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Original Article

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Detection of Prostate Cancer in Patient with Serum Prostate Specific Antigen (PSA) level 4-10 ng/ml by Trans-rectal Ultrasound (TRUS) Guided Biopsy

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Abstract

Background: *The objective of this study is to observe the frequency of prostate cancer detected by TRUS guided prostate biopsy in patients with serum PSA 4-10 ng/ml.*

Methods: *Patients aged 50-80 years were entered this study and 46 patients with serum PSA level 4-10 ng/ml underwent TRUS guided 12 cores systematic biopsy.*

Results: *The mean age of the patients was 63.1 (±10.0) years. All of them had serum PSA level 4-10 ng/ml and the mean PSA was 6.9 (±1.4) ng/ml. On digital rectal examination (DRE) hard nodule was found in 4 (8.7%) patients, among them 3 (42.9%) patients had malignant lesion and 1 (2.6%) patient had non-malignant lesion, that was statistically significant (P=0.009). A total 7 (15.2%) patients had malignant lesion on histopathology, all of them were adenocarcinoma, 5 (71.4%) patients had Gleason's score d" 6 while 2 (28.6%) patients had Gleason's score 7. The result was statistically significant.*

Conclusion: *This study concluded that, the overall detection rate of prostate cancer in Bangladesh was 15.2% with the diagnostic gray zone of serum PSA from 4 to 10 ng/ml. TRUS guided prostate biopsy had become a widely accepted and routinely performed technology to detect PCa.*

Introduction

Prostate cancer is the second most common cancer and the fifth leading cause of cancer-associated mortality among men worldwide[1]. A "normal" PSA has traditionally been deûned as d"4 ng/ mL, but there is no level of PSA below which prostate cancer risk falls to zero[2]. According to European Association of Urology (EAU) guidelines, the decision to undergo biopsy should be based on prostate specific antigen (PSA) and digital rectal examination (DRE)[3]. Although a serum PSA level of 4.0 ng/ml is used as a cut off point for CaP screening, it is relatively difficult to differentiate prostate adenocarcinoma from benign prostatic hyperplasia (BPH) in patients with gray-zone PSA levels (4–10 ng/ml)[4]. The presence of an abnormal digital rectal examination (DRE) or an elevated PSA level were associated with increased risk of prostate cancer. Systematic transrectal ultrasound- (TRUS-)

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guided prostate biopsy is currently the standard practice for the diagnosis of CaP[3]. Histologic grade is the most important information obtained from prostate needle biopsy, and the Gleason grading system is the most commonly used. At low-power magnification, the sum of a grade (1 to 5) assigned to the predominant pattern (occupying the largest area of the specimen) and the second most common pattern yield a score ranging from 2 to 10[5]. Alhough there is no such previous study in our country regarding the rate of prostate cancer detection in men with PSA 4-10 ng/ml, in some other Asian countries, the prostate cancer detection rates in men with normal DRE and PSA 4.1–10.0 ng/ml was reported to be 13%–36.2% in Japanese[6], 25.3% in Indian[7] and 19.5% in Korean population[8].

In the study by Gao et al.[9] (2005) the cancer detection rate was 14.8% in patients with serum PSA 4-10 ng/ml. Teoh et al.[10] (2015) showed that cancer detection rate by TRUS guided biopsy in relation to PSA level 4-10 ng/ml with normal DRE is 13.4% and with abnormal DRE 30.2%. Gretzer and Partin[11] (2002) describe 22-27% likelihood of prostatic cancer in patient with PSA value 4-10 ng/ml. In another study by Zheng et al.[12] (2008) the rate of prostate cancer was 18.6% in patients with PSA level 4-10 ng/ml.

Materials and methods

This cross sectional observational study was conducted in Urology department of Sylhet M A G Osmani Medical College Hospital, Sylhet from August 2019 to July 2021 in patients with aged 50-80 years and serum PSA level 4-10 ng/ml attending urology outpatient department (OPD). Patients with previous TRUS guided prostate biopsy, prior diagnosis of prostate cancer, previous prostate surgery, pelvic radiation treatment, patients receiving 5 alpha reductase inhibitors, evidence of acute urinary tract infection, coagulopathies and pathological conditions of anorectum (eg- painful anorectum, haemorrhoids, anorectal carcinoma etc) were excluded from the study.

Patient's assessment included detailed history taking, general and genital examination, routine urine analysis and urine culture, serum PSA, ultrasonography of KUB region and prostate with maximum cystometric capacity with post void residue.

Patients with serum PSA ranged 4-10 ng/ml were undergone transrectal ultrasound guided prostate biopsy with the help of transrectal 7.5 MHz transducer using a 18 G spring loaded biopsy gun, provided there was no evidence of urinary tract infection and normal coagulation profile.

Patients were on normal diet, a self administered cleansing enema performed on the morning of the procedure. In patients on low-dose aspirin (LDAP) who were at moderate to high risk for adverse cardiovascular or neurological events, the drug should be continued periprocedurally. Patients on dual antiplatelet drugs (LDAP and clopidogrel) should discontinue clopidogrel alone 1 week prior to the procedure. Anticoagulants (Warfarin) should be discontinued 5 days prior and restarted 24-48 hours after the procedure. Antibiotic prophylaxis was provided with quinolone (ciprofloxacin) 500 mg administered 2-3 hours before the procedure with advise to continue the prophylaxis beyond 24-hours after the procedure.

After ensuring privacy and comfort, the patient was placed in the left lateral decubitus position with the knees and hips folded towards the abdomen.

Per-rectal local anaesthetic (2% lignocaine) jelly was provided for topical anaesthesia and DRE was done prior to introduction of the TRUS probe. The endocavitary phased-array probe was kept ready covered with a condom and a sterile metallic needle-guide was attached. With gentle, but steadily increasing pressure, the probe was introduced into the rectum by experienced hand and periprostatic nerve block was ensured by 2% lignocaine injection. Subsequently, the prostate was examined for the anatomy, volume, and pathology in both transverse and sagittal planes.

12 cores systematic biopsy was taken along with the biopsy of suspicious lesion in sagittal plane. All the biopsy specimens were sent for histopathology in 6 separate jars with 10% formalin and proper labeling. Microscopic examination of specimens was done by Olympus BX51 microscope in Pathology department.

Histopathology reports were collected to confirm the presence of prostate cancer with Gleason score.

Ethical implications

The aim and objectives of the study along with its procedure, risks and benefits were explained to the study subjects in an easily understandable local language. A written informed consent was taken from all the study subjects without exploiting any of their weakness. All the study subjects were assured of adequate treatment of any complications developed in relation to the purpose of the study.

All the study subjects were assured about their confidentiality and freedom to withdraw themselves from the study at any time. Normal treatment proceeded as per the general treatment procedure of the hospital, even if patient did not participate in the research.

Results

Table I : *Age of the study subjects (N=46)*

Age group (in years)	Frequency	Percent
50-59	16	34.8
60-69	15	32.6
e"70	15	32.6
Mean ±SD	63.1± 10.0	
Total	46	100.0

Results were expressed as frequency, percentage and Mean ±SD

Table I shows the distribution of patient according to age group among the 46 patients. The mean age of the patients was 63.1 (±10.0) years. 16 (34.8%) were from 50-59 years age group, 15 (32.6%) were from 60-69 years age group and another 15 (32.6%) were from e"70 years age group.

Table II: *Correlation of histopathological findings with age of the study subjects (N=46)*

Mean ±SD (63.1± 10.0)	Malignant (Percentage)	Non-malignant (Percentage)	*P* value
Above mean age	2 (4.3%)	23 (50.0%)	0.220
Bellow mean age	5 (10.9%)	16 (34.8%)	
Total (N=46)	7 (15.2%)	39 (84.8%)	

Results were expressed as frequency, percentage and Mean ±SD.

Fisher Exact test was done as the test of significance. P- value <0.05 was considered significant.

Table II shows that the mean age of patients were 63.1 (± 10.0). Above the mean age group 2 (4.3%) had malignant and 23 (50.0%) had non- malignant lesion. On the other hand, 5 (10.9%) had malignant and 16 (34.8%) had non- malignant lesion bellow the mean age group. There was no statistically significant difference between two groups regarding malignant lesion (P>0.05).

Table III shows that 15 (32.6%) patients had PSA from 4-6 ng/ml while 31 (67.4%) had PSA from 6.1-10 ng/ml. The mean PSA of the patients was 6.9 (±1.4) ng/ml. Among 4-6 ng/ml PSA group, only 1(2.2%) had malignant and 14(30.4%) had non-malignant lesion. On the other hand, 6(13%) had malignant and 25(54.4%) had non-malignant lesion among PSA 6.1-10 ng/ml group. The result was not statistically significant (*P*>0.05).

Table III: *Correlation between Prostate-specific antigen (PSA) and histopathology (N=46)*

PSA	Frequency (Percentage)	Non-malignant (Percentage)	Malignancy (Percentage)	*P* value
4-6 ng/ml	15(32.6%)	14(30.4%)	1(2.2%)	0.399
6.1-10ng/ml	31(67.4%)	25(54.4%)	6(13%)	
Mean ±SD	6.9±1.4			
Total	46(100%)	39(84.8%)	7(15.2%)	

Results were expressed as frequency, percentage and Mean ±SD.
Fisher Exact test was done as the test of significance. P- value <0.05 was considered significant.

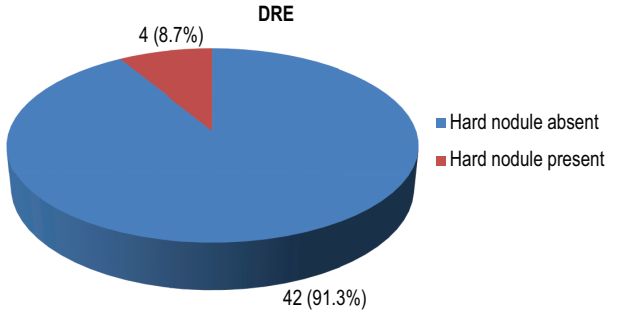

Figure 1: *Presence of hard nodule in digital rectal examination (DRE) (N=46)*

Figure 1 shows that hard nodule was found in 4 (8.7%) patients while 42 (91.3%) patients had normal prostate in digital rectal examination (DRE).

Result was expressed as frequency and percentage. Table IV shows that out of 7 patients with malignant lesion, 3 (42.9%) patients had hard nodule while out of 39 patients with nonmalignant lesion, only one (2.6%) patient had hard nodule. Fisher Exact test showed that there was significant statistical difference between presence of hard nodule in digital rectal examination (DRE) and histopathological type of the lesion (*P*<0.05).

Table IV : *Correlation between presence of hard nodule in digital rectal examination (DRE) and histopathological type of the lesion (N=46)*

Hard nodule	Malignant lesion	Non-malignant lesion	*P* value
Present	3 (42.9%)	1 (2.6%)	0.009*
Absent	4 (57.1%)	38 (97.4%)	
Total	7 (100.0%)	39 (100.0%)	

Results were expressed as frequency and percentage. Fisher Exact test was done as the test of significance. P- value <0.05 was considered significant.
*=Statistically significant.

Table V : *Gleason's score among positive subjects (N=7)*

Gleason's score	Frequency	Percent	P Value
d" 6	5	71.4	0.00001*
7	2	28.6	
Total	07	100.0	

Results were expressed as frequency and percentage. Z-proportion test was done as the test of significance. P- value <0.05 was considered significant.
*=Statistically significant

Table V shows that out of 7 patients with malignant lesion, 5 (71.4%) patients had Gleason's score d" 6 while 2 (28.6%) patients had Gleason's score 7. The difference was tested by Z-proportion test and found statistically significant (P<0.05).

Discussion

This study was conducted to see the rate of prostate cancer detected by transrectal ultrasound (TRUS) guided prostate biopsy in Bangladeshi population from year 2019 to 2021. Diagnosis of prostate cancer requires obtaining cancerous tissue from the prostate gland with biopsy. With the wide application of TRUS in clinical practice, TRUS-guided prostate biopsy has become the gold standard for diagnosis of CaP[13].

A total 46 patients were included in this study according to inclusion and exclusion criteria between 50 to 80 years of age with mean age 63.1 (±10.0) years. Above the mean age group 2 (4.3%) had malignant and 23 (50.0%) had non- malignant lesion. On the other hand, 5 (10.9%) had malignant and 16 (34.8%) had non-malignant lesion bellow the mean age group. There was no significant difference (*P>0.05*) among two aged groups.

All of the patients had PSA 4-10 ng/ml with mean PSA 6.9 (±1.4) ng/ml. 15 (32.6%) patients had PSA from 4-6 ng/ml while 31 (67.4%) had PSA from 6.1-10ng/ml. Among 4-6 ng/ml PSA group, only 1(2.2%) had malignant and 6(13%) malignant lesion found among PSA 6.1-10 ng/ml group. There was no significant difference (*P>0.05*) among these groups. Catelona et al.[14] (1994) found 10 men of the 19 men with advanced disease and PSA level 4.1-6 ng/ml. Thus, it may not be safe to assume that a slightly elevated PSA concentration does not require biopsy. The commonly regarded cut-off value of PSA to consider biopsy is 4 ng/ml[15], but to perform biopsy to all patients beyond that criteria would result in many unnecessary examinations and overdiagnosis for insignificant disease[16], and the great economic burden makes it difficult in developing countries like Bangladesh.

In this study, references were taken from several landmark papers published previously[12,17,18], and decided to perform prostate biopsy in PSA value 4-10.0 ng/ml, so as to facilitate the comparison of prostate cancer detection results with those available in the literature.

In Western country the likelihood of prostate cancer in men with PSA levels 4.1–10.0 ng/ml (intermediate level) was 22–27%[19]. In a study by Pelzer et al.[20] (2005) in Austria, the detection rate is 37.6%. In a European Prostate Cancer Detection (EPCD) study, the overall prostate cancer detection rate was 33.7% (354/1051), which involved Caucasian men with PSA ranged 4-10 ng/ml[21].

There are few data available on the prostate cancer detection rates upon TRUS-guided prostate biopsies in the Asian population. In a Japanese study, the reported cancer detection rates ranged from 13% in men with normal DRE up to 36.2% in men with PSA 4.01-10 ng/ml[22]. Kobayashi et al.[23] (2004) showed that prostate cancer was diagnosed 23.6% in this intermediate PSA level group.

This study demonstrated a lower cancer detection rate (15.2%) amongst men with PSA between 4.0 and 10.0 ng/ml in comparison with other Asian countries, such as China (26%)[24], Japan (22.2%)[25], South Korea (19.6%)[26], India (23.2%)[7], Singapore (20.9%)[27], and Thailand (22%)[28].

In this study, out of 4 abnormal DRE 3(42.9%) had malignant and 1(2.6%) had nonmalignant lesion compared to 42 normal DRE only 4 (57.1%) had

malignant and 38 (97.4%) had nonmalignant lesion. There was significant statistical difference between presence of hard nodule in digital rectal examination (DRE) and histopathological type of the lesion ($P<0.05$). This study illustrated the importance of a proper DRE. Biopsy is routinely recommended for patient with suspicious DRE. TRUS-guided prostate biopsies ranged from 13% in men with normal DRE and PSA 4.1–10 ng/ml to up to 36.2% in men with PSA 4.01–10 ng/ml[22,6] .

Out of 7 malignancy, 5 had Gleason's score d" 6 while 2 (28.6%) patients had Gleason's score 7. There are significant number ($P<0.05$) of patient had Gleason's score d" 6 (low grade) in PSA group 4-10 ng/ml. However, because of the small sample size (only 7 cases of CaP, five of which had Gleason 6 or less and all had adenocarcinoma), more meaningful analysis of the correlation with pathology was difûcult. Therefore, further studies in predicting pathology results in Bangladeshi populations are needed.

To the best of our knowledge, there is no study on prostate cancer detection upon TRUS-guided prostate biopsy in the Bangladeshi population. We believe our results provide important information for Bangladeshi men who would consider TRUS-guided prostate biopsy for suspected prostate cancer. Why the cancer detection rate was lower in the Bangladeshi population within the same range of PSA may not be simply explained by a lower incidence of prostate cancer in Bangladeshi men, and further basic science research would be necessary to look into the reasons behind. More importantly, apart from prostate cancer diagnosis, PSA also plays an important role in risk stratification of the disease. Further studies are warranted to investigate its prognostic role in the Bangladeshi population.

Conclusion

This cross sectional study showed that, the overall detection rate of prostate cancer in Bangladesh was comparatively lower than in the Western population with the diagnostic gray zone of serum PSA from 4 to 10 ng/ml. This study also demonstrated that PSA is most effectively used in conjunction with DRE to define the population who are at risk for prostate cancer and therefore, may require prostate biopsy. TRUS-guided biopsy helps in sampling from prespecified regions of the prostate gland that is accepted and routinely performed technology.

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