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Prostate - Specific Antigen, an Effective Screening Tool for Prostate Cancer - An Analysis of 932 TRUS Core Needle Biopsies

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ABSTRACT

Prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death among men in 2020. Since it is a slow growing tumour, an early detection leads to better chance of successful treatment. Prostate-Specific Antigen (PSA) is a protein found exclusively in prostatic tissue. It is elevated in different prostatic pathologies apart from carcinoma.

A cohort of 932 prostatic core needle biopsies was selected after necessary exclusions. The routine haematoxylin & eosin and immunohistochemistry slides were retrieved along with the histopathologic diagnosis rendered. The diagnosis was then correlated with PSA.

The mean age for diagnosis of prostatic disease and carcinoma was 68.39 years and 70.21 years respectively. 50.50% cases were premalignant or malignant whereas the remaining 49.50% cases were benign. A cut-off of 4 ng/ml had a sensitivity of 99.78% and a specificity of 7.33%. Gleason score 8 and 9 were most common, accounting for 56.39% of the malignant cases.

The present study showed a statistical correlation of age and PSA with prostatic carcinoma. PSA is a valid and sensitive marker and may be continued as an early marker for the screening of prostate cancer. The risk of cancer is minimal with a PSA less than 4 ng/ml whereas an elevated PSA is associated with pathology and hence even a borderline elevation should not be ignored. Due to a low specificity, PSA needs to be corroborated with DRE and transrectal ultrasonography followed by biopsy in cases with PSA > 4ng/ml.

Keywords: Prostate, Prostate - Specific Antigen, Prostatic Adenocarcinoma, Benign Prostatic Hyperplasia

INTRODUCTION

Diseases of the prostate range from inflammation to benign prostatic hyperplasia (BPH) to malignancy. BPH and carcinoma are increasingly frequent with advancing age. Prostate cancer is the second most frequent cancer and the fifth leading cause of cancer death among men in 2020.[1] It is usually a very slow growing cancer and most patients do not have significant symptoms until the cancer reaches an advanced stage. If detected early when it is

still confined to the prostate gland, it has a better chance of successful treatment. Here comes the role of Serum Prostate-Specific Antigen (PSA) as a tool for efficient, easy and cost-effective method of screening for prostatic cancer.[2] PSA is a protein found exclusively in prostatic tissue.[3] Different prostatic pathologies lead to raised PSA levels apart from carcinoma.

The aims of present study are

1. to determine the age distribution of patients with prostatic lesions
2. to determine histologic types and their correlation with Serum PSA levels
3. to correlate the Serum PSA levels across the Gleason scores & Grade Groups
4. to evaluate the utility of PSA as a screening test for Prostatic Carcinoma

MATERIALS AND METHODS

A 5-year retrospective study was carried out in a Global Reference Pathology Laboratory which gets samples from across 7 countries. A total 1524 prostate core needle biopsies were received in this period. All the biopsies which had Serum PSA levels available were included in the study. Inadequate biopsies, follow up cases, cases without Serum PSA, post therapeutic & recurrent tumours were excluded. The final study cohort had 932 cases. The routine haematoxylin & eosin slides and immunohistochemistry (IHC) slides where available of these cases were retrieved along with the pathologic diagnosis rendered. IHC used was a multiplex cocktail comprising CK5, CK14, p63 & P504S (AMACR) in suspicious cases/ atypical small acinar proliferation (ASAP) to confirm the histologic diagnosis. Synaptophysin was used to assess neuroendocrine differentiation. The final histopathology diagnosis was then correlated with PSA levels.

RESULT

A total number of 932 cases were studied.

Age and prostatic disease: The age ranged from 20 to 97 years. The maximum number of cases were in the age group of 60 to 80 years accounting for 70% cases. Only 2.6% cases were seen below 50 years of age and 8.80% above 80 years of age (Table 1).

Table 1: Frequency of cases in different age groups

Age interval (in years)	Frequency	Percentage (%)
< 40	3	0.32
41- 50	22	2.36
51 – 60	171	18.35
61 – 70	346	37.12
71 – 80	308	33.05
> 80	82	8.80
Total	932	100

Distribution of cases across histopathologic diagnoses:

The 932 cases were segregated based on the histopathologic diagnosis. The distribution showed 50.54 % malignant cases & 49.46% benign cases. Further segregation showed 48.7% Prostatic Adenocarcinoma, 25.8% BPH with prostatitis, 10.52% BPH, 8.15% benign prostatic tissue followed by lesser percentage of other diagnoses (Table 2).

Table 2: Percentage of cases and their histopathologic diagnosis

Diagnosis	Frequency	Percentage
ASAP	14	1.50
HGPIN	2	0.21
Prostatic adenocarcinoma	454	48.71
BPH	98	10.52
BPH with prostatitis	241	25.86
Nonspecific granulomatous prostatitis	1	0.11
Prostatic Abscess	1	0.11
Prostatitis	44	4.72
Small Cell Prostatic Carcinoma	1	0.11
Negative for malignancy	76	8.15
Total	932	100

Prostatic disease and PSA: A correlation of PSA level was done with the biopsies. Among the 932 cases, 35 cases had a PSA value between 0 & 4 ng/ml, 238 cases had a PSA value between 4 & 10 ng/ml & remaining 659 cases had a PSA value of more than 10 ng/ml (Table 3).

Of the malignant cases, 66 cases had a PSA between 4 ng/ml & 10 ng/ml, 404 cases had a PSA of >10 ng/ml and only one case had a PSA of <4 ng/ml. Of the 404 cases which had a PSA of >10 ng/ml, 277 cases had a PSA value >30 ng/ml. On the other hand, in benign lesions, most of the cases with Prostatitis had a raised PSA, with

most cases falling in the range of 4ng/ml to 30 ng/ml. (Table 4).

Table 3: Correlation of PSA with different prostatic pathologies

Diagnosis/ PSA (ng/ml)	<4	4 - 10	11 - 20	21 - 30	>30	Grand Total
ASAP		8	2	4		14
BPH	9	44	32	5	8	98
BPH with prostatitis	14	87	79	18	43	241
HGPIN		1			1	2
Negative for malignancy	6	27	22	6	15	76
Nonspecific granulomatous prostatitis			1			1
Prostatic Abscess			1			1
Prostatic adenocarcinoma	1	57	73	48	275	454
Prostatitis	5	14	11	5	9	44
Small Cell Prostatic Carcinoma					1	1
Grand Total	35	238	221	86	352	932

Table 4: PSA in benign and malignant cases

	< 4 ng/ml	4-10 ng/ml	>10 ng/ml	Total
Benign	**34 (7.37%)**	**172 (37.31%)**	**255 (55.31%)**	**461**
Malignant	**1 (0.21%)**	**66 (14.01%)**	**404 ((85.78%)**	**471**

The sensitivity and specificity and positive and negative predictive values were calculated with the cut-off point of 4 ng/ml. Values under 4 ng/ml were taken as negative for malignancy and values over the cut off were taken as positive for malignancy. The histopathology report was taken as the gold standard (Table 5).

Table 5: Probability of PSA in detecting malignancy with 4 ng/ml as cut-off

Sensitivity	**99.78%**
Specificity	**7.33%**
Positive Predictive Value	**52.06%**
Negative Predictive Value	**97.14%**
Diagnostic accuracy of test	**53.75%**

Distribution of malignant cases across Gleason scores and Grade Groups: Modified Gleason Grading System is the standard grading system in Prostatic Adenocarcinoma. [4] This is based primarily on the growth pattern of neoplastic glands on low – power magnification. This system defines five patterns with decreasing differentiation and the sum of the most common primary pattern & worst remaining pattern constitutes the Gleason score that ranges from 2 to 10. Based on the Gleason score, a grade group is assigned as per **new ISUP/WHO classification 2014** that ranges from 1 to 5. [4] In our cohort of 454 cases, the commonest Gleason score was 8 (4+4) with a grade group of 4 followed by Gleason score of 9 (4+5/ 5+4) with grade group of 5 (Table 6).

Table 6: Distribution of malignant cases across Gleason scores and Grade Groups

Gleason score	Grade Group	Number of cases	Percentage (%)
6	1	81	17.87
7 (3 + 4)	2	47	10.35
7 (4 + 3)	3	66	14.54
8	4	143	31.50
9 (4 + 5/ 5 + 4)	5	113	24.89
10	5	4	0.88
Total		454	100

Gleason scores/ Grade groups and PSA: The PSA levels were compared to the Gleason scores. It was seen that higher Gleason scores had higher PSA levels (Table 7).

Table 7: Correlation of PSA with Gleason score

PSA (ng/ml)	Gleason score					
	6	7 (3+4)	7 (4+3)	8	9 (4 + 5/ 5 + 4)	10
<4				1		
4 - 10	28	6	9	9	8	
11 - 20	25	12	10	16	7	
21 - 30	5	5	15	16	5	
>30	23	24	32	101	93	4
Total	81	47	66	143	113	4

DISCUSSION

Carcinoma of prostate is a common cancer in India & worldwide presenting a challenge to urologists, radiologists & pathologists. The approach to its diagnosis has changed with emphasis on an early

diagnosis while the process is still localised to the prostate. The gold standard triad for this comprises DRE, PSA level & transrectal ultrasonography.[5] The DRE has always been the primary method for evaluating the prostate, however, it is neither specific nor sensitive and has great inter-examiner variability. [6,7]

To improve the detection rate of carcinoma, the DRE should be aided by a test with high sensitivity and Serum PSA is one such test. The diagnosis of prostate cancer has increased substantially since the introduction of PSA screening. [8,9]

The serum PSA levels, however, can be influenced by other diseases like hyperplasia & inflammation.

Correlation of Prostatic carcinoma with age: In the present study, the age ranged from 20 to 97 years. The maximum number of cases were in the age group of 60 to 80 years accounting for 70% cases. Only 2.6% cases were seen below 50 years of age and 8.80% above 80 years of age.

The mean age for diagnosis of prostatic disease was 68.39 years.

The mean age for diagnosis of prostatic carcinoma was 70.21 years which is similar to other studies (Table 8).

Table 8: Comparison of mean age (in years) of prostatic carcinoma with other studies

Present study	Gopinath Barui et al (2019) [10]	Deepak Panasseril Jayapradeep et al (2017)[11]	Vani BR et al (2015)[12]	Jasani et al (2012)[13]
70.21	66.7	68.8	63.8	65.82

The mean age for diagnosis for BPH was 66.55 years which is similar to the mean age of 63.77 years seen by Gopinath Barui et al. [10]

There was statistical correlation of age with prostatic carcinoma with a p value of 0.0001.

Distribution of benign and malignant cases: In the present study, 50.50% cases were positive for either ASAP, PIN or carcinoma whereas the remaining 49.50% cases fell into the benign category. This is similar to that seen by Londhe et al (Table 9).[14]

Table 9: Comparison of distribution of benign and malignant cases with other studies

	Present study	Londhe et al (2018) [14]	Varsha Khant et al (2017) [15]	Vani BR et al (2015) [12]
Benign	49.46%	50.86%	60.91%	70.8%
Malignant	50.54%	49.14%	37.27%	29.2%

PSA levels and Prostatic carcinoma: Serum PSA is a tumour marker but its serum levels are under the influence of physiological and pathological processes and hence PSA is not highly specific for prostate carcinoma. Clinically applicable reference values for this marker are from 0-4.0 ng/mL, but they don't exclude carcinoma always. In the present study, one case having a PSA level less than 4 ng/ml had adenocarcinoma, rest all positive cases had a PSA value above 4 ng/ml.

As per as study conducted by Ghafoori M et al (2009), a serum PSA above 4 ng/ml is an indication of prostatic biopsy.[16]

Intermediary or gray zone PSA values of 4 to 10 ng/ml can be present in patients with benign hyperplasia of prostate, prostatitis, intraepithelial neoplasia as well as in prostate carcinoma cases.[17] Similar findings are seen in our study where cases with Prostatitis had a raised PSA, with most cases falling in the range of 4 ng/ml to 30 ng/ml.

In the current study, a statistical correlation of Serum PSA with prostatic carcinoma was established with a p value of 0.0001.

In the present study, a cut off of 4 ng/ml had a sensitivity of 99.78% and a specificity of 7.33%. If the cut off was increased to 10 ng/ml, the sensitivity was reduced to 85.89% and specificity was increased to 44.61%. A high specificity and

low specificity is in sync with that observed in other studies (Table 10).

Table 10: Comparison of sensitivity & specificity of PSA with 4 ng/ml cut-off with other studies

	Present study	Vani BR et al (2015) [12]	Deepak Panasseril Jayapradeep et al (2017) [11]	Ghafoori M et al (2009) [16]	Mbaeri TU et al (2018) [18]	Bannakij Lojanapiwat et al (2014) [19]
Sensitivity	**99.78%**	**100%**	**96.67%**	**93.4%**	**99.13%**	**98.0%**
Specificity	**07.32%**	**38.1%**	**38.57%**	**15.3%**	**02.15%**	**09.3%**

Distribution of cases as per Gleason score: The cases of prostatic adenocarcinoma were graded according to the Modified Gleason Grading System and the new ISUP/WHO classification 2014.[4] In the present study, Grade 4 and 5 (Gleason score 8 and 9) were most common, accounting for 56.39% of the malignant cases. Similar findings were also seen in study by Londhe et al in Grade 4 and 5 (Gleason score 8 and 9) accounted for 64.91% of the malignant cases.[14] In the studies done by Atchyuta M et al (2016) & Deepak Panasseril Jayapradeep et al (2017), the most common Gleason's score was 7 with Grade Group 3 in 43% & 51.61 % cases respectively, whereas in the study by Gopinath Barui et al (2019), Grade Group 3 and 4 (Gleason score 7 and 8) accounted for a total of 69.56% cases. [20,21,10]

Correlation between PSA and Gleason score: In our study, it was seen that higher Gleason scores had higher PSA levels. However, this trend was not seen in a significant cohort of cases, hence a statistical correlation between Gleason score and serum PSA level could not be established with a p value 0f 0.7100. This was similar to the study by Rashid et al. (2020), Londhe et al (2018) & Gurumurthy D et al (2015). [21,14,22] However, other studies like Atchyuta M. et al (2016), Karazanashvili G et al (2003) and Wei -Jen Shih et al (1992) showed that there is strong positive correlation between Gleason score given in prostatic adenocarcinomas and PSA values. [20,23,24]

Limitations

1. Inability to incorporate the PSA levels of all the study subjects
2. Serum PSA values obtained were not measured by the same method or on the same platform.
3. Inability to correlate the cases with other serum parameters like PSA velocity, PSA doubling time.
4. Lack of follow up assessment

CONCLUSION

There are very few studies comparing PSA levels with various prostatic lesions in core biopsies alone. Also, the sample size of the present study further increases the accuracy data of the study. The present study showed a statistical correlation of age with prostatic carcinoma with a p value of 0.0001. The mean age for diagnosis of prostatic disease was 68.39 years and of prostatic carcinoma was 70.21 years. The distribution of malignant and benign cases was 50.50% & 49.50% respectively. A statistical correlation of PSA with prostatic carcinoma was established with a p value of 0.0001. Grade 4 and 5 (Gleason score 8 and 9) were most common, accounting for 56.39% of the malignant cases. Although higher Gleason scores had higher PSA levels, a statistical correlation between Gleason score and PSA level could not be established with a p value 0f 0.7100. PSA had a sensitivity of 99.78% and a specificity of 7.33% with a diagnostic accuracy of 53.75% with a cut-off of 4 ng/ml. This showed that PSA is a valid and sensitive marker and may be continued as an early marker for the screening of prostate cancer. The risk of cancer is minimal with a PSA less than 4 ng/ml whereas an elevated PSA is associated with pathology and hence even a borderline elevation should not be ignored. Due to a low specificity, PSA needs to be corroborated with DRE and transrectal ultrasonography followed by

biopsy in cases with PSA > 4ng/ml to conclude.

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Ethical Approval: Approved

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