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PATTERN OF PROSTATIC DISEASE – A HISTOPATHOLOGICAL STUDY WITH CLINICAL CORRELATION"

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ABSTRACT

BACKGROUND: Study of prostatic diseases pattern is of importance because incidence of prostatic disease, Nodular hyperplasia and carcinoma increases with age. Histopathologic analysis is an invaluable tool for exact diagnosis. **OBJECTIVE**: The present study has been planned with an aim to analyze the incidence of various morphologic types of Benign, Premalignant and Malignant Prostatic lesions and its correlation of the age distribution along with clinical manifestations. **MATERIAL AND METHODS**: This prospective present study deals with evaluation of various histological lesions in prostatic specimens in the department of pathology, JLN MEDICAL COLLEGE, AJMER from January 2012 to December 2013, period of 2 years .The study was approved by the institutional human research ethics committee. During the period of present study, 763 prostatic specimens were analyzed. Brief clinical data were noted from the case records, which included age, presenting symptoms, DRE (Digital Rectal Examination) findings, serum PSA(Prostate Specific Antigen) levels and clinical diagnosis. Statistical analysis was performed using descriptive statistics of the collected data. **RESULTS**: Majority of specimens were TURP (Transurethral Resection of Prostate) (91.74%) followed by prostatectomy 7.86% and needle biopsy 0.4%.Benign lesions were most common, which accounted for 70.77% followed by PIN in 19.13% and malignant lesions 10.09%. It was observed that Benign and PIN (Prostatic Intraepithelial Neoplasia) lesions were most common in seventh decade where as carcinoma was commonest in eight decade. This indicates that PIN possibly predates carcinoma by 10 years or more indicating PIN to be the precursor lesion for carcinoma. The cause of concern is that majority of carcinomas are of higher grade tumors. The positive predictive value for carcinoma was maximum in patients with serum PSA level >10 ng/ml i.e.59.42%.The positive predictive value was 27.2% for abnormal findings of DRE, 33.33% for PSA>4 ng/ml and 69.23% for the combination of both. Thus, the combination improves the detection rate of prostate cancer than serum PSA or DRE alone. **CONCLUSION:** Prostatic adenocarcinoma is a common disease that account for considerable morbidity and mortality in the ageing population. PIN has a high predictive value as a marker for adenocarcinoma, and its identification warrants repeat biopsy for concurrent or subsequent invasive carcinoma. Interpretation of prostatic biopsies has been, and continues to be a challenge to the pathologist. The cause of concern is that majority of carcinomas are of higher grade tumors. Combined staging, grading and follow- up study are required to obtain best predictive values.

KEYWORDS: Prostatic adenocarcinoma, PIN, PSA.

INTRODUCTION

Incidence of prostatic disease, Nodular hyperplasia and carcinoma increases with age. Prostatitis, Nodular Hyperplasia (NH) and Prostatic tumors are the three important lesions to be studied in detail as they are frequently encountered. Carcinoma of prostate is the most common internal malignancy among men in the united states and is responsible for 10% of cancer death in this population. It is the leading cause of new cancer in men and is second only to lung cancers as a leading cause of cancer related deaths in men.[1] Prostate cancer is the fifth most common cancer overall (Ferlay et al., 2010).

Prostatic carcinoma is more common in India compared to other Asian countries. The estimated Age Adjusted-incidence Rates (AAR) of Prostate cancer in India was 3.7 per 10^5 persons during the year 2008 (Ferlay et al., 2010). Projected cases at All India level for Prostate cancer for the period 2010; 2015 and 2020 was estimated at 26,120; 28,079 and 30,185 (NCRP, 2009).[2]

Although nodular hyperplasia can almost be considered as an ageing process, the histological variations like different types of hyperplasia, low grade prostatic intraepithelial neoplasia (LGPIN) and high grade PIN (HGPIN) merits discussion as PIN is found in a significant fraction of patients undergoing transrectal

prostate biopsies. The importance of recognizing PIN is based on its strong association with prostatic cancer. It co-exists with cancer in more than 85% cases. There is little evidence that nodular hyperplasia or atrophy is directly related to the genesis of prostatic carcinoma. PIN finding in prostate biopsy is predictive of development of cancer in future. Hence, this study comprises of description of incidence of various lesions of prostate encountered at JLN Hospital, AJMER, associated clinical manifestations, morphological changes and also serum prostatic specific antigen (PSA) level correlation. In case of cancers, Gleason's score calculated and correlated with serum PSA level of the patient.

Histological type, grade, and stage of prostatic carcinoma are vital in planning treatment strategies and predicting survival rate. It is necessary to study prostatic diseases in the present situation as their incidence keep growing due to extended male longevity past the 60s.

MATERIAL AND METHODS

This prospective study was conducted in the department of pathology, JLN MEDICAL COLLEGE., AJMER from January 2012 to December 2013, period of 2 years. The study was approved by the institutional human research ethics committee .Samples received were of needle biopsy, TURP or suprapubic prostatectomy. Brief clinical data were noted from the case records, which included age, presenting symptoms, DRE findings, serum PSA levels and clinical diagnosis.

INCLUSION CRITERIA

All types of prostatic specimens including TURP and prostatectomy were considered in this study.

EXCLUSION CRITERIA

Inadequate biopsies and poorly preserved prostatic specimens were excluded.

The specimens thus obtained were fixed in 10% formalin for 12-24 hours after detailed and careful examination. In case of TURP, approximately 5gm of tissue/ some chips with firmer or yellow or orange-yellow appearance were preferentially submitted .However, if a carcinoma was detected in a TURP that was not entirely submitted then all the remaining tissue was processed entirely irrespective of the amount. Then section 4-6 microns thick were prepared and stained routinely with haematoxylin and eosin. Other special stains like PAS, Alcian blue pH 2.5 and Ziehl Nelson were performed wherever necessary. The procedure followed for tissue processing and staining technique are those given in 'Cellular pathology technique" by CFA Culling. Primary grade of adenocarcinoma is assigned to the dominant pattern and secondary to the subdominant pattern. The two numeric grades are added to obtain the combined Gleason grade or score. In tumors with one pattern the number is doubled. IHC (Immunohistochemical stain) was done in difficult cases.

Gleason's score

Score - 2 -4 - Well differentiated
Score - 5 -7 - Moderately differentiated
Score - 8 -10 - Poorly differentiated

Serum PSA Interpretation

Results are interpreted as follows:
1. <4ng/ml- normal
2. 4-10ng/ml –diagnostic gray zone
3. >10ng/ml –indicative of cancer

Digital Rectal Examination [DRE] was done in every case.

The classification of prostatic neoplasm recommended for general application is the current WHO Classification of Prostate.[3]

RESULTS

The present study deals with evaluation of various histological lesions in prostatic specimens. During the period of present study, 763 prostatic specimens were analyzed in the Department of Pathology, J.L.N. Medical College, Ajmer.

These prostatic specimens constituted 5.66% of 13,461 total specimens received in the department during the same period.

Table 1: Nature of prostatic biopsies and incidence of prostatic lesions

Nature Of Tissue	No. of Cases n (%)	Benign n (%)	PIN n (%)	Malignant n (%)
TURP chips	700 (91.74%)	491	135	74
Needle biopsy	3 (0.40)	2	-	1
Suprapubic prostatectomy	60 (7.86)	47	11	2
Total	763 (100)	540 (70.77)	146 (19.13)	77 (10.10)

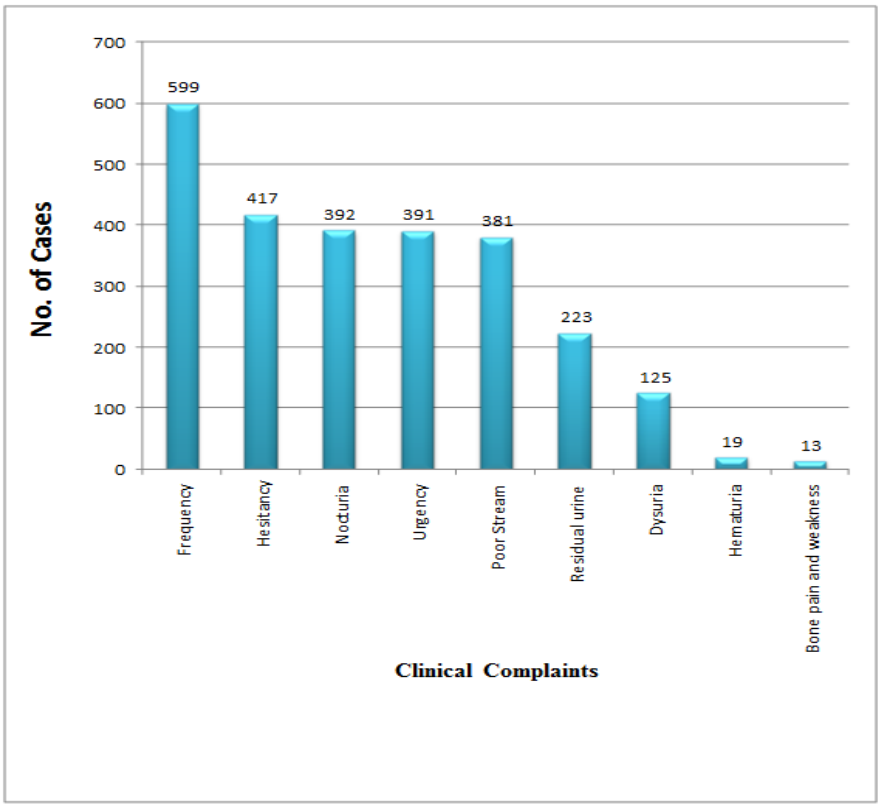
Most common were benign lesion (70.77%), Followed by PIN(19.13%) & malignant lesion were(10.10%).

Table 2: Distribution of Patients According to Age Group

Age(yrs)	Benign n (%)	PIN n (%)	Malignant n (%)	Total n(%)
40-49	8(1.48)	04(2.7)	2(2.60)	14(1.83)
50-59	72(13.33)	10(6.84)	2(2.60)	84(11.01)
60-69	202(37.40)	64(43.4)	24(31.17)	290(38.01)
70-79	185(34.25)	49(33.56)	29(37.66)	263(34.47)
80-89	64(11.85)	15(10.27)	18(23.37)	97(12.71)

90-99	9(1.66)	04(2.73)	2(2.60)	15(1.97)
Total	540	146	77	763

Majority of the benign cases (37.4%) belonged to the age group of 60-69 years. Youngest case was 40 years and oldest was 95 years. Maximum number of PIN cases (43.4%) was also found in age group 60-69 years while malignant lesions were common (37.66%) in the age group of 70-79 years. Youngest was 45 years and oldest patient was 90 years old in malignant group. The mean age of BPH patients was observed to be 67.97 years, of PIN is 68.03 years and carcinoma patients is 71.76 years. However, when benign and malignant lesions were compared, benign lesions occurred a decade earlier as compared to malignant lesions.



Graph 1: Distribution of Cases According to Clinical Complaints

The most common clinical symptom was frequency in 599(78.5%) patients, followed by hesitancy, nocturia and urgency in 417(54.65%), 392(51.37%) and 391(51.24%) patients respectively. Bony pain and weakness were the least common symptoms seen in 13(1.7%) patients.

TABLE: 4 DIGITAL RECTAL EXAMINATION FINDINGS

DRE findings	Positive findings	Nodularity	Hard
Malignant(n=77)	51(66.23%)	39	25
Benign (n=540)	97(17.63%)	80	23
PIN(n=146)	15(10.27%)	11	5

Hard consistency & nodularity were more common in Malignant lesions on DRE.

Table: 5 Microscopic findings in benign lesions

Microscopic findings		No. of cases	
NH	527	Mixed	
	09	Stromal	
	02	Glandular	
Basal cell hyperplasia		207	
Cribriform hyperplasia		13	
Clear cell hyperplasia		01	
Transitional metaplasia		12	
Squmaous metaplasia		17	
Prostatitis	Acute Chronic Lymphocytic Abscess	33 377 02 06	439
GRANULOMATOUS Xanthogranulomatous Tuberculosis		21 19 02	
Infarct		20	
Haemorrhage		08	
Atrophy of gland		01	

Table 6: Prostatic intraepithelial neoplasia

Lesion	No of cases	%
LGPIN	122	83.56
HGPIN	24	14.44
Total	146	100

In the present study, 146 cases showed PIN. LGPIN was observed in 122 cases and 24 cases showed HGPIN out of which 03 were isolated HGPIN.

Table 7: Incidence of carcinoma with reference to Gleason's score

GLEASON SCORE	NO. OF CASES	Differention Group
2	1	Well diffentiated (6.67%)
3	2	
4	2	
5	6	Moderately differentiated (49.33%)
6	14	
7	17	
8	12	Poorly differentiated (44%)
9	18	
10	3	
TOTAL	75	100%

Gleason score of 9 was the commonest pattern seen in 18 cases (24%) followed by Gleason score of 7 and 6 seen in 17(22.67%) and 14(18.67%) cases respectively. Gleason score of 10 was seen in 3 cases (4%). The Gleason's score of 2 was seen in only one case (1.34%).

The above table showed that maximum number of carcinoma patients (49.33%) were in moderately differentiated group (GS 5-7), (44%) of cases were found in poorly differentiated group (GS 8-10) and minimum number of patients (6.67%) were found in well differentiated group (GS 2-4).

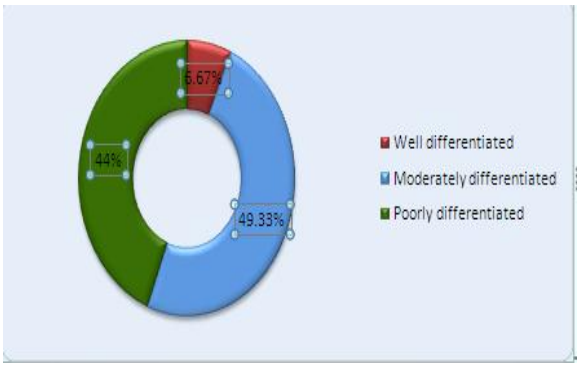


TABLE: 10 FINAL HISTOPATHOLOGICAL DIAGNOSIS

NH a)Without Prostatitis b)With Prostatitis	 101(13.24%) 437(57.27%)
Tubercular Prostatitis	02(0.26%)
PIN a)LGPIN b)HGPIN	 122(15.99%) 24(3.14%)
Adenocarcinoma	73(9.84%)
Adenocarcinoma of prostate and TCC Urinary bladder(Dual Primary)	01(0.13%)
Adenocarcinoma with focal Transitional pattern	01(0.13%)
Adenosquamous carcinoma	01(0.13%)
Metastatic TCC(from Urinary Bladder)	01(0.13%)
TOTAL	763(100%)

Among 77 cases of prostatic carcinomas encountered, 75 are adenocarcinoma (Fig1), one was primary adenosquamous carcinoma (Fig. 3a&b) and one case was metastasis from transitional cell carcinoma of bladder (Fig4a&b.). Associated focal transitional pattern was also observed in one case of adenocarcinoma.2a&b) Thus, adenocarcinoma was the most common pattern (97.40%) amongst the Prostatic Carcinoma. Also, simultaneous occurrence of TCC of urinary bladder as primary was observed in one case.

Table 11: Distribution of Cases According to Serum PSA level

PSA Level (ng/ml)	Benign (%)	PIN (%)	Malignant (%)	Total
0-4	385(86.71)	83(74.11)	1(2.22)	469
4.01-10	42(9.4)	14(12.5)	5(11.11)	61
>10	17(38.23)	15(13.39)	39(86.67)	71
Total	444	112	45	601

Total serum PSA levels were available in only 601 cases .While grouping the different lesions according to serum PSA; it was observed that maximum number of patients with NH (86.71%) and of PIN (74.11%) had serum PSA level below 4ng/ml while maximum number of carcinoma patients (86.66 %) had serum PSA levels above 10ng/ml.

Table: 12 Positive Predictive Value (PPV) of Serum PSA Level For Carcinoma

Serum PSA Level(ng/ml)	No of cases with malignancy	Total positive cases	PPV (%)
0-4	1	469	0.21
4.01-10	5	61	8.19
>10.01	39	71	54.92

PPV of serum PSA for carcinoma was observed to be maximum (54.92 %) in group of PSA >10ng/ml, it was found to be 8.19% in 4-10 ng/ml group and minimum of 0.21 % in group <4 ng/ml.

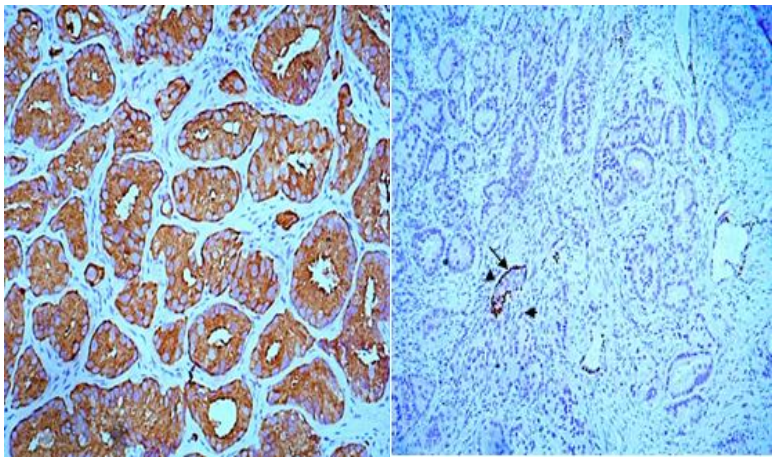


Figure1) Strong immunoreactivity for PSA (200x) b) Immunostain p63 reveals absence of basal cell around neoplastic acini and positivity in residual benign gland acting as internal control (↘)

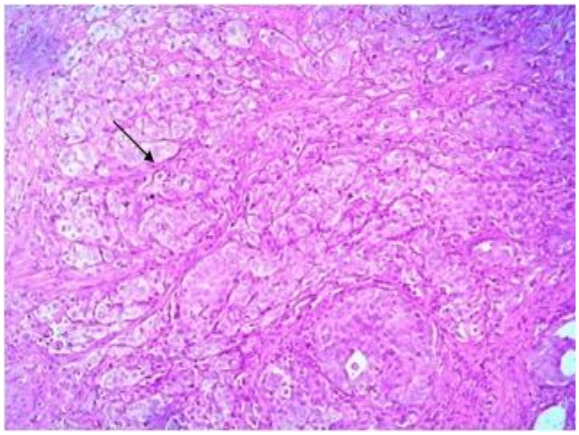


Figure 2:a&b) Adenocarcinoma with focal transitional pattern (↘) (H&E,100x) and

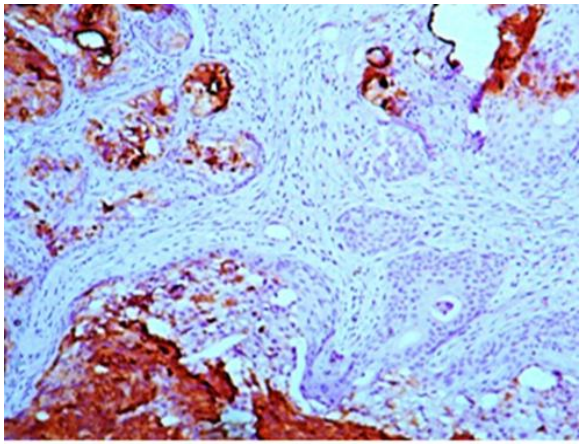


Figure2:b b)corresponding immunostain section showing PSA positivity in adeno component.

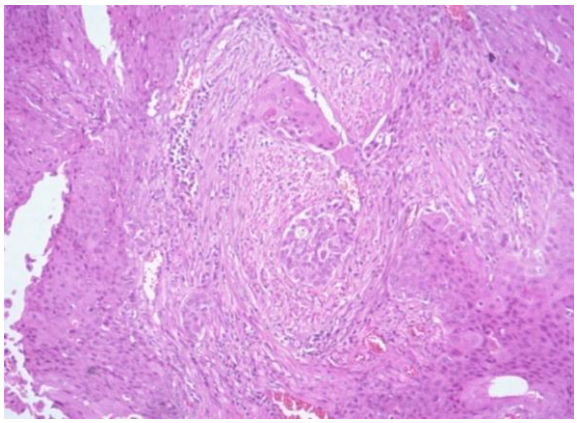


Figure 3a: Adenosqumous Carcinoma- section of prostate showing admixture of Adenocarcinoma and Squamous cell carcinoma ⟶ (H& E,100 x)

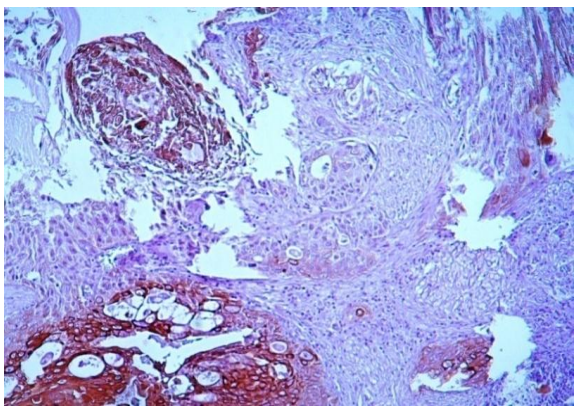


Figure 3b: Immuno stained section showing positivity for HMW cytokeratin staining in the Squamous cell carcinoma area (IHC 100x)

FIG4a&b: Transitional cell carcinoma of bladder Metastatic to prostate (H &E 100x) Inset showing the same (H & E, 200x)

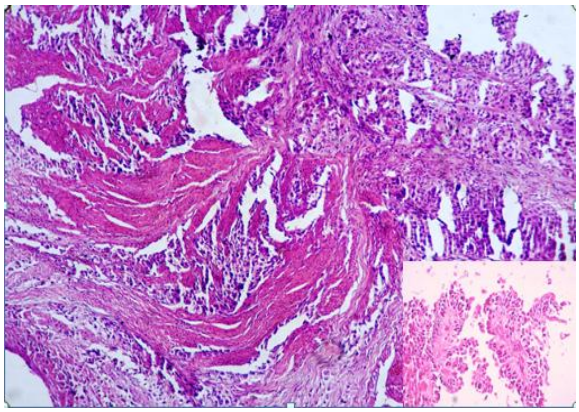


FIG4a: Transitional cell carcinoma of bladder Metastatic to prostate (H &E 100x) Inset showing the same (H & E, 200x)

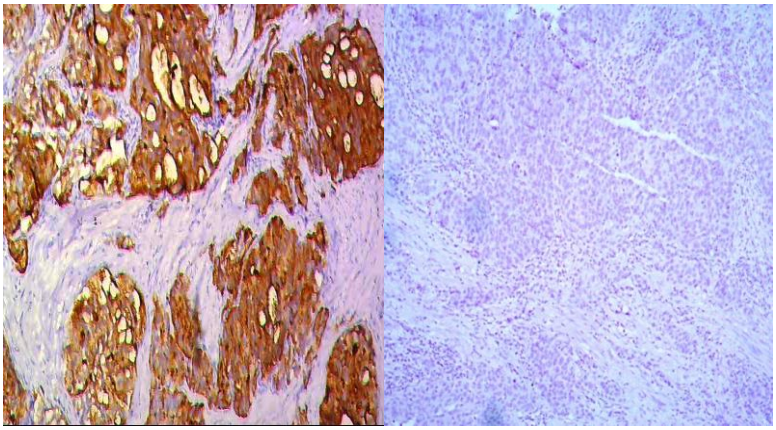


Fig 4b: Immunohistochemical stained section of above case showing a) cytoplasmic and membranous positivity in transitional cells for Uroplakin II b) negative for PSA.

DISCUSSION

Prostatism is a common malady in the geriatric age group. BPH and carcinoma of the prostate are increasingly frequent with advancing age. Prostatic specimens thus constitute a good percentage of surgical pathology workload. This study was undertaken to evaluate the various histological lesions in the prostatic specimens.

Majority of specimens were TURP (91.74%) followed by prostatectomy (7.86%) and needle biopsy 0.4%.Benign lesions were most common, which accounted for 70.77% followed by PIN in 19.13% and malignant lesions 10.09%. Common symptoms of presentation were frequency, hesitancy and nocturia. Least common were haematuria, bone pain and weakness which were commonly associated with malignant lesions.

The mean age of NH was found to be 67.77 years and the most common age group was 60-69 years. These findings correlated with findings of Mohammed AZ et al[4] who observed the mean age of NH as 63.7 years. The mean age of PIN was observed to be 68.03 years and the most common age group of presentation was 60- 69 years. In the study by Lee et al, the mean age of PIN was 65 years.[5]

The mean age of prostatic carcinoma was found to be 71.56 years in this study. The most common age group of presentation was 70-79 years. There was no case of carcinoma below the age of 40years.These findings correlate with the studies of Goswami A et al[6] and Gil et al[7] studies who found mean age of carcinoma cases as 70.3 years and 72. 7 years. Also, Lee et al observed mean age of carcinoma 70 years.[5]

PIN was most common in the 7th decade where as Prostatic Carcinoma was commonest in the 8th decade. Results of clinical studies indicate that PIN possibly predates carcinoma by 10 years or more.[7] Present findings are consistent with the observations indicating PIN to be the precursor lesion for Prostatic Carcinoma.

DRE findings in different lesions of prostate were recorded and positive findings on DRE were present in 66.23%, 17.63%, 10.27% in carcinoma, NH and PIN respectively. The findings are consistent with the observations of Lee et al[5] and Vukotic et al[8] who observed DRE positive findings in 68% and 65% of carcinoma patients respectively. However, there was dissimilarity with findings of PIN cases by Lee et al who found 41% of patients having positive DRE findings.

A wide variation in the incidence of basal cell hyperplasia with NH has been reported in the world literature, ranging from 5.4% to 51.5%. Our findings revealed an intermediate frequency (38.47%)'.[10,11,12,] mostly in the age group of 60-69 yrs.

Our analysis revealed inflammatory aspects were present in a higher percentage (57.53%) predominantly as chronic inflammation. Inflammation was chronic in 85.88%, acute in 7.52%, non specific granulomatous prostatitis in 4.33% and tuberculosis was least common present in 0.45% cases. These findings correlated with the study done by Anim JT et al[11] and Mittal et al[12] who also observed chronic prostatitis as most common inflammatory lesion.

In this study 97.4% of the malignant cases were adenocarcinoma while Adenosquamous carcinoma and metastasis from transitional cell carcinoma of bladder represented 1.3% cases of each. One adenocarcinoma was associated with high grade TCC of urinary bladder and in one transitional cell pattern was observed. Adenocarcinoma was most common in this study just like other parts of the world. The rarity of other histological subtypes of prostate cancer is in accordance with other studies. [4]

Diagnosis of Adenosqumous carcinoma was confirmed by IHC using HMWCK antibody which was negative for adeno component(Fig-3a&b). Metastatic TCC of bladder was confirmed by Uroplakin II positivity(Fig-4a). and negative for PSA along with the previous history of primary in Bladder. (Fig-4b).

Associated histological findings were HGPIN in 42.10%, prominent nucleoli in 33.77%, perineural invasion in 21(27.27%) cases and lymphovascular invasion in 04 (5.26%) cases. Mitotic figures, multiple nucleoli, inflammation, necrosis and NH were also observed. These changes have been well documented in literature.[13]

Table14: Incidence of HGPIN in prostates with carcinoma

Authors	Incidence of HGPIN In Prostates with carcinoma(%)
McNeal and Bostwick (1986)[7]	33
Kovi et al (1988))[9]	33
Troncoso et al (1989))[7]	72
Quinn et al (1990))[14]	100
W. Horinger (2001))[15]	61.4
Present study	**42.10**

The incidence of high grade PIN in Prostatic carcinoma was 42.10%. The incidence of HGPIN is relatively low in cases of prostatic carcinoma because most of the specimens were TURP which does not have enough material compared to radical prostatectomy which was studied in other studies.[16] It has also been suggested that transition zone carcinoma might not be associated with HGPIN).[17]

Adenocarcinoma cases were graded using Gleason's scoring system. Majority of our cases showed moderate to poor differentiation. Gleason score of 8 was the commonest score seen in 47.4% of cases. Gleason score of 7 & 9 was the next commonest pattern seen in 21% of cases each. In present study, low grade adenocarcinoma was detected in very low percentage probably as these lesions were asymptomatic.

Obiorah CC et al also found large percentage of cases in moderately and poorly differentiated carcinoma group and attributed to the lack of effective screening programme so that the most cases report late in the disease with obstructive symptoms. Lack of awareness about the disease could also be contributory to the predominant poor prognostic high Gleason score.)[18]

In the present study, serum PSA levels were available in only 601 cases. Out of 601 cases, 444 cases were benign, 112 were premalignant and 45 were malignant. A total of 42(9.46%) cases showed modest elevation of PSA levels and 17(3. 82%) cases showed elevation more than 10ng/ml in benign cases. The reasons for this false positivity can be attributed to acute prostatitis, severe chronic inflammation, increasing age.

Maximum patients of PIN (74.11%) had their serum PSA level <4ng/ml. Level of 4-10 were observed in 12.5% and >10 in 13.39% of patients of PIN. Bostwick stated that PIN has little or no influence on serum PSA. Serum PSA levels in patients with PIN ranging from 0.3 to 22.3 ng/ml (mean 4.0) has been observed in previous studies.)[19]

86.67% of carcinoma patients were having serum PSA exceeding 10ng/ml and 11.11% were having their serum PSA level of 4-10 ng/ml while only 2.2% were having less than 4ng/ml respectively. Thus, PSA pointed to the

diagnosis of prostatic carcinoma in 97.28% of cases. These results are comparable to those previously reported by J.Galic et al)[20] and Catalona et al)[21] i.e. 91.4% and 82% respectively. Studies reveal that prostate cancers detected at lower PSA levels are more likely to have a small volume and are of low grade. [22]

The positive predictive value for serum PSA at different levels was 0.21% in serum PSA less than 4 ng/ml, 8.19% in 4-10 ng/ml and 54.92% in >10ng/ml. These findings are consistent with Chandanwale S et al who found positive PPV of 10.3% and 58.33% in serum PSA levels of 4-10ng/ml and >10ng/ml respectively. Also, reported that with increasing levels of serum PSA, PPV for carcinoma increased)[23]

Table15: Diagnostic value of PSA and/versus DRE (n=601)

Method of screening	No. of biopsies	No. of prostate cancer	Positive predictive value (%)
Abnormal DRE	136	37	27.21
PSA>4ng/ml	132	44	33.33
Abnormal DRE and PSA>4ng/ml	52	36	69.23

The positive predictive value 27.21% for abnormal DRE in which Serum PSA was also available ,33.33% for PSA >4 ng/ml and 69.23% for the combination of both. Although PSA determination detected a considerable proportion of tumors missed on DRE but the combination of both escalates the probability of prostatic carcinoma, as also suggested by other authors.)[20,21]

Gleason's grading and serum PSA level are important markers for estimating prognosis of prostatic cancer. According to Hammond et al the serum PSA level is related to the prognosis of prostatic cancer as an indirect indicator of tumor volume, tumor extension and response to therapy. Thus, PSA is potentially useful in cancer screening, aiding diagnosis assessing prognosis, predicting in advance a likely response to therapy and monitoring patients with diagnosed disease.)[24]

CONCLUSION

Prostatic adenocarcinoma is a common disease that account for considerable morbidity and mortality in the ageing population. PIN has a high predictive value as a marker for adenocarcinoma, and its identification warrants repeat biopsy for concurrent or subsequent invasive carcinoma. Interpretation of prostatic biopsies has been, and continues to be a challenge to the pathologist. The cause of concern is that majority of carcinomas are of higher grade tumors. Combined staging, grading and follow- up study are required to obtain best predictive values.

SCOPE FOR IMPROVEMENT

The correct diagnosis of mimickers of adenocarcinoma should be made in order to
prevent radical prostatectomy, which has high rate of morbidity in elderly males. Since serum PSA was increased in few benign and most of the malignant cases, newer modalities of measuring PSA like PSA density, PSA velocity, age specific reference rates should be adopted to distinguish between benign and malignant lesions.

Most of the cases of prostatic adenocarcinoma encountered were of high grade. Since low-grade lesions are usually asymptomatic, awareness of serum PSA level estimation, digital rectal examination should be brought among elderly males who are prone for malignancy. Male individuals with a positive family history for prostatic carcinoma must undergo relevant screening test.

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