Correlation of serum PSA level with histomorphologic study in prostatic diseases

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Abstract

Introduction: Worldwide, diseases of prostate gland are responsible for significant morbidity and mortality among adult males. Prostate cancer is the second common cause of cancer related death in men after lung cancer but it can be completely cured if detected in early stage.

Aim: To evaluate the histomorphological spectrum of non-neoplastic and neoplastic lesions of prostate and to establish the correlation of histomorphological findings with serum prostate specific antigens levels.

Materials and Methods: 1 year Prospective Study was done on 110 patient at Department of Pathology , Indira Gandhi Medical College, Shimla, H.P from 1st July 14 to 30th June 15. Unwilling patient, inadequate biopsies and patient with metastatic carcinoma to prostate were excluded from study. Paraffin embedded sections were stained with routine haematoxylin and eosin stain. The PSA levels were estimated in biochemistry department using automated Chemiluminescence method on Beckman Coulter Access –II System. These values were correlated with histopathological diagnosis.

Result: With 63.3%, benign prostatic hyperplasia was the most common lesion followed by Malignancy in 29.1% and prostatic intraepithelial neoplasia in 7.3% of total cases. Serum prostate specific antigens level was increased in 65.5% cases. Mean serum prostate specific antigens value of benign prostatic hyperplasia with and without inflammation is and10.9ng/ml and9.8ng/ml respectively. Mean serum prostate specific antigens value is 18.9 ng/ml in Low Grade and78.5 ng/ml in high grade prostatic intraepithelial neoplasm. Mean serum prostate specific antigen in malignancy was 101.2ng/ml antigen in.

Conclusion: On statistical analysis PSA is found to be a sensitive and early marker for the diagnosis of prostate cancer. With a cut off value of 4ng/ml sensitivity was found to be 93.75% and specificity was 46.15%.

Keywords: Adenocarcinoma prostate, Benign prostatic hyperplasia, Prostatic intraepithelial neoplasia, Prostatitis Serum prostate specific antigens.

Introduction

Prostate cancer is the most common malignant tumor in men over the age of 65 years. In India average annual cancer incidence rates for prostate ranged from 5.0 to 9.1 per 100,000/year.[1] Prostatic diseases are usually present as lower urinary tract symptom. Histological, the prostate gland consists of compound tubulo alveolar glands lined by double layer of cells, a basal layer of low cuboidal epithelium along with scattered neuroendocrine cells covered by columnar secretory cells. The glandular epithelium secrets prostate specific antigen. Stroma has large content of smooth muscle fibers.

Most frequently encountered diseases of prostate are benign prostatic hyperplasia, prostatitis, and carcinoma.[2] Of these, benign prostatic enlargements are the most common. Clinically prostatitis can be classified into three broad categories including acute, chronic, and granulomatous prostatitis.

The most likely precursor lesions of prostate cancer namely prostatic intraepithelial neoplasia (PIN) and atypical adenomatous hyperplasia (AAH) are being recognized with high frequency and progresses to frank malignancy in about 50% and 6.5% of patients respectively.[3] High grade prostatic intraepithelial neoplasm, a higher level of hyperchromatisms and pleomorphism exists with presence of nucleoli and suggests an increased risk for adenocarcinoma, however it can be up to 10 years before prostate carcinoma presents.[4] Adenocarcinoma of the prostate is one of the most common form of cancer in men, accounting for 29% of cancer in the United States in 2007.[5] Rate in India is less than 1/10 of rate in USA. The incidence of prostate cancer is higher in Bangalore, Chennai, Delhi and Mumbai than other areas.[6]

PSA, a glycoprotein is produced by the epithelial cells of prostatic tissue with normal levels of 0-4ng/ml.[7] Increased PSA levels are seen in all prostatic diseases but markedly elevated levels are indicative of carcinoma prostate. It is considered as most effective test currently available for detection of carcinoma prostate and predicting tumor recurrence months before its detection by any other method.

Materials and Methods

The present study is a prospective study of 1 year period done from 1st July 14 to 30th June 15 in the Department of Pathology, Biochemistry, Urology and Radio diagnosis, Indira Gandhi Medical College, Shimla H.P.

Prostatic tissue of 110 patients was collected through transurethral resection (TURP), trans rectal

ultra sound (TRUS) guided biopsy and prostatectomy for histopathological examination. (Fig. 1a and 1b) Serum samples for biochemical analysis (S.PSA) were collected and estimated in biochemistry department using automated Chemiluminescence method on Beckman Coulter Access –II System.

After clinical examination, blood examination and radiographic examination samples of prostatic tissue were obtained and immediately fixed in 10% buffered formalin followed by grossing, processing and staining of tissue. Routine staining was done by haematoxylin and eosin staining. Special stain used where ever necessary.

Analysis

Serum prostate specific antigen cut off point was fixed at 4ng/ml .Sensitivity and Specificity were calculated regarding the diagnostic efficacy of biochemical marker for malignancy.

Results

The present study was conducted on 110 patients with prostatomegaly. 97.3% patients presented with lower urinary tract symptoms, out of which 8 patients also had associated hematuria.

Most frequent age group in benign prostatic hyperplasia patients ranged between 60-69 years. The mean age was 67.4. Prostatic intraepithelial neoplasm and malignancy were common in 8th decade with mean age 69.25 and 68.3 years respectively. (Table 1)

Table 1: Age wise distribution of prostatic lesion (n=110)

Age wise Groups (years)	Total No. of Patients	Benign		Prostatic intraepithelial neoplasm		Malignancy	
		No. of Patients	Percentage	No. of Patients	Percentage	No. of Patients	Percentage
50-59	20	12	17.2	02	25	06	18.8
60-69	38	29	41.4	-	-	09	28.1
70-79	41	22	31.4	05	62.5	14	43.8
80-89	11	07	10.0	01	12.5	03	09.3
Total	110	70	100	08	100	32	100

Out of a total of 110 patients, benign lesions constituted 63.6% cases, followed by malignancy in 29.1% and prostatic intraepithelial neoplasm in 7.3%. (Table 2)

Benign enlargement of prostate was due to benign prostatic hyperplasia with or without inflammation. Hyperplasia without inflammation BPH (Fig. 2) was present in 75.7% patients and, hyperplasia associated with inflammation in 24.3%. (Fig. 3a &b) Three cases of benign prostatic hyperplasia showed squamous /transitional metaplasia. Five cases had associated basal cell hyperplasia. (Fig. 4)

Out of 7.3% patients of prostatic intraepithelial neoplasm 75% was of low grade prostatic intraepithelial neoplasm and 25% of high grade prostatic intraepithelial neoplasm. **(**Fig. 5)

Out of 29.1% cases of malignancy 96.8% were adenocarcinoma **(**Fig. 6**)**, and only 3.2% showed feature of undifferentiated carcinoma.

Table 2: Spectrum of prostatic lesions (n=110)

S. No.	Prostatic Lesions	No. of Patients	%age
1	**Benign**	70	63.6
	a)Benign prostatic hyperplasia without prostatitis	53	48.2
	b)Benign prostatic hyperplasia with prostatitis	17	15.4
2	**Prostatic intraepithelial neoplasm**a	08	7.3
	a)Low grade prostatic intraepithelial neoplasm	06	5.5
	b)High grade prostatic intraepithelial neoplasm	02	1.8
3	**Malignant**	32	29.1
	a)Adenocarcinoma	31	96.8
	b)Undifferentiated carcinoma	01	03.3
	Total	110	100

Most of the study cases with benign lesions and prostatic intraepithelial neoplasm showed normal digital rectal examination constituting 64.3% and 62.5%cases respectively, where as majority of prostatic carcinoma patients 87.5% had abnormal digital rectal examination having either nodular and/or hard prostate on palpation.

In the present study 106 patients had their prostatic assessment through USG. In present study size of the prostate did not correlate well with benign and malignant lesions.

Increased levels of serum prostate specific antigens were found in 65.5% cases, of which 44.4% showed

levels more than 20ng/ml followed by 40.2% patients with levels up to 10ng/ml. Levels between 10-20 ng/ml. was found in 15.2% cases. (Table 3)

The mean serum prostate specific antigens value in benign prostatic hyperplasia without inflammation was 9.8 ng/ml, whereas as patients of benign prostatic hyperplasia with inflammation showed slightly raised value of 10.8 ng/ml Mean serum prostate specific antigens value was 18.9 ng/ml for low grade prostatic intraepithelial neoplasm and 78.5 ng/ml for high grade prostatic intraepithelial neoplasm. Mean serum prostate specific antigens level was 101.2ng/ml. for malignancy.

Table 3: Serum prostate specific antigens correlation with prostatic lesions (n=110)

S. PSA(ng/ml)	Total No. of Patients	Benign		Prostatic Intraepithelial Neoplasm		Malignancy	
		No. of patients	%age	No. of Patients	%age	No. of Patients	%age
Upto 4	38	33	47.1	03	37.5	02	06.2
4-10	29	20	28.6	01	12.5	08	25.0
>10-20	11	06	08.6	01	12.5	04	12.5
>20-50	16	08	11.4	01	12.5	07	21.9
>50	16	03	04.3	02	25.0	11	34.4
Total	110	70	100	08	100	32	100

Sensitivity: likelihood that the patient with disease has positive test (malignancy) results. In our study the sensitivity of the test was 93.75%.

Specificity: likelihood that the patient without disease has negative test results. The present study showed that the test is 46.15% specific.

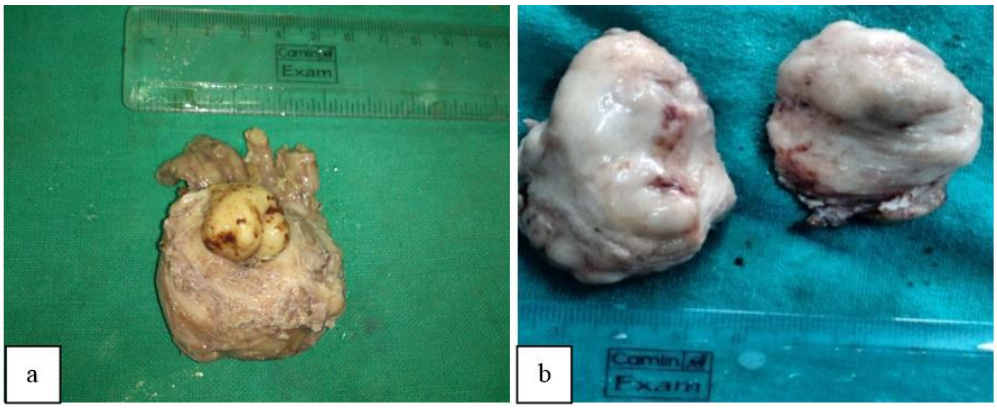

Fig. 1: Gross photograph of (a): radical prostatectomy; (b): Frayer's prostatectomy

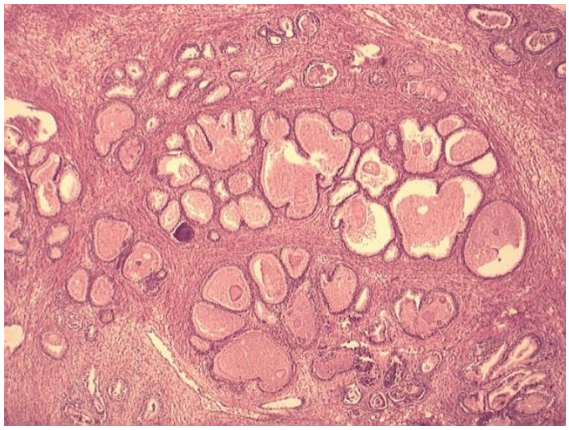

Fig. 2: Benign prostatic hyperplasia (40x,H &E stain)

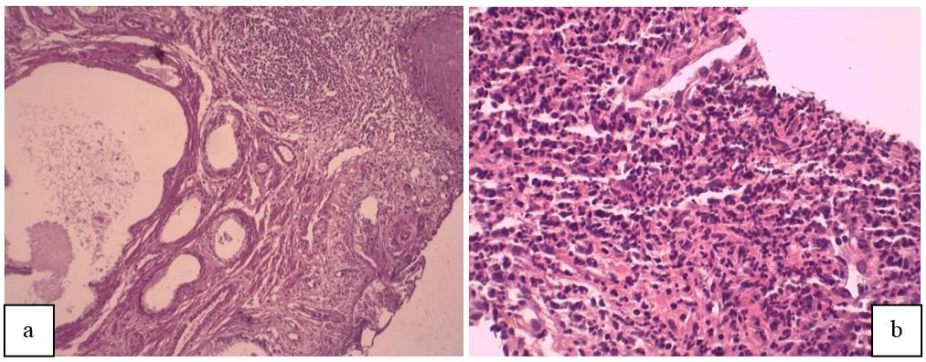

Fig. 3a: BPH with Chronic nonspecific prostatitis; 3b: Acute prostatitis (100x, H&Estain)

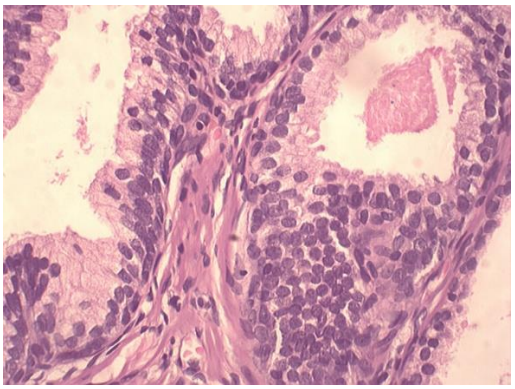

Fig. 4: Basal cell hyperplasia (400x, H &E stain)

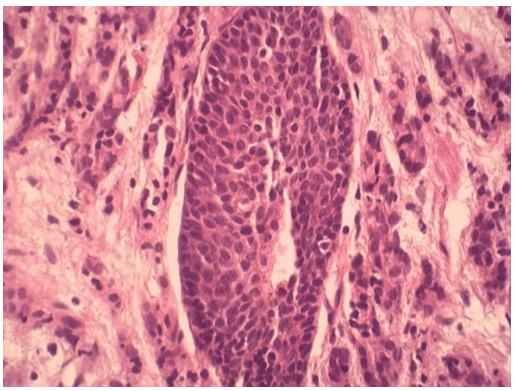

Fig. 5: High grade prostatic intraepithelial neoplasm (400x,H&E stain)

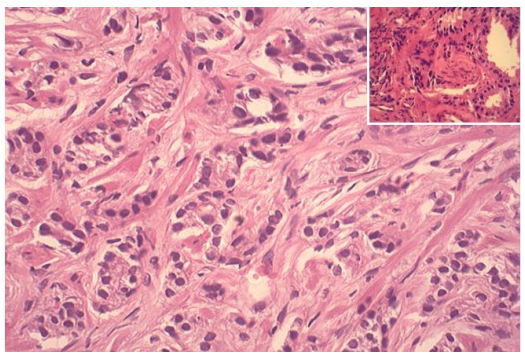

Fig. 6: Adenocarcinoma prostate, Gleasons grade 3 and perineural invasion (inset)(100xH&E stain)

Discussion

The results of study group of 110 patients were compared with those of previous studies.

97.3 percent of the patients in the present study complaint of lower urinary tract symptoms with or without hematuria, in 2015 Raza et al[8] also published a similar study in which they found lower urinary tract symptoms as most common presenting symptom.

The age of patients suffering from prostatic disease ranged from 50 to 85 years, with mean age being 68 years. The maximum numbers of cases were seen in 7th and 8thdecades. The peak incidence of benign prostatic hyperplasia in present and previous studies were in 7th decade of life followed by 8th decades. The mean age being 67.4 years. The peak age group of prostatic intraepithelial neoplasm in our study was 70-79 years with mean of 69.25 years. The age range of patients of benign prostatic hyperplasia and prostatic intraepithelial neoplasm is comparable to the study conducted by Wadgaonkar et al (2013).[9] The peak age incidence of malignancy in our study was in 7th and 8th decades with a mean of 68.3 years similar to the study by Jasani et al[10] (2012) and Albashari et al (2014).[11]

The present study classified the prostatic lesions in three major categories as benign, and malignant, Prostatic Intraepithelial Neoplasm. Like all other studies benign prostatic hyperplasia observed as the major group among prostatic diseases.

Benign prostatic hyperplasia with inflammation and benign prostatic hyperplasia without inflammation constituting 24.3 and 75.7 percent respectively, Inflammatory prostatic lesions are further subcategorized as benign prostatic hyperplasia with acute prostatitis, chronic nonspecific prostatitis, and granulomatous prostatitis as also reported by and correlated well with studies conducted by Wadgaonkar et al (2013) and Lakhey et al (2010).[12] They also observed that chronic nonspecific prostatitis was the commonest inflammatory lesion. Granulomatous lesion was not reported in Lakhey et al (2010) study whereas no case of acute prostatitis was observed in Wadgaonkar et al (2013) study.

Of 110 cases in this study, prostatic intraepithelial neoplasm accounted for 7.3 percent which included low grade prostatic intraepithelial neoplasm (75 percent)

and high grade prostatic intraepithelial neoplasm (25 percent). Jasani et al reported the percent incidence being 7.2% of 180 cases. Rukhsana et al (2014)[13] studied 60 cases and observed high grade prostatic intraepithelial neoplasm in 75% and low grade prostatic intraepithelial neoplasm in 25% of their subject.

Carcinoma prostate constituted second commonest group next to benign prostatic hyperplasia and its incidence varied from 15 to 32.2 percent as reported by different author.

Adenocarcinoma was the most common (31/32 cases) histological type of malignancy in our study and this observation was similar to other studies in literature. (Table 4)

Table 4: Comparisons of carcinoma prostate in various studies

Author	Year	No. of Patients	Total No. of Carcinoma Patients	Total %age	No. of Adenocarcinoma	Relative % age of Adenocarcinoma
Jishani et al	2012	180	60	33.33	58	96.7
Present study	2015	110	32	29.1	31	96.9%

Preoperative Serum prostate specific antigen estimation was done in all patients in our study and the levels were found to be increased in 65.5% Cases. Most (44.4%) of them had levels more than 20 ng/ml. Percent proportion of cases with increased serum prostate specific antigens is similar to the observation reported by Wadgaonkar et al (2013) who studied 80 cases in 2 years. (Table 5)

Table 5: Comparisons of serum prostate specific antigens levels

Author	Years	No. of Patients	0-4ng/ml	>4ng/ml
Wadgaonkar et al	2013	80	33.75%	66.25%
Present study	2015	110	34.5%	65.5%

Serum prostate specific antigen level was up to 10 ng /dl in 75.7 percent of benign cases. More than 10 ng/ml were seen in 24.3 percent cases. Study by Xess et al (2001)[14] had almost similar observation in 21.3 percent cases had serum prostate specific antigens level more than 10ng/mg.

50 percent (4/8) of our patients with prostatic intraepithelial neoplasm had serum prostate specific antigens levels more than 10 ng/ml which included 25% cases of low grade prostatic intraepithelial neoplasm and 100% cases of high grade prostatic intraepithelial neoplasm.

The serum prostate specific antigens levels were increased in 93.8 percent cases of adenocarcinoma. 6.2 percent case was within normal limits. Which could be due to, biochemical and technical error. Zivkovic S et al (2004)[15] also found 2.5 percent patients had serum levels within normal limits.

The Sensitivity and specificity of serum prostate specific antigens in diagnosis of malignancy of prostate is found to be 93.75% and 46.15% when the cut off value is up to 4 ng/ml. This study is comparable to Lakhey. M et al (2010) and Shalini Agnihotri et al (2012).[16] (Table 6)

Table 6: Comparision of sensitivity and specificity of serum prostate specific antigens in diagnosis of malignancy of prostate

Study	Sensitivity%	Specificity%
Lakhey. M et al(2010)	100	49
Shalini Agnihotri(2012)	79	59
Present study	93.75	46.15

Conclusion

The serum prostate specific antigen levels are a good indicator for the glandular proliferation of the prostate. It is a highly sensitive tumor marker with a low specificity as many benign and iatrogenic conditions also increase its level. A more specific screening test for prostatic adenocarcinoma is needed as the Serum prostate specific antigen levels alone are less specific.

Conflict of Interests: The authors have not declared any conflict of interests.

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