

## Study of transrectal ultrasound guided biopsies of prostate in correlation with serum prostate specific antigen level

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### Abstract

**Introduction:** Prostatic carcinoma has been increasing in India in the recent past. It is routine clinical practice to test for serum PSA followed by prostatic biopsy in all the suspected cases of prostatic carcinoma.

**Aims and Objectives:** To study the histopathology of prostate biopsies and to correlate the serum PSA levels with TRUS guided biopsy findings of carcinoma and BPH.

**Materials and Method:** This was a retrospective study carried out in the department of Pathology at Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, over a period of three years. A total of 128 patients underwent TRUS guided prostate biopsy out of which only 61 cases were considered for the study as they had also undergone simultaneous prebiopsy serum PSA testing. The biopsy findings of carcinoma and BPH were correlated with serum PSA level.

**Observations and Results:** The mean age for carcinoma and BPH was 66.5 and 64.6 years respectively. A total of 17 (27.8%) cases had serum PSA in the grey zone of 4-10 ng/ml. Among BPH cases, 33.3% showed an elevated serum PSA in the 20.1- 100 ng/ml range. A Gleason score of 3+4 was the most common score and was seen in 63.3% cases. The mean PSA for carcinoma was 48.7 ng/ml. High serum PSA in the range of 20.1- 100 ng/ml range was seen in 46.6% cases of carcinoma. Also 16.6% (5 out of 30) cases of carcinoma showed PSA in the grey zone.

**Conclusion:** Serum PSA levels more than 20 ng/ml point towards carcinoma many cases of BPH can show values in the grey zone area that can cause unnecessary anxiety in patients. TRUS biopsies are useful for diagnosing prostatic adenocarcinoma.

**Keywords:** Carcinoma prostate, BPH, Serum PSA, Grey zone, TRUS biopsies

### Introduction

Incidence of carcinoma of prostate has gradually increased worldwide since the last fifty years due to the availability of better diagnostic techniques, widespread use of the test for serum prostate specific antigen, increased life expectancy and awareness of the population in general.<sup>(1)</sup>

Among the male population, prostatic carcinoma ranks at second position and holds sixth place for causing cancer related mortality worldwide.<sup>(2)</sup>

In our own Indian population too it holds second and third position as a cause of cancer among males in

various metropolitan cities. Data from Indian population based cancer registries shows it to be in the first ten common cancers in males. Prostatic cancer prevalence rate is more or less similar all over India. It is thought that the number of cases of prostatic cancer will double in a couple of years.<sup>(3)</sup> Hariharan et al<sup>(4)</sup> have observed wide variation in the incidence of prostatic cancer in different parts of our country. But they agree that the overall incidence is definitely less than the incidence in western population and that this malignancy is on the rise in India. Whenever carcinoma of prostate is suspected clinically, a digital rectal examination (DRE),

serum PSA testing, and biopsy of the prostate are performed.<sup>(5)</sup>

Ours being a tertiary care centre, we get patients of symptomatic prostatomegaly from neighbouring rural areas who are referred by physicians or surgeons for the TRUS guided biopsy procedure. As many of the cases are referral patients, their DRE findings; and serum PSA level in some cases are not available. In our study we attempted to correlate the serum PSA levels with the histopathology on TRUS guided prostate biopsies.

### Aim of the study

To study the histomorphological features of prostate biopsies and to correlate the serum PSA levels with biopsy findings in cases of carcinoma and BPH with emphasis on those cases who had serum PSA in the grey zone area.

### Materials and Method

This was a retrospective study done in the department of Pathology at Kamineni Academy of Medical Sciences and Research Centre, Hyderabad, over a period of thirty-six months from January 2013 to December 2015. In this period a total of 128 TRUS biopsies were received out of which only 61 cases had undergone simultaneous serum PSA testing in our hospital in the department of Biochemistry. The study group consisted of these 61 cases. The patient age ranged from 40 to 79 years.

#### Inclusion criteria

- Cases of prostatomegaly who underwent TRUS guided prostatic core biopsy.
- Only those cases were included for which simultaneous prebiopsy serum PSA testing was performed in our laboratory.

#### Exclusion criteria

- Cases who underwent only TRUS biopsy without serum PSA testing.
- Serum PSA was tested after the biopsy procedure.
- Serum PSA values were tested at other laboratories.
- Histopathology specimens of transurethral resection of prostate (TURP) were excluded.
- Known cases of carcinoma of prostate on treatment

undergoing repeat TRUS biopsies were excluded.

- Recent history of instrumentation.

The TRUS (transrectal ultrasound) guided biopsies were carried out in the Radiology out-patient unit. Patients on antiplatelets or anticoagulants were reviewed by their primary care physician or cardiologist for stopping the drug 5 to 6 days prior to the procedure. A prophylactic broad spectrum oral antibiotic was given to all the patients prior to the procedure. The procedure was carried out in the left lateral decubitus position under local intrarectal lidocaine gel application. A spring biopsy device (biopsy gun) with 18 G needle was used. On an average, 6 to 12 core biopsies were obtained from each patient and especially any suspicious areas as seen on ultrasound were thoroughly sampled. The tissue cores were put in 10% buffered formalin fixative and were sent to the department of Pathology. All the biopsies were subjected to routine tissue processing. Five micron thick sections were cut and stained with hematoxylin and eosin (H and E) and examined under the microscope.

The pre-biopsy serum PSA values for all patients were noted from the department of Biochemistry. The serum PSA of all the patients was tested on Beckman Coulter Access 2 instrument based on the method of Chemiluminescence (CLIA).

The biopsy and serum PSA levels were analyzed.

### Observations and Results

**Table 1: Histopathological diagnosis of TRUS guided biopsies**

Histopathologic categories	No. of cases	Percentage
Adenocarcinoma (Ca)	30	49.18
Suspicious of malignancy	03	4.91
Benign nodular hyperplasia with focal atypia	04	6.55
Benign nodular hyperplasia (NH)	24	39.34
Total	61	100

Out of total 61 cases, adenocarcinoma was reported

in 49.18% and benign nodular hyperplasia in 39.34% cases of adenocarcinoma. cases. Perineural infiltration was present in 13 (43.3%)

**Table 2: Age wise distribution in relation to histopathology**

Age	Carcinoma	Suspicious of malignancy	Nodular hyperplasia with focal atypia	Nodular hyperplasia	No. of cases	Percentage (%)
40 - 49	3	0	0	0	3	4.9%
50 - 59	3	1		7	11	18.0%
60 - 69	11	2	3	09	25	40.9%
70 - 79	10	-	1	6	17	27.8%
80 - 89	3	-	-	2	5	8.1%
Total	30	3	4	24	61	100%

Most number of patients indicated for TRUS biopsy and also of adenocarcinoma and BPH were in the 60 to 80 year age range. The mean age for carcinoma and BPH was 66.5 and 66.4 years respectively.

**Table 3: Histopathological categories and Serum PSA levels (ng/ml). N= 61**

Histopathology	< 4	4 - 10	10.1- 20	20.1 - 100	> 100	Total no. of cases
Carcinoma	0	5	7	14	4	30
Suspicious of malignancy	0	2	1	0	0	03
Nodular hyperplasia with atypia	0	1	2	1	0	04
Nodular hyperplasia	1	9	6	8	0	24

For 46.6% cases of prostatic carcinoma and 33.3% of BPH cases, the serum PSA values were between 20.1- 100 ng / ml.

13.3% cases of carcinoma had serum PSA value >100 ng/ml. Not a single case of BPH had serum PSA >100 ng/ml.

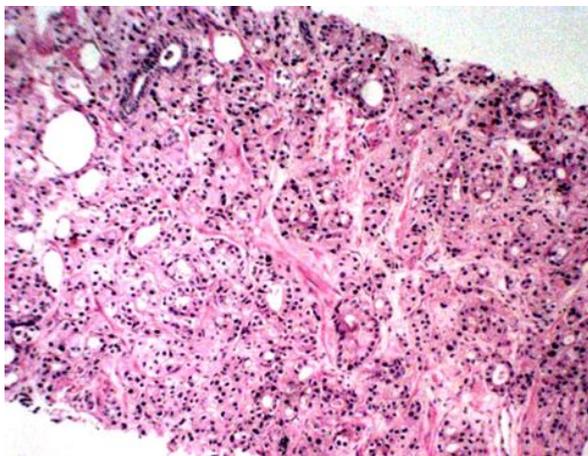
The grey zone of 4-10 ng/ml was seen in 27.8% cases.

The mean PSA for carcinoma was 48.7 ng/ml. Among carcinoma cases, 16.6% had serum PSA value in the grey zone.

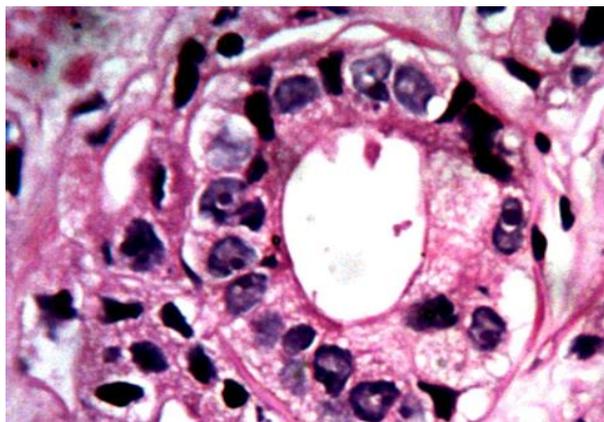
**Table 4: Gleason score in carcinoma prostate (n=30)**

Gleason score	No. of cases	Percentage (%)
3+3	3	10%
3+4	19	63.3%
3+5	2	6.6%
4+3	1	3.3%
4+5	1	3.3%
5+4	2	6.6%
5+5	2	6.6%
Total	30	100%

The most common score on histopathology was 3+4.



**Fig. 1: Trucut biopsy of carcinoma prostate with Gleason score of 3+4. (Hematoxylin and eosin stain, 100 X)**



**Fig. 2: Trucut biopsy of carcinoma prostate with pleomorphic vesicular nuclei and prominent nucleoli in the glandular cells. (Hematoxylin and eosin stain, 400 X)**

## Discussion

The incidence of prostatic carcinoma is higher in Western population as compared to Indian population. At present prostatic carcinoma is being diagnosed more and more frequently in the urban Indian population. (4) In our study 61 cases of prostatomegaly who underwent TRUS guided biopsies were studied and their serum PSA levels were correlated with the histopathology reports.

**Manual and TRUS biopsy:** Biopsy of the prostate can be performed with or without ultrasound guidance. (6) Carter et al. Digitally guided biopsies may miss

localized lesions as it is a blind procedure. The guided biopsies are better and yield representative material in most of the cases. Lippman et al<sup>(7)</sup> also reported higher rate of detection of malignancy in prostate by the TRUS guided biopsy as compared to biopsies where there was no imaging guidance. As ours is a tertiary care centre, all the biopsies were TRUS guided biopsies.

**Age:** In the present study, the mean age of prostatic carcinoma was 66.5 years. This compares well with the findings of Hariharan et al,<sup>(4)</sup> and Malathi et al,<sup>(8)</sup> Ganesh et al,<sup>(9)</sup> and Ghagane et al<sup>(10)</sup> who reported the mean age in their studies as above 65years, 65, 64, and 70 years respectively.

**Serum PSA levels in BPH and PC:** Serum PSA is the most accurate of the three diagnostic tests evaluated. The addition of DRE and TRUS improves the detection rate of prostate cancer over PSA alone.<sup>(11)</sup> However, other workers like Neal et al have concluded that PSA is not the optimal test for prostate cancer as it lacks the features of a good screening test. They have recommended its use to identify the disease in high risk groups only such as men with first degree relatives with prostate cancer.<sup>(12)</sup>

In spite of some drawbacks, PSA estimation is a popular screening test for prostate cancer. PSA level varies with age and nomograms are available that are mostly applicable to western population. The PSA depends on the ethnicity of the individuals and is variable among different ethnic groups. Sin-Eng Chin et al<sup>(13)</sup> observed similar median PSA values in people of different ethnic groups in Singapore. They also observed a positive correlation between the PSA value and the age of the individuals and also recorded lower values in Singaporean population as compared to white population in the United States. Mochtar et al<sup>(14)</sup> observed that the PSA predictive values for cancer detection were almost similar to the Western Countries. Malathi et al<sup>(15)</sup> did a study on the serum PSA in South Indian males who were healthy and also gave reference value for this population. They observed lower serum PSA in their study population when compared to other populations from different areas of the world.

Ganpule et al<sup>(16)</sup> also studied the serum PSA in a

limited Indian population in the state of Gujarat and found slightly lower serum PSA levels than the western population. Though serum PSA estimation is advocated for detecting prostate cancer in the early stages, Dubey et al<sup>(17)</sup> do not recommend it in Indian males as this cancer has a lower incidence in our country.

Shah et al<sup>(18)</sup> compared four ethnic groups in India and found that the free PSA levels correlated well with the patients' age but did not correlate well with the ethnicity.

Gupta et al<sup>(19)</sup> also observed that healthy Indian men have lower age-specific serum PSA ranges compared to certain other populations of the world. They also confirmed that serum PSA correlates well with advancing ages.

Agnihotri et al<sup>(20)</sup> in their study have recommended prostate biopsy in only those symptomatic men whose serum PSA level was more than 5.5 ng/ml and who had a negative DRE. Ghagane et al<sup>(10)</sup> also reported mean PSA level as 37.71ng/ml in prostatic carcinoma patients.

Malathi et al<sup>(8)</sup> in their 2006 study reported higher serum PSA levels in cases of BPH and carcinoma when compared with healthy males. In our study also 46.6% and 33.3% cases of carcinoma prostate and of BPH respectively had higher serum PSA value in the 20.1-100 ng/ml range. Serum PSA can be elevated in non-carcinoma conditions such as BPH, prostatitis, infarcts of prostate, prostatic massage and prostatic biopsy.<sup>(21)</sup> Markedly elevated serum PSA, above 100 ng/ml points towards carcinoma of prostate. In our study, 13.3% cases of carcinoma had serum PSA more than 100 ng/ml. Such high levels were not seen in cases of BPH.

Malathi et al<sup>(8)</sup> in their study have reported mean PSA concentration as 3.6 ng/ml and the maximum PSA concentration as 28 ng/ml in patients of BPH. In our study the mean PSA was 17.6 ng/ml for BPH patients. The maximum PSA was 31 ng/ml for the BPH patients. Our findings are similar to those of Stamey et al<sup>(21)</sup> who also reported a maximum PSA concentration of 37 ng

/ml in patients of BPH. The adenocarcinoma group in the study by Malathi et al<sup>(8)</sup> showed a mean PSA concentration of 408 ng/ml, and minimum and maximum PSA values in the carcinoma group as 10 and 9800 ng/ml respectively, whereas, in our study the mean PSA for carcinoma was 48.7 ng/ml and the minimum and maximum PSA values in the carcinoma group were 5.2 ng/ml and 155 ng/ml. Various authors all over the world have reported mean PSA values for BPH as 7.9, 2.1 and 9.8 ng/ml.<sup>(21,22,23)</sup>

Different authors working in different geographic areas all over the world have published serum PSA values in the grey zone area i.e. 4 to 10 ng/ml, for e.g. 46%, 18%, and 31%.<sup>(23,24,25)</sup> In the present study we found 27.8% cases to be in the grey zone. In our study 37.5% patients of BPH had serum PSA in the universally accepted grey zone of 4-10 ng/ml and this is similar to the findings of Malathi et al<sup>(8)</sup> where 20.8% cases of BPH had serum PSA value in the grey zone. Higher PSA values of >10 ng/ml were reported as 7% and 14% by Partin et al and Barak et al.<sup>(23,26)</sup> On the other hand, some studies have reported PSA greater than 10 ng/ml only in 2-3% of BPH patients.<sup>(25)</sup> Malathi et al<sup>(8)</sup> reported >10 ng/ml PSA in 8.2% BPH cases. In our study 58.3% of patients of BPH had serum PSA level more than 10 ng/ml. Many patients with elevated PSA also had acute inflammation in the biopsies which could explain the rise in serum PSA. These patients were advised follow up PSA estimation. Whenever transient rise or fluctuating PSA levels are observed malignancy is unlikely.<sup>(8)</sup>

Prostate cancer can occur even when the PSA is less than 4.0 ng/ml and reverse is also true.<sup>(27)</sup>

Table 5 shows comparison of serum PSA in cases of BPH and carcinoma in our study with that of other studies.

**Table 5: Serum PSA in BPH and prostatic carcinoma**

Study	Serum PSA in BPH (ng/ml)	Serum PSA in Carcinoma (ng/ml)	% of cases with BPH having serum PSA in Grey zone
Present study	3.2-31	5.2-155	37.5%
Malathi et al <sup>(8)</sup>	0-28	10-9800	20.8%
Amayo et al <sup>(28)</sup>	0.34-36	1.78-4339	29.6%
Naz et al <sup>(29)</sup>	3-24	3.2-80.6	50%
Shetty et al <sup>(30)</sup>	0.4-4.6	10-1525	45%
Akhter et al <sup>(31)</sup>	-	3.15-4240	30%

**Histopathological findings:** In the present study, carcinoma was seen in 49.1% cases similar to the findings of Hosein et al<sup>(32)</sup> who encountered carcinoma in 51.8% cases out of 546 patients studied.

Kanya Kumari et al<sup>(33)</sup> (n=70) observed 44.28% cases with adenocarcinoma, and 20% having benign prostatic hyperplasia.

A Gleason's score of 6 was seen in 10% patients. The most common Gleason score reported in our study was of 7 and was seen in 20 (66.6%) patients. Ghagane et al<sup>(10)</sup> observed the most common score as  $\geq 8$  which was seen in 88.7% of their cases. They also found significant positive correlation between serum PSA level and Gleason score. Other authors<sup>(32)</sup> have reported Gleason's score 7 as the commonest score in prostatic carcinoma. In a study by Kanya Kumari et al<sup>(33)</sup> also the most common Gleason score was reported as 7 (3+4) and was found in 51.61% of patients. In our study we observed perineural infiltration in 43.3% cases. Bismar et al<sup>(34)</sup> observed 11% perineural infiltration in prostatic carcinoma in their study. Presence of perineural infiltration is considered a poor prognostic factor.

### Conclusions

Prostate cancer is common above 65 years. Higher serum PSA values especially above 20 ng/ml are more likely in malignancy of prostate. Cases of BPH can show PSA values in the grey zone area that can cause unnecessary alarm in patients. Both urologic and non-urologic clinicians need to be aware of this so as to allay the anxiety in patients till the final TRUS biopsy

report is available.

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