The Efficacy of Transrectal Ultrasound Guided Biopsy Versus Transperineal Template Biopsy of the Prostate in Diagnosing Prostate Cancer in Men with Previous Negative Transrectal Ultrasound Guided Biopsy.

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Purpose: We have previously demonstrated that transperineal template prostate biopsy (TPTPB) has a significantly higher cancer detection rate compared to transrectal ultrasound guided (TRUS) biopsy in biopsy naive men with a PSA < 20 ng/mL. We, therefore, performed a prospective study to determine whether TPTPB is still superior to TRUS biopsy in the detection of prostate cancer in men with persistently elevated PSA after one previous negative set of TRUS biopsies.

Materials and Methods: 42 patients with a background of one previous negative set of TRUS biopsy, persistently elevated PSA (but < 20 ng/mL) and benign feeling digital rectal examination (DRE) underwent simultaneous standard 12-core TRUS biopsy and 36-core TPTPB under general anaesthesia. We determined the prostate cancer detection rate between the two diagnostic modalities.

Results: Mean age was 65 years (range: 50-75), mean prostate volume was 59 cc (range: 21-152), mean PSA is 8.3 ng/L (range: 4.4-19), mean time difference between the study and the previous TRUS biopsy was 33 months (range: 1-150) with mean PSA velocity of 0.7 ng/mL/year (range: 0-8). Out of the 42 patients, 22 (52%) had benign pathology. Of the 20 patients (48%) diagnosed with prostate cancer, 4 (10%) had positive results in both TRUS biopsy and TPTPB, 1 (2%) had positive result in TRUS biopsy with negative TPTPB, while 15 (36%) had negative TRUS biopsy with positive TPTPB. Hence, TRUS biopsy detected cancer in 5/42 (12%) patients versus (19/42) 45% detected by TPTPB ($P < 0.01$). 13/19 (68%) of cancers detected by TPTPB had Gleason score □7. A total of 82/141 (58%) of positive cores was found in the anterior zone. One patient (2%) experienced urosepsis, 2 (5%) temporary urinary retention, 14 (34%) mild haematuria and 13 (32%) haematospermia.

Conclusion: TPTPB still shows a significantly higher prostate cancer detection rate compared to TRUS biopsy (12% versus 45%, $P < 0.01$) in men with a previous set of negative TRUS biopsy, persistently elevated PSA (but < 20 ng/mL) and benign feeling prostate on DRE.

Keywords: biopsy; cancer; prostate; transperineal; transrectal; ultrasonography.

INTRODUCTION

In the absence of a highly specific biomarker, obtaining biopsies from the prostate gland remains the gold standard investigation for establishing a diagnosis of prostate cancer (CaP). Over the last three decades, transrectal ultrasound guided (TRUS) biopsy of the prostate has been regarded the technique of choice as it is a well tolerated quick procedure that can be carried out under local anaesthesia in the outpatient setting. However, it is associated with a relatively low specificity of around 30% and confers a 5% risk of urosepsis.

On the other hand, transperineal template prostate biopsy (TPTPB) has been previously shown to have a significantly higher cancer detection rate (CDR) compared with TRUS biopsy (60% versus 32%, respectively) in biopsy-naïve men with an abnormally elevated PSA < 20 ng/mL and a benign feeling prostate on digital rectal examination (DRE).[1] Furthermore, TPTPB was shown to have a CDR of 58% in men with a persistently elevated PSA following 2 previous sets of negative TRUS biopsies.[2]

In order to determine whether TPTPB would still prove to be superior to TRUS biopsy in detecting CaP in patients with a background of one negative set of TRUS biopsy but still at risk of cancer, we carried out a prospective study, directly comparing both biopsy modalities by performing simultaneous TPTPB and TRUS biopsies in this group of patients.

PATIENTS AND METHODS

Study population: Between August 2012 and August 2014, subjects were selected if they had a history of one previous negative TRUS biopsy with benign pathology result, benign feeling prostate on DRE and a persistently elevated serum PSA more than the age specific range but < 20 ng/mL. All of our participants were given a comprehensive information leaflet explaining the nature of the study and gave written consent. The research protocol was registered and approved by the National Research Ethics Service (NRES) committee of East Midlands and by the research and development (R&D) department at the University Hospitals of Leicester

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Table 1. Difference in PSA levels, Prostate volumes and PSAD between initial and study biopsies

Mean (± SD)	Study Biopsy	Initial Biopsies	*P* Value
PSA	8.3 (± 3.0)	6.6 (± 2.5)	0.0003
Prostate Volume	59 (± 26.9)	56 (± 23.7)	0.71
PSAD	0.20 (± 0.1)	0.15 (± 0.1)	0.55

Abbreviations: PSA, Prostate Specific Antigen; PSAD, Prostate Specific Antigen Density; SD, Standard Deviation.

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Procedure: All the patients underwent both biopsies under general anaesthetic by the same surgeon (MAK) as a day case under antibiotic cover. Each patient was given a single dose of oral Ciprofloxacin 500 mg at least 30 minutes before anaesthesia. At induction of anaesthesia, 120 mg of Gentamicin and 1.2 g of Augmentin were administered intravenously unless the patient was penicillin allergic, in which case 400 mg of Teicoplanin was intravenously administered.

After placing the patient in the left lateral position, an ultrasound probe (BK Medical Pro-Focus 2202; BK Medical, Mileparken, Denmark) was placed in the rectum to visualise the prostate and calculate the prostate volume. Then, 12 TRUS guided core biopsies were taken from the right and left peripheral zones as previously described by Presti et al.[3] The ultrasound probe was taken out of the rectum. The patient was subsequently placed in the extended lithotomy position. The perineal area was shaved, the scrotum was secured away from the biopsy area using mepore tape, then the perineum and the genital area were prepped and draped. Thereafter, a 14-Fr urethral catheter was inserted in order to mark the urethra and determine the degree of haematuria at the end of the procedure. TPTPB were then performed as previously described.[4] In short, the ultrasound probe was reinserted in the rectum, A STEPPER (Galil Medical; Crawley, Sus- sex, UK) with an articulated arm and a stabilizer was used to fix the ultrasound probe, then a standard 0.5 cm brachytherapy template grid was attached to the STEPPER and positioned over the perineum. With the prostate at its widest in the transverse plane, the gland was divided on the ultrasound screen into six sectors (right anterior, left anterior, right mid, left mid, right posterior and left posterior). In each sector six 18-gauge biopsy needles (Pro-Mag™ Biopsy Needle, 18G x 20cm, MCXS1820AX) were placed into the prostate in the transverse plane view using the brachytherapy template grid. Once all six needles were inserted, the probe was switched to the sagittal plane view and the needles were gently withdrawn, one at a time. In every case, the biopsies were performed in exactly the same systematic manner starting with the right anterior sector followed by left anterior and then right mid and so on ending with the left posterior. It was decided that TRUS biopsies would be performed before the TPTPB in order not to alter the sensitivity of TRUS biopsies in picking up cancer cells.

Evaluations: Histological analysis was undertaken by the same pathologist (JPD), using standard haemotoxylin and eosin stained, formalin fixed and paraffin embedded sections. Standard 4µm sections were examined over three levels from each core. Where necessary immunoperoxidase to p63, 34betaE12 and AMACR (p504s) antigens were also employed to render a diagnosis.

Statistical analysis: Analysis was carried out using Fisher's exact test to evaluate the association of nominal variables, and Student t-test to evaluate the difference in categorical variables. All calculated values were 2-sided, considering $P < 0.05$ statistically significant. Power analysis was conducted using a power model based on a one-proportion Z, Chi-squared test within STATISTICA (StatSoft, Tulsa, Ohio). This analysis indicated that to obtain a power of 0.9 (using alpha value of 0.05, a TRUS frequency of 0.32 and a TPTPB frequency of 0.6) would require 30 cases. Furthermore, power analysis was undertaken for a 2-way 2-proportion Z-test, this analysis indicated that to obtain a power of 0.8 (using the same alpha value and the same frequencies) would require 50 cases. This was based on a null hypothesis that the proportions of positive cases detected were equal. After performing 42 cases, the data was analysed and a large significant difference was determined in CDR between both biopsy modalities. Hence, continuing further with the study was felt unethical, as eight further cases would not have altered the overall trend in the study outcome.

RESULTS

A cohort of 42 men were enrolled in our study, they had a mean age of 65 years (range: 50-75), mean prostate volume of 59 mL (range: 21-152), mean PSA of 8.3 ng/L (range: 4.4-19) and mean PSA density (PSAD) of 0.2 ng/mL/cc (range: 0.07-0.47) at the time of performing the study. At the time of the initial TRUS biopsy,

Table 2. Pathological findings of initial/new TRUS biopsies and TPTPB

Pathology	Initial TRUS Biopsy	Study TRUS Biopsy	Study TPTPB
Gleason 6	0 (0%)	3 (7%)	6 (14%)
Gleason 7	0 (0%)	2 (5%)	13 (31%)
Benign	24 (57%)	10 (24%)	5 (12%)
Atypia	1 (2%)	8 (19%)	8 (19%)
ASAP	7 (17%)	4 (10%)	2 (5%)
High PIN	10 (24%)	15 (35%)	8 (19%)

Abbreviations: ASAP, Atypical Small Acinar Proliferation; PIN, Prostatic Intraepithelial Neoplasia.

Table 3. Cancer detection in TRUS biopsy and TPTPB

	TPTPB (negative Cancer)	TPTPB (positive Cancer)
TRUS (-ve Cancer)	22	15
TRUS (+ve Cancer)	1	4

Abbreviations: TRUS, Transrectal Ultrasound; TPTPB, Transperineal Template Prostate Biopsy.

they had a mean PSA of 6.6 ng/mL (range: 3.1-15) with mean PSA density of 0.14 ng/mL/cc (range: 0.06-0.42). The time interval between the initial TRUS biopsy and the study biopsies ranged from one month up to 150 months, with median of 19 months and mean of 33 months. Mean PSA velocity was 0.65 ng/mL/year (range: 0-3.5). There was a significant difference in PSA levels ($P < 0.05$) between the time of the initial TRUS biopsy and the study biopsies, but not in PSAD or PSA volumes as shown in **Table 1**.

In total, 22/42 (52%) patients had benign pathology by both TRUS biopsy and TPTPB, while 20/42 (48%) patients had cancer pathology in their biopsies. Of those 20 patients diagnosed with prostate cancer, 15 (36%) had negative TRUS biopsies but positive TPTPB, 4 (10%) had positive biopsies with both TRUS and TPTPB and 1 (2%) had positive TRUS biopsies but negative TPTPB. Therefore, the overall CDR of TPTPB was 45% (19/42) versus 12% (5/42) for TRUS biopsies ($P < .001$). Calculated Cohen's Kappa was 0.17 indicating poor concordance between TPTPB and TRUS biopsy results, denoting the genuine difference in the ability of TPTPB to detect prostate cancer compared to TRUS biopsy in this setting. The histopathological findings of the initial TRUS biopsy, the study TRUS biopsy and the TPTPB are all listed in **Table 2** and **Table 3**.

Out of the 19 patients who had cancer detected by TPTPB, 13 (68%) had Gleason score of 7. Furthermore, 11/15 (73%) of cancers that were exclusively detected by TPTPB and missed by TRUS biopsy had Gleason score of 7. A total of 82/141 (58%) of the positive cores detected by TPTPB were found in the anterior sector of the prostate as shown in **Figure 1**.

Only one patient (2%) experienced urosepsis, 2 (5%) had temporary urinary retention, 14 (34%) had mild haematuria and 13 had (32%) haematospermia that resolved spontaneously within two to three days.

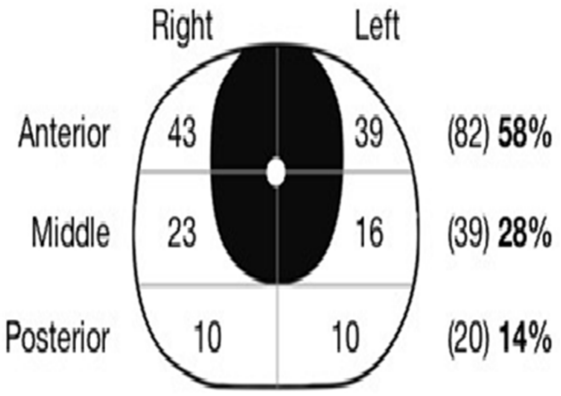

Figure 1. Site of cancer positive cores detected by TPTPB (n=141)

DISCUSSION

Over the last decade, TPTPB has been recognized as a more clinically efficient diagnostic modality than TRUS biopsy in the initial and repeated biopsy settings. However, few studies have compared the two methods directly in a head-to-head comparison as we performed in this study. Performing both biopsy modalities in each patient provided us with the best control group, as the patients acted as their own controls. In our case, the TRUS biopsy (presenting the conventional practice) was compared to the TPTPB (presenting the newly evaluated practice) in the same

Our study further reinforces the superior clinical efficiency of TPTPB over TRUS biopsy. TPTPB is particularly indicated when a patient has been subjected to one or more negative sets of TRUS biopsy and a suspicion of prostate cancer remains. Furthermore, a large proportion of cancers detected in the repeat biopsy setting are located anteriorly. Studies have shown that approximately 20% of all prostate cancers are anterior and these cancers are more likely to have extracapsular extension at the time of treatment, potentially resulting in a higher positive surgical margin rate[5].

Over the last decade, TPTPB has been recognized as a more clinically efficient diagnostic modality than TRUS biopsy. In 2014, we[1] compared TRUS biopsy and TPTPB in 50 biopsy-naïve men with suspicion of prostate cancer where TRUS and TPTPB were performed at the same setting. Overall, 60% were diagnosed with CaP, with 25% detected by only TPTPB but missed by TRUS biopsy. On the contrary, all cancers detected by TRUS biopsy were also detected by TPTPB. In 2007 Kawakami et al. published a study of 324 men who underwent 12-core TRUS biopsy followed by 24-core combined TRUS biopsy and TPTPB. 12 men were diagnosed with cancer by the combined technique but missed by TRUS biopsy alone. Subsequent mpMRI showed that 92% of cancers were located anteriorly.[6]

In 2015 Ong et al. conducted a study in which TPTPB was performed in 160 biopsy-naïve men with clinical suspicion of CaP underwent 12-core TRUS biopsy and 12-core TPTPB simultaneously. Most cancers detected by TPTPB and missed by TRUS biopsy were located anteriorly, and although most cancers missed by TRUS biopsy were low grade and low volume, some clinically significant cancers were also missed.[7]

In 2014, Our clinical group also performed TPTPB in 122 men with two negative sets of TRUS biopsy and persistently elevated PSA. CaP was detected in 58% of these men and 46% of those diagnosed had clinically significant cancer based on criteria of Gleason score of ≥ 7, or more than three positive cores of Gleason 6.[1] A larger study in 2013 by Bittner examined a cohort of 485 men who underwent TPTPB following negative TRUS biopsy due to either persistently elevated PSA, atypical small acinar proliferation (ASAP) or high grade prostat-

ic intraepithelial neoplasia (PIN). Cancer was detected in 226 men (46.6%), 196 of which were clinically significant according to the Epstein criteria and most of them were anterior. (8) Results of other published series support the aforementioned findings, demonstrating a higher CDR from TPTPB in the repeat biopsy context (4,7,9–11) as well as superior antero-apical sampling with TRUS biopsy[5,8,10,12].

TPTPB is associated with a much lower risk of sepsis compared with TRUS biopsy. A study from Melbourne of 245 patients undergoing TPB showed that there were no readmissions with sepsis post-operatively.[13] Similarly, in our experience from over 500 patients who have undergone TPTPB we have not had a single case of urospesis (unpublished data). Further published series support this with an overall risk of sepsis following TPTPB approaching zero in some studies. On the contrary, the risk of sepsis following TRUS is in the region of 5% including infection with multi-resistant organisms.[13] Therefore, TPTPB is particularly favourable when selecting a procedure for patients who are diabetic or immunocompromised or those with previous antibiotic resistance.[14]

Studies have also shown that TPTPB offers the benefit of mapping of the prostate, thereby decreasing the risk of under-grading patients compared with TRUS biopsy. A study published in 2015 of 431 patients who underwent RP following either TRUS biopsy or TPTPB compared the final Gleason grade with the initial grade on diagnosis.[15] TPTPB was found to be more accurate than TRUS biopsy in predicting final Gleason score. Furthermore, a prospective randomized study comparing 12-core TPTPB with 12-core TRUS biopsy in 200 men demonstrated a significantly higher diagnostic efficiency with TPTPB in men with PSA values in the lower end of the pathological range (i.e. 4.1 - 10ng/ml).[16] Finally, TPTPB also has the ability to diagnose CaP in patients who have previously undergone abdomino-perineal (AP) resection for rectal cancer.[10]

It is well known that more time is required to perform TPTPB, including general anaesthetic time, and that more training is needed for the surgeon. Although its provision is increasing, it is still less widely available than TRUS biopsy.[14] It has also been shown to be more painful than TRB and harbor an increased risk of acute urinary retention in those with larger prostates. Moreover, despite the majority of studies showing a higher CDR overall with TPTPB compared with TRUS biopsy, some studies, although few in number, have shown statistically similar CDRs between the two techniques both in the initial[17,18] and the repeat biopsy setting [19]. This could reflect variance in levels of operator experience. Finally, a potential drawback of a higher CDR might be an increased detection of clinically insignificant cancer, which could be cause for concern particularly if TPTPB becomes the modality of choice in diagnosing prostate cancer.[20] This could potentially subject some patients to further unnecessary tests downstream as well as increase financial burden on the healthcare system.

There is emerging evidence that multiparametric MRI (mpMRI) may increase the efficiency of TPTPB, whilst reducing the number of biopsies required for a diagnosis. This could result in reduced pain levels following the procedure as well as a lower risk of urinary retention. However, early studies show that mpMRI may have a false negative rate of up to 20% and may miss some Gleason 3 cancers.[20,21] The significance of the latter is uncertain. The PROMIS trial which is currently taking place consists of a RCT of 714 men and could help answer some critical questions, namely: whether mpMRI could exclude clinically insignificant cancer, thus reducing the number of unnecessary biopsies; and whether prebiopsy MRI increases the detection rate of clinically significant cancer. Finally, it will hopefully determine the sensitivity, specificity, negative predictive value and overall cost-effectiveness of mpMRI versus TPB and TRB.[22]

In this study we compared TRUS biopsies versus TPTPB without the advantage of MRI to determine whether we should abandon TRUS biopsies and look specifically for TPTPB. Our results have clearly shown that TPTPB outperformed TRUS biopsies in the diagnostic yield for CaP in men who had previous negative TRUS biopsies and persistently elevated PSA.

CONCLUSIONS

TPTPB has a significantly higher prostate cancer detection rate in comparison to TRUS biopsies in men with persistently abnormally elevated PSA < 20 ng/mL, benign feeling prostate on DRE and one previous set of negative TRUS biopsies. Our findings are consistent with the contemporary literature, which also demonstrates additional advantages in selecting TPTPB, particularly in patients with an inherently higher risk of sepsis as well as those who have undergone previous AP resection. Performing mpMRI may further enhance the CDR from TPTPB by performing TB and SB simultaneously. However, it is still not widely available and results from the PROMIS trial are awaited to elucidate its role.

CONFLICT OF INTEREST

The authors report no conflict of interest.

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