsies and the Detection of Clinically Insignificant Cancer in Men With Large Prostates

Eugene J. Pietzak, Matthew J. Resnick, Philip Mucksavage, Keith Van Arsdalen, Alan J. Wein, S. Bruce Malkowicz, and Thomas J. Guzzo

OBJECTIVE To determine the impact of repeating prostate biopsies on the risk of detecting clinically insignificant prostate cancer (PCa) in larger prostate glands.

METHODS We performed a retrospective cohort study using patients enrolled in our institutional PCa registry from 1991 to 2008 to assess the association of prostate volume and clinically insignificant PCa in men undergoing multiple prostate biopsies. Patients were stratified by prostate volume into 2 cohorts (<50 cm^3 or ≥ 50 cm^3). Additionally, patients were stratified by prostate biopsy on which PCa was identified (1 biopsy or ≥ 3 biopsies).

RESULTS Within the subgroup of patients with prostate volume ≥ 50 cm^3 requiring ≥ 3 biopsies before cancer diagnosis, 72.6% (45/62) had pathologic Gleason scores ≤ 6 and 81.6% (49/60) had an estimated tumor volume of $\leq 10\%$ at the time of radical prostatectomy. This was significantly different from patients with prostate volume <50 cm^3 diagnosed on their first biopsy, in which only 48.5% (656/1349) were found to have Gleason scores ≤ 6 and 54.2% (705/1300) had estimated tumor volume $\leq 10\%$ ($P < .01$). There was no significant difference in the rate of Gleason score upgrading at time of prostatectomy between any of the subgroups.

CONCLUSION PCas detected in men with prostatic enlargement requiring multiple biopsies are more likely to be low-grade, low-volume tumors at final pathology than men without prostate enlargement. Men with larger prostates who have already had prior negative biopsies should be counseled regarding the increased risk of detecting clinically insignificant PCa with additional biopsies. UROLOGY 84: 380–385, 2014. © 2014 Elsevier Inc.

Since the inception of prostate-specific antigen (PSA) screening, there has been a well-documented increased incidence of prostate cancer (PCa) with a concomitant downward stage migration.[1,2] These tumors tend to manifest with lower grade and volume and have been shown to be associated with less risk of adverse pathologic features at the time of radical prostatectomy (RP).[1,2] Controversy exists over the clinical significance of many cancers detected by PSA screening.[3-6] This has led to a legitimate concern regarding the potential for overdiagnosis and subsequent overtreatment of a tumor that is unlikely to result in cancer-specific mortality.[5,6]

Recent attention has shifted to the dilemma of how to optimally diagnose and treat biologically aggressive PCa early in its course, when it is still curable, while sparing those with clinically insignificant PCa from the morbidity of unnecessary treatment.[3,4] To this end, attempts have been made to optimize PCa detection.[7-9] Despite these efforts, there are few data to guide management of the patient with a persistently elevated PSA despite a previous negative biopsy. The concern for some is that PCa may have been "missed" by the biopsy needle and these patients may still be harboring an aggressive tumor.[7,10,11] Whether PCa identified with additional biopsies has true clinical significance or leads to overdiagnosis of clinically insignificant tumors remains controversial, particularly in men with prostatic enlargement.[12,13]

The purpose of this study was to elaborate the interaction of prostate volume on PCa detected on first PNBx (prostate needle biopsy) compared with cancer detected after multiple repeat needle biopsies. Our hypothesis is

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From the Division of Urology, Department of Surgery, Hospital of the University of Pennsylvania, Philadelphia, PA; and the Department of Urologic Surgery, Vanderbilt University Medical Center, and the Tennessee Valley VA Health Care System, Nashville, TN

Reprint requests: Eugene J. Pietzak, M.D., Division of Urology, Department of Surgery , Hospital of the University of Pennsylvania, Perelman Center for Advanced Medicine, 3400 Civic Center Boulevard, 3rd Floor, West Pavilion , Philadelphia, PA 19104. E-mail: eugene.pietzak@uphs.upenn.edu

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that men with prostatic enlargement may confound the documented relationship between number of prostate biopsies and risk of indolent PCa. Specifically, we believe that the presence of prostatic enlargement will increase the risk of detecting indolent disease in men undergoing multiple biopsies.

MATERIAL AND METHODS

Patients were selected from our prospectively maintained institutional database of 2411 consecutive men who underwent radical retropubic prostatectomy (RP) at our institution from 1991 to 2008. Preoperative baseline clinical characteristics and biopsy features were recorded, including total number of previous prostate biopsies. Prostate volume was determined by transrectal ultrasound (TRUS) or magnetic resonance imaging (MRI), using standard techniques. We included an MRI-based volume calculation when TRUS volume was not available, as it has been demonstrated to have a high correlation to that of a TRUS-calculated prostate volume at our institution.[14] Pathologic characteristics of RP specimens were also recorded and analyzed. Prostatectomy specimens were processed and estimated tumor volume calculations were recorded according to our institution's previously published and validated protocol.[15] Patients without a recorded prostate volume, either by TRUS or MRI, were excluded (n = 266). Patients were also excluded if the number of PNBx performed before cancer detection could not be determined (n = 106). We also excluded men who were diagnosed with PCa on their second PNBx (n = 281). After applying these exclusion criteria, our cohort comprised 1758 men.

The indication for initial prostate biopsy was either an elevated PSA or abnormal digital rectal examination. Subsequent biopsies were performed at the discretion of the treating urologist. Indications for subsequent biopsy included a rising PSA, a change in rectal examination, or previous abnormal finding on biopsy (high-grade prostatic intraepithelial neoplasia or atypia).

Prostatectomy specimens were analyzed according to our institution's standardized protocol. After the fresh RP specimens were weighed and measured, the capsule was inked to maintain orientation. The specimen was then sectioned from apex to base, perpendicular to the urethra in 6- to 8-mm intervals. The sections were then inspected for tumor involvement and subsequently fixated in neutral buffered formalin. After fixation, the apex was cut perpendicular to the margin and the remainder of the gland was sectioned into 3- to 4-mm blocks and embedded. Orientation of the specimen was maintained throughout the process. Tumor volume was estimated by multiplying the percentage of nonmargin, nonseminal vesicle slides by the estimated average percentage of cross-sectional area containing tumor, stratified in an asymmetric categorical classification system.[15]

We defined clinically insignificant PCa as an estimated tumor volume <10%, Gleason score ≤6, with no extracapsular extension, negative lymph nodes, no seminal vesicle invasion, and negative surgical margins on final RP specimen.[16] This definition is consistent with the literature on clinically insignificant cancer being low-volume, low-grade disease without any pathologically aggressive features.[17,18] These are the patients who are lowest risk of PCa mortality and the least likely to need treatment.[17,18]

In this study, patients were categorized based on the number of PNBx they underwent before PCa detection. Patients were dichotomized into 2 groups, one in which PCa was diagnosed on the first biopsy, and the other in which PCa was diagnosed after ≥biopsies. Each group was then substratified by prostate volume (≥50 or <50 cm^3). The cut-off of 50 cm^3 was selected based on previously published studies, which have reported the impact of prostate volume on PCa detection rates.[10,12]

Baseline clinical parameters and pathologic characteristics were compared between subgroups using STATA version 11.0 (STATA Inc., College Station, TX). Statistical analysis included chi-square test for categorical variables and for continuous variables 2-sample t test was used. Multivariable regression modeling was also performed. Statistical significance was declared if $P \leq .05$.

RESULTS

Of the 1758 patients included in this analysis, 1430 (81.3%) had prostate volume <50 cm^3 and 328 patients (18.7%) had prostate volume ≥50 cm^3. The baseline clinical characteristics of this cohort are reported in Table 1. The proportion of patients with prostatic enlargement (>50 cm^3) increased with the number of PNBx required for detection of PCa. Specifically, 16.5% of patients diagnosed on first PNBx had prostatic enlargement compared with 41.3% of those who requiring ≥3 PNBx before diagnosis ($P \leq .001$). With respect to clinical Gleason score, patients with prostatic enlargement were more likely to have low-grade disease (Gleason score ≤6) both in men diagnosed on first biopsy (74.4% vs 66.4%; $P = .012$) and those requiring ≥3 PNBx (98.4% vs 76.1%; $P \leq .001$).

The pathologic characteristics of the study population are presented in Table 2. There was an increased likelihood of having Gleason score ≤6 PCa in the RP specimens of patients with prostatic enlargement when compared with patients without prostatic enlargement, for those patients diagnosed with PCa on their first PNBx (60.7% vs 48.5%; $P \leq .001$). This effect was greater for patients who underwent multiple PNBx, with 72.6% of patients with prostatic enlargement having pathologic Gleason scores of ≤6, compared with 52.3% for smaller prostates ($P = .01$). This is demonstrated in Figure 1. Interestingly, the incremental within-group risk of low-grade disease with serial prostate biopsies was far more pronounced in patients with prostatic enlargement (3.8% vs 11.9%).

Similarly, as shown in Figure 1, a significantly higher proportion of men with prostatic enlargement had estimated tumor volumes <2% on first PNBx and multiple PNBx ($P = .001$). Again, within-group comparisons revealed the incremental risk of low-volume disease with serial biopsy to be 26.7% and 8.2% in the prostatic enlargement and no enlargement subgroups, respectively.

With regard to adverse pathologic features on RP specimens, extraprostatic extension ($P \leq .001$), nodal involvement ($P = .68$), and seminal vesicle involvement ($P = .05$) was less often seen in patients with prostatic enlargement when compared with those without prostatic enlargement. Although prostate volume had no statistically significant impact on these adverse features in the multiple PNBx group, lower rates of adverse features were seen in the multiple biopsies groups when compared with those diagnosed on first PNBx. The rate of Gleason