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Original Research Article

Is it High Time to Redraw the Boundaries of Grey Zone of Serum PSA in Indian Patients

M. Tamilmuthu[1], B. Sridhar[2], S. Vivek[3]

[1]Assistant Professor, Dept. of Urology, Government Mohan Kumaramangalam medical college, Salem
[2]Assistant Professor, Dept. of General Surgery, Govt. Krishnagiri Medical College, Krishnagiri.
[3]Assistant Professor, Dept. of General Surgery, Govt. Dharmapuri Medical College, Dharmapuri

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Corresponding Author: Dr. M Tamilmuthu
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Abstract:

Introduction: Incidence of Prostate Cancer (PCa) is higher in western countries compared to Asian countries. The cancer detection rates in India have been lower than the western world for serum PSA values less than 20 ng/ml. The reported cancer detection rate of Trans-Rectal Ultrasonography (TRUS) biopsies has been around 30 percent in western countries. However, it is much lower in Asian countries, including India. This study was conducted to find out the TRUS biopsy yield in Indian population at different PSA Cut-off values. Aim of our study is to find out the cancer detection rate of TRUS biopsy in Indian population at different serum Prostate-Specific Antigen cut off levels

Materials and Methods: A prospective study was carried out our institute. All symptomatic patients who underwent TRUS guided biopsy for indication of raised serum PSA level (>4 ng/ml) or suspicious DRE findings from March 2017 to March 2019 were included. Serum PSA estimation was done using fully automated chemi-luminescent immune assay method. 12-core biopsies were taken in all cases. Biopsy was taken using end-firing transrectal ultrasonography probe (7.5 MHz). All patients were given tablet bisacodyl (10 mg) along with tablet ciprofloxacin (500 mg) one night prior to biopsy. Post-biopsy, oral antibiotics were continued for three days.

RESULTS: Out of the 75 patients included, 28 patients had malignancy .overall cancer detection rate was 37.33%. The cancer detection rate for PSA ranges of (4-10) and (10-20) ng/ml was as low as 0% and 3.7% respectively. Patients with malignant disease had significantly smaller prostate gland size than patients with benign disease. On the other hand, cancer detection rate was 100% for PSA greater than 100ng/ml.

Conclusion: The current serum PSA cut offs of 4 ng/ml derived from western literature have a lower positive predictive value in Indian patients as compared to western population, especially for serum PSA range of (4-10) and (10-20)ng/ml . This leads to a large number of patients undergoing unnecessary biopsies. Hence increasing the present serum PSA cut-off for TRUS biopsy in Indian patients may help in avoiding unnecessary biopsies. Also Serum PSA being prostate specific and not cancer specific, we should look forward for a better tumor marker in future which is cancer specific to avoid unnecessary biopsies.

Keywords: Serum Psa, Prostate Cancer, Cancer Detection Rate, Psa Cut Off.

Introduction

Because of the widespread use of PSA screening, the incidence of prostate cancer (PCa) is higher in western nations [1]. African countries have a higher incidence than Asian countries, but a lower incidence than industrialized countries [1]. With significant regional heterogeneity, Asia has the lowest incidence of PCa [2]. Due to rising PSA usage, fast urbanization, and a western diet, the incidence has been steadily rising in Asian nations [3-5]. Despite this, the low incidence of PSA screening in India has prevented its adoption [6].

Previous studies from India have suggested that the lower cancer pickup rate may be because the PSA elevation was due to chronic prostatitis and not cancer. [4,5] This limits the use of PSA in determining an indication for biopsy. The value of PSA, which triggers a prostate biopsy, is poorly defined in many populations. In India, a PSA value of 4 ng/mL is used as a cutoff for recommending a biopsy. [1]

However, the cancer pickup rate among all men who undergo a prostate biopsy varies with the PSA level and may be less than 50% for PSA less than 20 ng/mL.[2] This does not mean that the remaining patients do not have cancer and may be a limitation of the biopsy techniques. Patients with a negative biopsy require ongoing surveillance with serum PSA, and a repeat prostate biopsy is

indicated if serum PSA is persistently elevated.[3] Prostate-specific antigen exists in multiple forms in serum and is predominantly complexed to protease inhibitors; however, one form of PSA, free PSA, is not bound to these proteins.

Measurement of PSA forms in serum helps discriminate between prostate cancer and benign prostatic disease. For unknown reasons, the percentage of free PSA is lower in serum samples from patients with prostate cancer than in serum samples from patients with a normal prostate or benign disease. Preliminary evidence also suggests that a lower percentage of free PSA may be associated with a more aggressive form of prostate cancer. Low percentages of free PSA are well established as indicators of prostate cancer, but the selection of cutoffs for use in clinical practice is complicated by the partial dependence of percentage of free PSA on patient age, prostate size, and the total PSA level.

Since the early 1990s, transrectal ultrasound (TRUS)-guided biopsies have been the standard method for detecting PCa [8]. In western nations, TRUS biopsies have been reported to have a 30% cancer detection rate [9]. Serum PSA levels below 20 ng/ml have been associated with lower cancer diagnosis rates in India than in the western world [10–12]. The purpose of this study was to determine the TRUS biopsy yield at various serum PSA cut-off levels in the Indian population.

Materials and Methods

From March 2017 to March 2019, our institute conducted this prospective study. The study included all symptomatic patients who had a TRUS guided biopsy because of a suspicious DRE finding (nodule, irregularity, hard consistency, or immobile rectal mucosa) or an elevated serum PSA level (>4 ng/ml). The study excluded patients who had undergone transurethral instrumentation or surgery within six weeks of serum PSA estimate, or who had experienced acute urinary retention or perurethral catheterization within a week.

Patients on 5-alpha reductase inhibitors and those with UTIs were also not allowed to participate in the trial.

Serum PSA estimation was done using fully automated chemi-luminescent immune assay method. Prostate volume estimation was done in all cases using the formula:

Prostate volume = (π/6) x (AP diameter) x (transverse diameter) x (cranio-caudal length)

A 12-core biopsies were taken in all cases. Biopsy was taken using end-firing transrectal ultrasonography probe (7.5 MHz). All patients were given tablet bisacodyl (10 mg) along with tablet ciprofloxacin (500 mg) one night prior to biopsy. Post-biopsy, oral antibiotics were continued for three days.

Statistical Analysis: The age, prostate size and PSA between benign and malignant disease patients were compared using Mann-Whitney test. A p-value less than 0.05 was considered to be significant. Median calculator was used to calculate the medians. Web info develops P value statistical tool software was used to calculate the P value.

Results

Around 75 patients were included in the study. 28 patients were diagnosed with carcinoma prostate. Among 75 patients 28 was malignant and rest 47 was non-malignant. The mean age was 65 years in our study group.

Table 1: Descriptive statistics

Observation	All Patients	Malignant Disease	Benign Disease	p-value
Total patients	75	28	47	-
Age (years)	65(32-90)	64.5(50-85)	65(32-90)	>0.05
Prostate Size (grams)	50(25-100)	40(25-75)	50(30-100)	<0.001
Total PSA (ng/ml)(median)	24.48 (1.55-2000)	77.90 (9.18-2000)	16.80 (1.55-79.47)	>0.05
PSA Distribution(ng/ml)				-
• <= 4	01	01	00	
• 4 –10	06	06	00	
• 10 –20	27	26	01	
• 20 –40	14	10	04	
• 40-100	22	04	18	
• > 100	05	00	05	

There was no significant difference in the age group of patients with benign and malignant disease. Patients with malignant disease had significantly smaller prostate gland size than patients with benign disease (40 vs 50 ; p=<0.001). The overall cancer detection rate of TRUS biopsy in our series was 37.33%.

Table 2: Cancer detection rates

Observation	Cancer Detection Rate (Percent)
Overall (All patients)	37.33
PSA Ranges	
• 4 –10	00
• 10 –20	3.70
• 20 –40	28.57
• 40-100	81.81
• > 100	100

However a majority of patients detected with malignancy has serum PSA greater than 40 ng/ml. The cancer detection rate for PSA ranges of (4-10) and (10-20) was as low as 0% and 3.70% respectively. On the other hand, cancer detection rate was 100% for PSA greater than 100 ng/ml.

Table 3: Positive predictive value of Cancer detection rates

Observation	Positive Predictive Value (%)
PSA Cut offs	
• 4 ng/ml	0
• 10 ng/ml	0
• 20 ng/ml	2.94
• 40 ng/ml	10.41
• 100 ng/ml	32.85
• >100 ng/ml	100

The positive predictive value for serum PSA cut offs of 4, 10 and 20 ng/ml was 0%, 0% and 2.94% respectively. None of the patients who underwent Transurethral Resection of Prostate (TURP) for benign disease had PCa on final histopathology of prostatic chips in our series. Two patients had haematuria, which was self-limiting, managed conservatively on out-patient basis.

Discussion

Northern and Western Europe, North America, and Australia/New Zealand have the greatest incidences of PCa (79.8–111.6 per 1,000,000 population) [1]. The incidence of PCa is higher in southern African countries than in northern African countries (10.6–61.7 per 1,000,000 population), with Nigeria having the highest prevalence [3]. The frequency ranges among Asian nations (4.5–10.5 per 1,000,000 people), with the Philippines having the highest rates and Iran having the lowest [4]. India is in the middle. According to several population-based cancer registries across India, the incidence of PCa ranges from 2 to 11.1 cases per 1,000,000 people [5]. Patients with gleason's grade greater than or equal to 7 are more likely in Indian population [14], and the result of our study confirms the above finding.

For the serum PSA range of 4–20 ng/ml, this study demonstrates a modest positive predictive value for PCa. This information may be helpful in advising patients on the results of TRUS biopsies prior to biopsy. If DRE results are normal, patients might feel more at ease knowing that there is a greater chance of a benign outcome with serum PSA levels between 4 and 20 ng/ml. Majority of the studies had 10-12 core biopsy scheme performed for the patients except three studies which performed 6-core biopsies. Regardless of DRE results, Agnihotri et al.'s study had a higher overall cancer detection rate (57.5%) than the other two Indian trials. They also had higher rates for serum PSA levels of (4-10) and (10-20) ng/ml, which were 43.35% and 36.57%, respectively [11]. To save 10% of needless biopsies, they proposed increasing the serum PSA cut-off to 5.4 ng/ml in symptomatic males with negative DRE for TRUS biopsy in India. This recommendation was in line with India's low TRUS biopsy cancer detection rates. The results of Sinha et al., who had an overall cancer detection rate of 24.37%, are more in line with our study. Their rates for serum PSA ranges of 4–10 and 10–20 ng/ml were as low as 7.14% and 6.67%, respectively [12].

Numerous research from various Asian nations have documented significant differences in the yield of TRUS biopsies. Among all the studies, Yu et al. from Taiwan found the lowest prevalence at 14.6%, although they only included patients whose serum PSA was between 4.1 and 20 ng/ml [15]. Patients with prostatic inflammation on final histopathology, who made up 23.2% of the study sample, were not excluded from this investigation. The low TRUS biopsy yield may be explained by this. Despite not eliminating individuals with prostatic inflammation, two Iranian investigations by Ghafoori et al. and Janbaziroudsari et al. revealed higher yields of 32.4% and 35%, respectively [8,16]. Leibovici et al.'s study from Israel found that patients with larger prostates had lower yields from the 12-core biopsy protocol. They recommended taking extra cores for patients

whose prostates were larger than 72 ml or using other modalities, such as the PCA-3 test or endorectal MRI guided biopsies, to increase the yield [17]. Lower yield was observed by Narayanaswamy et al. from Kuwait for serum PSA levels of (4–10) and (10–20) ng/ml [18]. A potential confounding factor in this study could be the fact that a greater proportion of patients in this series underwent 6-core biopsy as opposed to 12-core biopsy (mean 6.83 cores).

Despite an overall high output, a large retrospective study from China by Na R et al. found decreased yield for patients with serum PSA levels below 10 ng/ml and (10-20) ng/ml [19]. The reduced yield for serum PSA below 10 ng/ml, which was less than 21%, was corroborated by two Singaporean studies conducted by Lee et al. and Teo et al. [20,21]. The Lee et al. study found a greater yield of 38.4% for serum PSA range of (10-20) ng/ml, which is in contrast to other Asian studies [20]. Additionally, they noted a significant proportion of sepsis-related post-biopsy admissions (1.5%). Teoh et al. conducted a large study in Hong Kong and found that males with normal DRE who had symptoms and a blood PSA of less than 20 ng/ml (22%) had a lower yield [22]. Two studies from Japan by Miyoshi et al., and Imazu et al., were the only studies from Asia showing much higher TRUS biopsy yield in contrast to all other Asian studies [23,24].

With the exception of one research, the yield of TRUS biopsy was much higher in European studies than in Asian studies. For the first biopsy, Vida et al. from Romania reported a yield of up to 69.77% [25]. Contradictory TRUS biopsy yields were found in two Spanish studies by Rodriguez et al. (n = 6000) and Gonzalez et al. (n = 115) [26,27]. Even though the majority of the patients in the former trial had 6-core biopsies, the yield was higher. A significantly lower yield of 4.76% and 5.12%, respectively, was found in the latter trial for serum PSA ranges of less than 4 ng/ml and (4–10) ng/ml. Two studies from North America showed high TRUS biopsy yield more than 35%. The largest study was reported by Orozco et al., from the Unites States, showing higher overall yield despite performing 6-core biopsies [28].

According to the 2019 EAU guidelines, when compared to standard of care, the ExoDx Prostate IntelliScore urine exosome assay prevented 27% of needless biopsies. But as of right now, the ExoDx test and the MiPS-score are both regarded as experimental. The commercially available Progensa urine test for PCA3 is better than total and percent-free PSA for detecting PCa in men with elevated PSA because it exhibits significant increases in the area under the receiver-operator characteristic curve for positive biopsies. However, only Seisen et al. found a significant difference between PCA3 and PHI in six head-to-head comparison studies. PCA3 score increases with PCa volume, but there are conflicting data about whether it independently predicts the ISUP grade, and its use for monitoring in active surveillance (AS) is, as yet, not confirmed. Currently, the main indication for the Progensa test is to determine whether repeat biopsy is needed after an initially negative biopsy, but its clinical effectiveness for this purpose is uncertain.

As a result, with very few exceptions, the TRUS biopsy yield is lower in Asian populations (including India) than in other continents, particularly when the serum PSA levels is less than 20 ng/ml. The results above have been validated by our investigation. Therefore, the conventional 4 ng/ml serum PSA cut-off used in western nations results in a decreased TRUS biopsy yield for the Indian population. The PSA cut-offs that are currently in use have limited specificity and high sensitivity. Therefore, without increasing the false negative rate, the TRUS biopsy yield can be increased by raising or modifying the serum PSA cut-offs for the Indian population, preventing needless biopsies. Our study's extremely low percentage of admission-requiring post-biopsy problems suggests that, when carried out correctly and under antimicrobial supervision, the surgery is safe.

Conclusion

The current serum PSA cut offs of 4 ng/ml derived from western literature have a lower positive predictive value in Indian patients as compared to western population, especially for serum PSA range of (4-10) and (10-20)ng/ml . As a result, many patients have needless biopsies performed. Therefore, it may be possible to prevent needless biopsies by raising the current serum PSA cut-off for TRUS biopsy in Indian patients. Furthermore, since serum PSA is specific to the prostate rather than cancer, we should wait for a better tumor marker that is specific to cancer in the future to prevent needless biopsies.

Limitations

The limitation of our study is that repeat biopsies were not done in patients with high serum PSA but negative initial biopsy. Ours is not a multicentre study. Also our sample size is small. Also, all the patients with serum PSA below 4 ng/ml were not subjected to TRUS biopsy

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