An overview of serum prostatic surface antigen cut points for recommendation of prostatic biopsy

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Abstract

Introduction: Patients in India frequently present with prostatic surface antigen (PSA) report and request for prostatic biopsy to rule out malignancy. With fear of harboring malignancy set in patient’s mind, it becomes difficult to counsel them about absolute indications and need of biopsy. Whether serum PSA has same predictability in symptomatic patients in the Indian context for advising prostatic biopsy at same reference ranges as in western countries, remains to be answered.

Materials and Methods: Symptomatic patients between 45 and 70 years of age presenting with either raised serum PSA (>4 ng/ml) reports or abnormal digital rectal examination (DRE) were considered as cases. Standard 12 core transrectal ultrasound-guided prostatic biopsy was done. Statistical analysis using optimal cut points, an R package was done to overview different PSA cut points for the recommendation of prostatic biopsy.

Results: A total of 534 patients were included. Mean age was 64 years. Malignancy was detected in total 77 patients (14.42%). Malignancy was identified in 3.59% (10/279) and 30% (63/210) patients at serum PSA ranges 4–10 ng/ml and serum PSA >10 ng/ml, respectively. Both, maximum sensitivity and specificity were found at PSA cut point 9.7 ng/ml. We evaluated these patients to identify the PSA cut point above which unnecessary biopsies will be avoided. We kept power of study maximum, i.e., 1 with confidence interval of 0.95.

Conclusion: PSA value 9.7 ng/ml should be considered as the cut point above which prostatic biopsy should be done to avoid unnecessary biopsies. Unless accompanied by abnormal DRE finding at PSA range 4–10 ng/ml, morbidity of prostatic biopsy procedure can be avoided using this cut-point.

Keywords: Biopsy, lower urinary tract symptoms, prostatic surface antigen, transrectal ultrasound

INTRODUCTION

Worldwide serum prostatic surface antigen (PSA) is being done in symptomatic patients presenting with lower urinary tract symptoms (LUTS) to detect prostatic malignancy on the earlier basis.[1] Prostatic biopsy is generally advised to symptomatic patients with serum PSA >4 ng/ml by various physicians in India. A number of patients presents to tertiary health-care centers with raised PSA reports (>4 ng/ml) and request for prostatic biopsy advised elsewhere, to rule out prostatic malignancy. With the fear

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of harboring malignancy set in the mind of patients, it becomes difficult to counsel them about the absolute need for biopsy and the pros and cons of prostatic biopsy with known low detection rate of prostatic malignancy in the Asian population.

Significant geographical variation is seen in the incidence of prostate cancer, with the lowest rate reported from Asian countries. Whether serum PSA has same predictability in the Indian population for advising prostatic biopsy in symptomatic patients at the same reference range as in the western countries remains the question to be answered. In general, at PSA level 4–10 ng/ml, PSA velocity, PSA density, prostate cancer antigen-3 gene (PCA 3) test or percent free PSA are done in order to assess the need of trans‑rectal ultrasound (TRUS) guided prostatic biopsy. This study was carried out to identify the serum PSA cut point in Indian scenario in symptomatic patients which will reduce the unnecessary prostatic biopsies and above which biopsy will identify maximum number of patients harboring prostatic malignancy, simultaneously. Furthermore, we tried to evaluate the role of digital rectal examination (DRE) at different PSA levels and to judge its role in indicating prostatic biopsy.

MATERIALS AND METHODS

After approval from the Institutional Ethical Committee, this study was conducted from January 2009 to August 2014. This was a prospective observational study.

Male patients between 45 and 70 years of age, from Mumbai and suburban areas presenting to our outpatient department with LUTS, were explained the study, and informed consent was obtained in language understandable to them. Family history of prostatic carcinoma among relatives was ruled out. Participants were evaluated with detailed history and physical examination which included DRE to assess the prostatic surface, its consistency and any irregularity or nodule. Digital rectal examination was considered abnormal when any nodule was palpable in prostatic lobes, or when the prostatic surface was irregular with hard consistency. Routine investigations and serum PSA were done. Prostatic specific antigen was measured by chemiluminescence assay kits from a single National Accreditation Board for testing and calibration Laboratories accredited laboratory. Serum PSA was repeated in all patients presenting with PSA report done outside. All PSA determinations were made before any prostatic manipulations. Patients with either two raised serum PSA (>4 ng/ml) reports or abnormalities on DRE were considered as cases. Patients with following scenarios were excluded.

1. Unwilling to participate in the study
2. Clinical evidence of prostatitis
3. Positive urine culture
4. Urethral catheter in situ
5. Taking 5 α-reductase inhibitors
6. History of any prostatic surgery or biopsy done in past 3 months
7. Patients with serum PSA <4 ng/ml without DRE abnormality
8. Moribund patients and
9. Patients in severe sepsis.

TRUS-guided standard twelve cores prostatic biopsy was done in all patients with PSA >4 ng/ml irrespective of their DRE findings, and in all patients with abnormal DRE findings irrespective of their serum PSA levels. All biopsies were done by single senior urologist. All prostatic biopsy cores were evaluated by a single senior uropathologist in our center. Histopathology report of each prostatic biopsy was assessed. The relationship between histopathology reports, various PSA ranges and DRE findings were evaluated.

We used optimal cut points, an R (R Core Team 2014) packages DiagnosisMed (Brasil 2010), pROC (Robin, Turck, Hainard, Tiberti, Lisacek, Sanchez, and Muller 2011) and Epi (Carstensen, Plummer, Laara, and Hills 2013), dated 28/10/2014) to overview different PSA cut points for the recommendation of prostatic biopsy. We calculated sensitivity, specificity, false positive, false negative, positive predictive, and negative predictive values for each cut point so as to select a cut point with maximum sensitivity and specificity simultaneously with least false positivity (FP) and false negativity (FN), so as to decrease the number of patients (not harboring malignancy) undergoing unnecessary TRUS biopsy and its associated complications. This was done to maximize the identification of patients harboring prostatic malignancy while avoiding unnecessary biopsies in benign cases. We applied Chi-square test between DRE findings and histopathology report of prostatic biopsy at PSA ranges 4–10 and 10–20 ng/ml to assess the association between DRE finding and prostatic malignancy at those PSA ranges.

RESULTS

Total 534 patients were included as cases. Mean age in our study was 64 years. Details of age, DRE findings, serum PSA and histopathology reports are given in Table 1.

We evaluated these patients to identify the PSA cut point above which unnecessary biopsies will be avoided. We kept the power of study maximum, i.e., 1 with a
confidence interval of 0.95. For this, sample size of 534 patients included in the study was sufficient. In this study, 77 patients (14.42%) were detected to have prostatic carcinoma. We calculated different cut points and multiple statistical parameters at those cut points, such as sensitivity, specificity, false positive, and false negative values as given in Table 2. Using standard screening test table format, we arranged true positive, true negative, false positive, and false negative values for each cut-point in Tables 3 and 4. Details of the DRE findings and histopathology report at PSA ranges 4–10 and 10–20 ng/ml are given in Tables 5 and 6.

DISCUSSION

As per recommendation by United State Preventive Service Task Force, regardless of age, men without symptoms should not have their PSA done routinely. American Urology Association’s new guidelines, however, recommend a shared decision-based screening for prostatic carcinoma using serum PSA, as an appropriate option for screening in men between 55 and 69 years of age. In India, physicians generally follow western literature guidelines for advising TRUS-guided prostatic biopsy in symptomatic patients in whom serum PSA is found to be elevated, i.e., >4 ng/ml while evaluating for his LUTS.

For diagnosing carcinoma prostate, PSA has been described as having the highest positive predictive value (PPV). Serum PSA level tends to change in different races. It is believed that Asian men generally have lower detection rate of prostate cancer than American men.[4,5] In Caucasians, the PPV of PSA to detect prostate cancer in the range of 4–10 ng/ml was found to be around 30%, which rose to 67% at PSA level >10 ng/ml.[6] In Korean men, the prostate cancer detection rates observed at PSA <4 ng/ml and 4–10 ng/ml were 12.4% and 15.95%, respectively.[7] Similarly, 15.8% detection rate was found in Japanese population at PSA range 4–10 ng/ml.[8] At PSA level >10 ng/ml, the detection rate of prostatic cancer was 59.5% in both Korean and Japanese men.[4,5] This study demonstrated a still lower detection rate of prostate cancer as compared to our Asian counterparts. The detection rate of prostate cancer was 3.59% (10/279) and 30% (63/210) at PSA ranges 4–10 ng/ml and >10 ng/ml, respectively [Table 1].

In the study by Chavan et al in the Indian scenario, the yield of prostatic biopsy for detection of prostate cancer was 0.6%, 2.3%, 2.5% and 34.1% at PSA ranges <4, 4-10, 10-20 and 20-50 ng/ml.[9] Detection rate of prostate cancer was 12.4%, 15.9%, 34.1%, 66.2%, and 93.8% at PSA level <4, 4–10, 10–20, 20–100, and >100 ng/ml in Korean population.[4] It was 3.5% (10/279), 12.27% (13/106), 33.34% (24/72), and 81.25% (26/32) at PSA ranges 4–10, 10–20, 20–100, and >100 ng/ml respectively, in our study [Table 1].

At PSA cut point >4 ng/ml for TRUS-guided prostatic biopsy, we found 5.19% (4/77) FN and 91.02% (416/457) FP, i.e., at this cut point, 91.02% of the biopsies will be unnecessary procedures [Table 3]. Sensitivity was 94.8% (73/77), but specificity was 8.9% (41/457) only, which is very less.

HPE: Histopathological examination, PSA: Prostatic surface antigen
At PSA cut point 9.7 ng/ml, we found sensitivity of 86.12% (62/72), specificity of 85.3% (87/102), PPV of 80.52% (62/77), and negative predictive value of 89.7% (87/97), thus getting both maximum sensitivity and specificity at this cut point simultaneously. Ten patients (13.89%) will be missed. This was the second lowest false negative value among the false negative values at different considered cut points (lowest at PSA cut-point 1.5 ng/ml). At PSA cut point of 19.3 ng/ml, sensitivity was 73.61% (53/72) and specificity was 100% (102/102). Positive and negative predictive values were 100% and 84.3% (102/121), respectively [Tables 2 and 4]. Using this value as cut point, we can avoid unnecessary TRUS-guided biopsy in maximum number of patients who do not have malignancy, but the number of patients who will be missed on initial evaluation will be large (FN-26.39% [19/72] cases). Although sensitivity and specificity at cut points 17.4 and 18.4 appear adequate, false negative value is higher. While considering cut points with maximum sensitivity and specificity at the same time, it appears that false negative value is least at 9.7 ng/ml, i.e., least patients with prostatic carcinoma will be missed at this point while possessing maximum sensitivity and specificity [Tables 2 and 4].

In patients with normal DRE in our study, only 1.389% (5/360) had prostatic malignancy where as in patients with abnormal DRE, there were 41.37% (72/174) chances to have prostatic malignancy [Table 1]. The incidence of malignancy was 3.5% (10/279) at PSA range of 4–10 ng/ml with abnormal DRE which dropped to 1.3% (3/223) if DRE was normal and it was 30% (63/210) with PSA level >10 ng/ml with abnormal DRE which dropped to 1.45% (2/137) with normal DRE in this study. Higher PSA values in symptomatic benign prostatic hyperplasia (BPH) patients could be due to associated underlying prostatic inflammation with BPH. Similar observation of higher PSA level due to underlying prostatic inflammation in symptomatic BPH patients with normal DRE was also found in another study conducted in the Indian context.[13]

Positive predictive values of PSA alone, DRE alone, and combined raised PSA and abnormal DRE: finding for diagnosing prostate cancer were 1.39% (5/360), 41.38% (72/174), and 55.2% (68/129), respectively. At PSA level <4 ng/ml, there was very low rate of detection of malignancy if only abnormal DRE was considered as an indication for biopsy (8.89%). We found a significant association between abnormal DRE and histopathology report of prostatic malignancy at PSA ranges 4–10 and 10–20 ng/ml [Tables 5 and 6]. In patients with serum PSA value above 20 ng/ml, all patients with abnormal DRE had prostatic malignancy on prostatic biopsy. Further, all three patients (1.08%) in our study with serum PSA <10 ng/ml and normal DRE had localized (T1c) disease with single core positive for malignancy, Gleason score <7 and volume of malignancy <0.2 cc (insignificant tumor).[14]

As per the study by Catelona et al., the approximate chances of cancer on biopsy at PSA levels 4–10 and >10 ng/ml were 25% and 50%–66.6%, respectively.[15] The incidence of malignancy at PSA <10 ng/ml in our study is in stark contrast with that of western literature. Prostatic surface antigen alone detected 90.5% and 90.0% of cancers at first and follow-up visits respectively, compared to 41.1% and 25.0% detection rate by DRE alone at first and
follow-up visits, in the study by Candas et al.\textsuperscript{[16]} In our study, 41.38\% (72/174) patients with abnormal DRE turned out to be malignant on biopsy, which approximates to the 50\% incidence of malignancy on the evaluation of suspicious lesions on DRE found in the study by Jewett et al.\textsuperscript{[17]}

Considering all these calculations, we can say that the incidence of prostatic carcinoma in patients with normal DRE and PSA in the range of 4–10 ng/ml is low in our study, which predominantly consisted patients from Mumbai and suburban areas. However, as the serum PSA increased above 10 ng/ml, the yield of biopsy for prostatic malignancy also increased. If we set PSA cut point 9.7 ng/ml for indicating prostatic biopsy, maximum number of patients harboring prostatic malignancy will be detected while at the same time unnecessary biopsies will be avoided, as it is the cut point at which we found maximum sensitivity and specificity at the same time.

Majority of the studies done till now have advised for TRUS biopsy when PSA level is found to be $>4$ ng/ml while screening asymptomatic patient. Screening in asymptomatic patients using PSA is not practiced in India, but opportunistic screening in symptomatic patient is routinely followed in clinical practice. There is no such study done in India which has suggested a serum PSA level in symptomatic patient, above which TRUS-guided prostatic biopsy should be done. All the patients included in the study were symptomatic, i.e., had presented with LUTS. It appears that higher PSA range in Indian population is common in symptomatic BPH patients. It can be due to associated underlying inflammation in prostate.\textsuperscript{[13]} Tests done to identify patients at high risk of prostatic malignancy at range 4–10 ng/ml so as to decide for prostatic biopsy are not widely available in India (percent-free PSA, PCA 3 test). Cost of TRUS biopsy in a government hospital in India is negligible, but in private setup, cost increases to Rs. 10,000 minimum. Further, TRUS-guided prostatic biopsy is associated with a number of complications.\textsuperscript{[6–8]} Hence, it appears that PSA value 9.7 ng/ml is descent enough to reduce the cost and unnecessary biopsy risk burden while at the same time it will help in diagnosing prostatic malignancy effectively. This option can be restricted to those patients who stay in cities with access to healthcare available and who are ready for follow-up. However, this cut point is associated with false negativity of 13.89\% (10/72). At the time of consideration of this cut point as an indicator for prostatic biopsy, those patients who will be missed (patients with PSA in the range of 4–9.6 ng/ml) will be asked to keep follow-up with repeat serum PSA and DRE every 3 months. We will be able to identify malignancy in these patients on follow-up as they will show trend of either persistently elevated or rising levels of PSA (PSA velocity $>0.75$ ng/ml/year) or abnormal DRE. At this point, biopsy should be advised. If facility available, PSA density or percent-free PSA should be done in these patients.

Our study limited in repeating the biopsy. Standard TRUS-guided prostatic biopsy was done in all patients by senior urologist only once. On follow-up, however, no malignancy was detected in any of patients who had nonmalignant initial biopsy report. This was a single center study which included population from Mumbai and nearby suburban areas. This study can be considered as an indicative study. More such multi-centric study needs to be done to confirm the findings.

**CONCLUSION**

It appears that the incidence of prostate cancer on prostatic biopsy at PSA range $<10$ ng/ml is low in Indian population. New PSA cut point of 9.7 ng/ml should be considered in order to avoid unnecessary biopsies. Unless accompanied by abnormal DRE finding, the morbidity of prostatic biopsy procedure can be avoided using this new cut point and further follow-up.

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**Conflicts of interest**

There are no conflicts of interest.

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