ORIGINAL RESEARCH

Transperineal Biopsy Under Ultrasound Guidance For Prostate Cancer Detection as an Initial and as a Repeat Biopsy Strategy

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Objective: To present the authors' experience on transperineal prostate sector biopsy (TPSB) in detecting prostate cancer, in identifying both low Gleason prostate cancers as well as clinically significant prostate cancer (Gleason 7 and higher), and in determining anatomical distributions of prostate cancer in the both initial and repeat biopsy settings.
Methods: All patients from June 2014 to September 2016 who underwent TPSB, as initial biopsy or repeat biopsy after previous negative transrectal ultrasound-guided biopsy (TRUSPNB) were included. Data for each patient were collected prospectively and subjected to statistical analysis. T test was used for continuous variables while Chi square test or Fisher exact test was used for categorical variables. Multiple logistic regression models were used to identify factors predictive of a positive biopsy result.
Results: A total 130 patients were included in the study, 73 had TPSB as initial biopsy and 57 as repeat biopsy after previous negative TRUSPNB. The mean patient age of the Initial Biopsy Group (IBG) was 66 years while the mean age for the Repeat Biopsy Group (RBG) was 68 years. The IBG had a lower mean serum PSA level (9.07 ng/mL for IBG and 9.59 ng/ml for RBG) and smaller prostate volumes (42.9 mL for the IBG and 44.3ml for the RBG). Prostate cancer was detected in 65.8% (48/73) of the IBG and 40.4% (23/57) of RBG, of which 77.1% (37/48) and 73.9% (17/23) respectively, were clinically significant, defined as a Gleason score of ≥7. Of the cancers detected in IBG , 29.2% (14/48) exclusively involved the anterior sector (based on the Ginsburg Study Group's biopsy map), while 30.4% (7/23) were con?ned exclusively within the anterior sector for the RBG. Increasing PSA level and lower prostate volumes were predictive of cancer detection in RBG, while only increasing PSA level was predictive of a positive result in IBG.
Conclusion: Transperineal prostate sector biopsy demonstrated a high prostate cancer detection rate for both the initial and repeat biopsy settings. Likewise it provides for excellent sampling of the anterior region of the prostate, as it affords a more accurate sampling of the prostate gland based on a preplanned map and template to sample areas of interests. Similarly, it detects a high proportion of patients with clinically significant prostate cancer.This technique should therefore be highly considered as a first line option for all patients in whom a prostate biopsy is warranted.

Key words: prostate cancer, transperineal biopsy

Introduction

Lower transrectal ultrasound guided prostate needle biopsy (TRUSPNB) is presently the gold standard for detection of prostate cancer (PCA).[1,2] The indication for a biopsy is a clinical suspicion of PCA due to an elevated serum prostate specific antigen (PSA) or an abnormal digital rectal

examination (DRE). This technique primarily samples the peripheral zone of the prostate, from which 75% of cancers arises.[3] Numerous biopsy modifications, which include increasing the number of cores, laterally directed cores and even saturation biopsy failed to improve the detection rates significantly.[4,5,6]

There is increasing trend in the utility of Transperineal Prostate Sector Biopsy (TPSB).[7,8,9] Evidences from radical prostatectomy series showed as high as 30% of PCA arise from the anterior region of the prostate. These tumors would not have been detectable using TRUSPNB due to their high anterior location.[10,11] The transperineal approach, by virtue of its ability to access the anterior and apical regions of the prostate, have shown to increase the diagnostic yield of prostate biopsy.[12,13]

As there is an increasing utilization of active surveillance for the so-called "clinically insignificant cancers" which may not eventually need treatment, it is imperative to be able to obtain a more accurate histological profile of the prostate. A Gleason score of 7 and greater signifies a more clinically significant cancer that warrants a more aggressive approach. Several studies have shown that TPSB provides a more accurate assessment of the presence of aggressive histology.[14,15,16]

Furthermore, there is an increasing incidence of septic complications after a TRUSPNB due resistant strains of microorganisms from the rectal flora. The transperineal approach, bypassing the rectal route, could decrease or virtually eliminate sepsis. Moreover, it could potentially lower the risk of rectal bleeding after the procedure as there is no puncture of the rectum.[17,18]

This reports a single-operator experience on the use of TPSB in a cohort of men, who underwent initial biopsy as well as repeat biopsy after a previous negative TRUSPNB.

Materials and Methods

This is a retrospective study based on a review of a prospectively collected biopsy database. From June 2014 to September 2016, a total of 130 patients underwent TPSB, 73 of which as initial biopsy and 57 as repeat biopsy after a previous negative TRUSPNB.

For the purpose of this study, patients with abnormal DRE and serum PSA of greater than 20ng/ml were excluded. Patients with previously diagnosed prostate cancer and who had TPSB for active surveillance were also excluded, as the focus of the current study was prostate cancer detection among patients with no prior diagnosis. Patients were likewise excluded if they presented with acute prostatitis or proven urinary tract infection. Patients with hypersensitivity reactions or did not tolerate the IV anesthetic used were withdrawn from the study.

Written informed consent was obtained from all the men before the procedure. All procedures were performed under total intravenous sedation anesthesia. Pre-biopsy preparation included oral broad-spectrum antibiotics (fluoroquinolones) 2 days prior to the procedure. Parenteral antibiotic (3rd generation cephalosporin) was given 60 minutes prior to the procedure. Oral laxative in the form of bisacodyl was given to all patients the night before the procedure.

To eliminate variability, measures were taken to standardize the biopsy technique. The samples were obtained following the Ginsburg Study Group Protocol for Enhanced Prostate Diagnostics.[19] All biopsy procedures were performed by a single operator at the UST Hospital. The BK Falcon Flex Focus 800 Ultrasound Unit and the Bard core needle biopsy device was utilized in obtaining biopsy specimen on all the procedures. Histopathologic review of all tissue specimen of were performed by the same pathologist in all the procedures.

TPSB Procedure

Patients were placed in the lithotomy position. A three-way Foley catheter was inserted to facilitate identification of urethra and prostato-vesical junction. (Figure 1).

The number of biopsy cores taken was based on the prostate volume. Additional samples were taken upon the discretion of the senior author. Samples were obtained in such a way as to cover the anterior, mid gland and posterior sectors of both the right and the left side of the prostate gland. (Table 1)

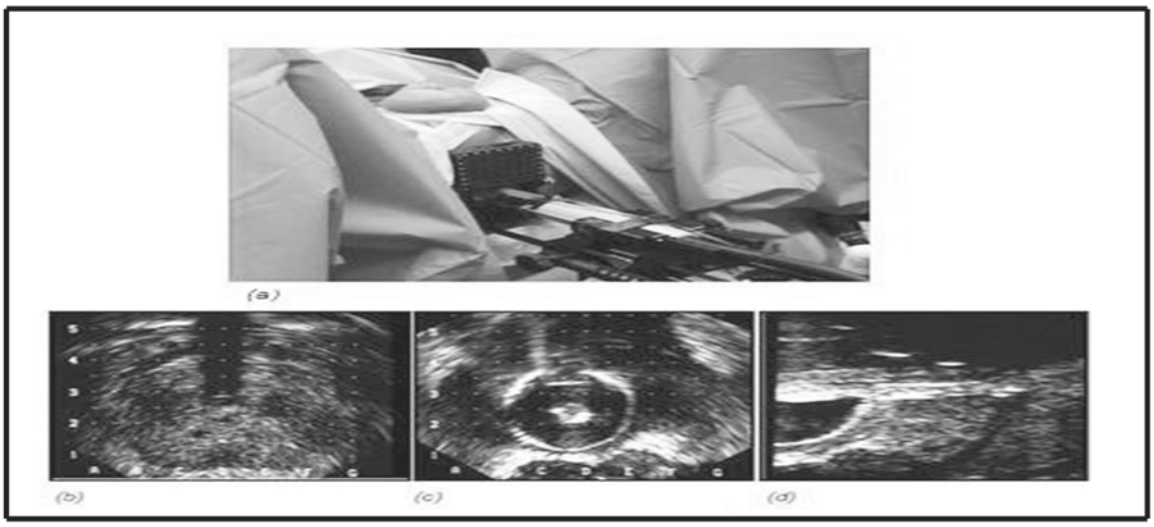

Figure 1. Patient positioning for TPSB; Patient is placed an lithotomy position and draped. (A) Sonographic images showing the urethra at the center of the grid (B) as well as images of the prostato-veiscal junction (C & D)

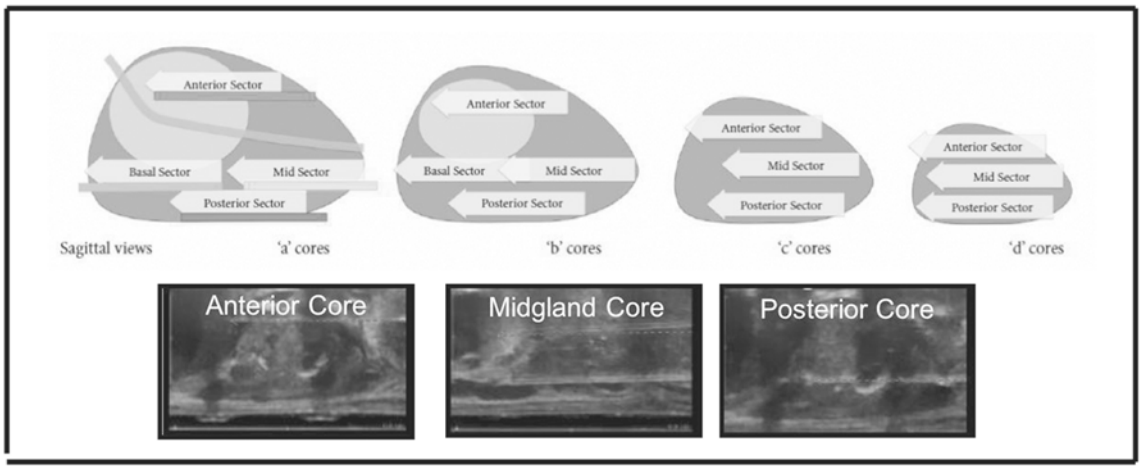

Figure 2. Standard technique of sampling in the Transperineal Prostate Sector Biopsy; Standardization approach of the Ginsburg Study Group for Enhanced Prostate Diagnostics.

Table 1. Number of cores obtained based on prostate size.

Prostate Size (in mL)	Number of Biopsy Cores
< 30	24
31 - 60	32
> 60	38

Data Analysis Plan

Data were encoded in MS Excel. Stata SE version 12 was used for further processing and analysis. T test was used for continuous variables while chi square test or Fisher exact test was used for categorical variables. The effect of each characteristic to the likelihood of cancer detection was assessed using multiple logistic regression models. The variables (age, PSA level and prostate volume) were fitted in the model and variables with $p<0.05$ were considered as significant predictors. Separate models were created for initial and repeat TPSB groups. A two-sided p value of 0.05 was chosen to indicate statistical significance in all analyses performed.

Results

The study population consisted of 130 patients; of these, 73 patients had TPSB as initial biopsy and 57 had TPSB as repeat biopsy after previous negative TRUSPNB. Patients in the initial biopsy group (IBG) had a lower mean age than the repeat biopsy group (RBG). Mean PSA level and prostate gland volume were likewise lower in the IBG compared to the RBG. (Table 2)

Prostate Cancer Detection and Characterization

Prostate cancer was detected in 48 out of 73 patients in the IBG for an overall cancer detection rate of 65.8%. In the RBG, 23 out of 57 patients were identified to have PCA for a detection rate of 40.4%.

The cancers detected were further analyzed based on their Gleason characteristics. Clinically significant prostate cancers were defined as those which have a Gleason score of 7 or higher. Of the

Table 2. Patient demographics, cancer detection rates, prostate cancer characterization.

	Initial Biopsy (n=73)	Repeat Biopsy (n=57)
Age (in years), mean	66.48 ± 7.64	68.46 ± 7.93
PSA (in ng/ml), mean	9.07 ± 4.57	9.59 ± 4.52
Prostate volume (in grams), mean	42.88 ± 21.40	44.30 ± 23.40
Cancer Detection	Initial Biopsy (n=73)	Repeat Biopsy (n=57)
Overall cancer detection rate	48/73 (66%)	23/57 (40%)
Clinically significant (Gleason>=7)	37/48 (77.1%)	17/23(73.9%)
Clinically insignificant (Gleason<7)	11/48 (22.9%)	6/23(26.1%)
Anatomic Distribution of Cancers Detected	Initial Biopsy	Repeat Biopsy
Anterior Sector		
Anterior sector only	14/48 (29%)	7/23 (30%)
Anterior and other sectors	22/48 (46%)	6/23 (26%)
Middle Sector		
Middle sector only	6/48 (13%)	4/23 (17%)
Middle and other sectors	18/48 (38%)	3/23 (13%)
Posterior Sector		
Posterior sector only	2/48 (4%)	2/23 (9%)
Posterior and other sectors	17/48 (35%)	3/23 (13%)
Characterization of Tumors Exclusively Detected on Each Sector	Initial Biopsy	Repeat Biopsy
Anterior Sector		
Clinically significant	7/14 (50%)	4/7 (57%)
Clinically insignificant	7/14 (50%)	3/7 (43%)
Middle Sector		
Clinically significant	4/6 (67%)	2/4 (50%)
Clinically insignificant	2/6 (33%)	2/4 (50%)
Posterior Sector		
Clinically significant	1/2 (50%)	1/2 (50%)
Clinically insignificant	1/2 (50%)	1/2 (50%)

48 cancers detected in the IBG, 37 (77.1%) were clinically significant. In the RBG, 17 out of 23 (73.9%) cancers were clinically significant.

Anteriorly Located Cancers

Among the 48 patients in the IBG identified to have cancer, 14 (29.1%) had cancer confined exclusively within the anterior region. For the RBG, of the 23 patients with a known positive core position, 7 (30.4%) had cancer exclusively involving the anterior region.

Cancers detected exclusively on the anterior sector were likewise characterized based on their Gleason scores. In the IBG, 7 out of the 14 (50.0%) cancers detected on the anterior sector were clinically significant cancers. For the RBG, 4 out of 7 (57.1%) cancers in the anterior sector had a Gleason score of 7 or higher.

Characteristics of Patients with Negative and Positive Biopsy Findings

Among the patients in the IBG , the mean PSA of those with positive biopsy results were significantly higher compared to those with negative biopsy (P=0.0093). In the RBG, there were statistically significant differences in the mean PSA value (P=0.0210) and mean prostate sizes (P=0.0161) between those with positive biopsy and negative biopsy findings. There was a higher mean PSA and a lower mean prostate volume in patients who were positive for cancer in the RBG (Table 3)

Odds Ratio for Overall Cancer Detection

Higher PSA level was observed to be associated with increased likelihood of cancer detection in both the IBG and RBG. Present data show that for every 1 ng/ml increase in PSA level, cancer detection rate increased by 25% and 17% in the IBG and RBG respectively. In the RBG, a lower prostate volume is associated with increased likelihood of cancer detection such that for every gram decrease in prostate volume, cancer detection increases by 4% (Table 4)

Post Biopsy Complications

Minor hematuria was observed in 25 out of 73 (34.2%) patients in the IBG and 6 out of the 23 (26.1%) patients in the RBG. There was no patient who developed sepsis nor excessive bleeding that required hospital readmission. There were, however, 6 patients in the IBG and 4 patients in the RBG who developed mild perineal bruising, without any pain nor discomfort, which eventually resolved spontaneously.

Discussion

The optimal biopsy technique for prostate cancer detection still remains to be undefined. The gold standard for identifying patients with prostate cancer at this point is still TRUSPNB. However, TRUSPNB does not accurately reflect the extent and grade of disease when compared with radical

Table 3. Characteristics of patients with negative and positive biopsy findings.

Characteristics		Initial Biopsy (N=73)			Repeat Biopsy (N=57)	
	Positive biopsy (n=48)	Negative biopsy (n=25)	P-value	Positive biopsy (n=23)	Negative biopsy (n=34)	P-value
Age, mean (years)	65.71 ± 7.35	67.96 ± 8.12	0.2349	68.74 ± 7.30	68.26 ± 8.43	0.8268
PSA level, mean (ng/mL)	10.06 ± 4.94	7.16 ± 3.02	0.0093*	11.25 ± 3.91	8.46 ± 4.61	0.0210*
Prostate volume, mean, (grams)	40.13 ± 19.00	48.16 ± 24.93	0.1287	35.35 ± 10.87	50.35 ± 27.51	0.0161*

Table 4. Odds ratio of patient parameters to predict presence of cancer.

Characteristics	Initial Biopsy			Repeat Biopsy		
	OR	95% CI	P-value	OR	95% CI	P-value
Age, mean	0.93	0.87 - 1.00	0.06	1.05	0.97 - 1.14	0.253
PSA level, mean	1.25	1.06 - 1.49	0.01*	1.17	1.01 - 1.36	0.03*
Prostate volume, mean	0.98	0.96 - 1.01	0.13	0.96	0.92 - 0.99	0.03*

prostatectomy specimens.[20] In an effort to improve the detection and grading of prostate cancer by biopsy, strategies such as biopsy location optimization and increasing number of biopsy cores taken have been developed.[21,22] The TPSB may provide for a more accurate sampling of the prostate gland. The biopsy cores are obtained using needles inserted through a fixed template for a more accurate and more evenly distributed sampling of the prostate. This intuitively translates into accuracy in proper patient selection and optimum treatment planning for standard definitive treatment, targeted therapies, and active surveillance.

A wide range of cancer detection rates of TPSB in the initial biopsy setting have previously been reported. Furuno, et al. reported a 51% detection rate in patients who underwent the transperineal technique in the setting of an initial biopsy.[23] Likewise, Vyas and Emiliozzi observed similar detection rates (54% and 51%) in their respective studies involving TPSB as initial biopsy technique.[24,25] In the present study, the cancer detection rate of TPSB as an initial biopsy protocol is 65.8% (detecting 48 out of 73). This study's detection rate in the IBG is in congruence with the results of the study done by Symons et. al, who similarly obtained a 65% cancer detection rate on the same cohort of patients.[26]

In patients who had TPSB in the repeat biopsy setting, the authors found a 40.4% (23 out of 57) cancer detection rate, which was notably lower than that in the initial biopsy patients. This finding is consistent with most published TPSB studies which have also reported a lower cancer detection rate in repeat biopsy settings, in the range of 32%-51%.[27,28,29]

Accurate characterization of the cancer is of utmost importance as it can determine if the patient can be managed conservatively or active intervention is warranted. It is therefore, critical to identify the clinically aggressive Gleason 7 and greater cancers so as not to miss the window of opportunity for cure. In the present study, a subgroup analysis of patients who were positive for cancer was conducted to determine the proportion of patients with clinically significant lesions. In the IBG, 37 out of 48 (77.1%) patients were identified to have tumors with Gleason scores of 7 or higher. Similar results were observed with the RBG in which 17 out of 23 (73.9%) had clinically significant cancers.

Radical prostatectomy specimen have shown that as high as 30% of prostate cancers arise from the anterior region of the prostate.[30] TPSB results in better access to the anterior and apical regions of the prostate which affords the urologist an unparalleled comprehensive sampling of the gland.[31] This advantage was evident in the present study as a substantial number of cancers in the IBG (14 out of 48; 29.1%) and RBG (7 out of 23; 30.4%) were identified exclusively in the anterior zone. These tumors would not have been detectable using the TRUSPNB approach due to their high anterior location.

The lesions detected exclusively in the anterior zones showed low percentages of clinically significant cancers at 50% (7 out of 14) and 57.1% (4 out of 7) in the IBG and RBG respectively. However, it cannot be definitely stated that the insignificant cancers in this series are indeed insignificant because they have not been compared with actual radical prostatectomy specimens.

In a multivariate analyses of the patient parameters on both groups, an increasing PSA level was the only predictive factor for cancer detection in the IBG. On the other hand both increasing serum PSA levels and lower prostate volumes were both predictive of cancer detection in the RBG.

The transperineal technique avoids the rectal route of needle insertion, thus, virtually eliminating the risk of infection and eventual sepsis.[32] This is the other accepted advantage proposed by advocates of this procedure. Furthermore, it could potentially lower the risk of rectal bleeding after the procedure as there is virtually no puncture of the rectum. Minor complications such as hematuria, not different from the transrectal approach, and perineal discomfort or bruising may occur in some cases but are usually self limiting. Available data suggest no statistically significant difference between the incidence of these complications on both techniques.[33]

Conclusion

Transperineal prostate sector biopsy demonstrated a high prostate cancer detection rate for both the initial and repeat biopsy settings. Likewise it provides for excellent sampling of the anterior region of the prostate, which is often under-sampled using the TRUS approach. Similarly, it detects a high proportion of patients with clinically significant prostate cancer. This technique should therefore be highly considered as a first line option for all patients in whom a prostate biopsy is warranted.

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