

## Study of morphological spectrum of prostatic lesions and its correlation with Ki-67 in a tertiary care hospital in rural South India

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**Abstract:** *Background:* Diseases of the prostate cause considerable morbidity and mortality in elderly population. There is limited literature regarding the prevalence of neoplastic and non-neoplastic lesions of prostate in rural Indian population. The current study attempts to document the occurrence of prostatitis, nodular hyperplasia (NH), prostatic intraepithelial neoplasia (PIN), prostate carcinoma (PCa) in patients operated at the study institution. *Objective:* To study the morphological spectrum of prostatic diseases. To correlate histopathological findings with serum prostate specific antigen (Sr.PSA) levels and evaluate the proliferative index by Ki-67 antibody in neoplastic and non-neoplastic lesions. *Materials and Methods:* Cross-sectional study comprising of 90 patients who underwent transurethral resection of prostate from January 2012 to June 2013. Routine tissue processing and immunohistochemistry with primary antibody Ki-67(Biogenex,USA) was performed to know the proliferative activity in all the cases. Statistical analysis was done by SPSS 11 software. *Results:* Out of 90 cases, 88.7% were benign and 12.3% malignant lesions. In 72 % of NH, 65.6% of Low grade PIN (LPIN), and 57.1% of HPIN the Sr PSA was in the range of 4.1-10 ng/ml. 81.8% of PCa had a PSA > 20ng/ml. The association between Sr PSA levels (>20ng/ml) and PCa was found to be highly significant. 62.8% of NH and 55.1% of LPIN had a PI between 2.1-25, whereas 71.2% of HPIN and 72.7% of PCa had higher index between 25.1-50. A significant association was found between the PI >25 and PCa. Multiple logistic regression suggest that Ki-67 acts as an independent parameter to indicate malignancy. *Conclusion:* NH comprised 48% of the total number of cases, followed by LPIN (32.3%) and HPIN (7.7%). Sr PSA is a reliable parameter to differentiate between benign and malignant diseases of prostate. PI bears a highly significant association with malignancy and is a independent parameter to indicate PCa.

**Keywords:** Nodular hyperplasia, Prostate cancer, PSA, Proliferative index

**Abbreviations:** AAH -Atypical Adenomatous Hyperplasia; AR- Androgen Receptor; BCH -Basal Cell Hyperplasia; BPH -Benign Prostatic Hyperplasia; DRE- Digital Rectal Examination; DTH - Dihydrotestosterone; H&E -Haematoxylin And Eosin; HPIN- High Grade Prostatic Intraepithelial Neoplasm; HMW-CK High Molecular Weight Cytokeratin; IHC- Immunohistochemistry; LPIN- Low Grade Prostatic Intraepithelial Neoplasm; NE -Neuroendocrine Tumors; NH -Nodular Hyperplasia; PAH- Post Atrophic Hyperplasia; PAP -Prostatic Acid Phosphatase; PCa- Prostate carcinoma; PIN -Prostatic Intraepithelial Neoplasia; PIA- Post inflammatory atrophy; PI- Proliferative index; STUMP- Stromal Tumor of Unknown Malignant Potential; Sr PSA- Serum Prostate Specific Antigen; TURP -Transurethral Resection of Prostate;

### Introduction

The three main pathologic processes that affect the prostatic gland are inflammation, nodular hyperplasia (NH) and tumors. The benign nodular enlargement is the most common, followed by Prostatic carcinoma (PCa) [1]. Prostatic intraepithelial lesion (PIN) is the abnormal proliferation within the prostatic ducts, ductules, and large acini of premalignant foci of cellular dysplasia and carcinoma in situ without stromal invasion. The only method of detecting PIN is biopsy and it does not significantly elevate serum

prostate-specific antigen (PSA) concentration or its derivatives and cannot be detected by current imaging techniques, including ultrasound. Most patients with PIN develop carcinoma within 10 years [2].

Atypical adenomatous hyperplasia (AAH; also termed adenosis), is a putative precursor of transition zone adenocarcinoma and even mimics it in needle settings [3]. PCa is now the sixth most common cancer in the world, and third in importance in men. The incidence

varies with geographic location, ethnic background, and age. The incidence rises dramatically with age. The diagnosis of PCa is readily made on morphological grounds by use of histological parameters, including architecture, nuclear features and the presence or absence of basal cell layer. However, in morphologically equivocal cases the use of immunohistochemistry clinches the diagnosis [4]. Important differential diagnosis of PCa includes atrophy, post-atrophic hyperplasia, atypical adenomatous hyperplasia, granulomatous prostatitis, xanthogranulomatous prostatitis, malakoplakia, seminal vesicle-type tissue, metaplastic and hyperplastic processes of prostate.

The biological behavior including prognosis can be understood by studying the proliferative activity of tumors. Tumor kinetics have been investigated by mitotic counts, thymidine labeling, bromodeoxyuridine incorporation, AgNOR quantitation, and cytometric DNA analysis [4]. Antibodies directed against nuclear antigens expressed in certain phases of the proliferation cycle, such as Ki-67 is a simple and convenient way to estimate the proliferation index (PI). It is of great utility in a number of prostatic diseases ranging from hyperplasia to neoplasia. PI of benign acini is consistently lower (0.19-4.0%) than that of malignant acini (1.6-16%) [5-6].

#### Objectives:

1. To study the morphological spectrum of neoplastic and non-neoplastic lesions of prostate.
2. To correlate histopathological findings with serum PSA levels.
3. To evaluate the proliferative index in neoplastic and non-neoplastic lesions by immunohistochemistry using Ki-67 antibody.

### Material and Methods

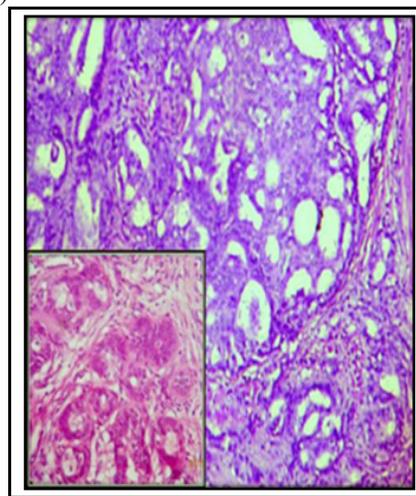
**Study Design & Source of Data:** Cross-sectional study was done on 90 TURP specimens which were received from January'2012 to June'2013 operated in Department of Urology at R.L Jalappa Hospital & Research Centre, Kolar attached to Sri Devaraj Urs medical College, Kolar. Brief clinical data, like age, presenting symptoms, Sr PSA levels, prostate size on ultrasound and clinical diagnosis was noted from

the case records. We excluded patients having recurrent prostatic adenocarcinoma or on chemo/ radiotherapy.

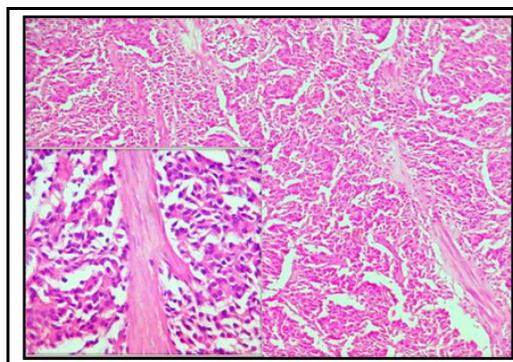
**Estimation of PSA:** 3 ml of Patients' blood samples were collected in plain tubes with a clot activator. After centrifugation, PSA was measured in the serum by chemiluminescence. Values >4ng/dl were considered as increased.

**Grossing & tissue processing:** All the prostatic specimens were subjected to careful and detailed gross examination especially for firm and yellow or orange yellow areas suspicious of malignancy. 10% Formalin fixed TURP specimens underwent routine tissue processing. 4-6 $\mu$  thick sections were cut and staining with Hematoxylin and Eosin (H & E). Microscopic diagnosis was made based on WHO criteria [7] (Figure-1 and 2).

**Fig-1:** NH with HPIN (H&E, x100). Inset showing coarse chromatin & prominent nucleoli (H&E, x400)

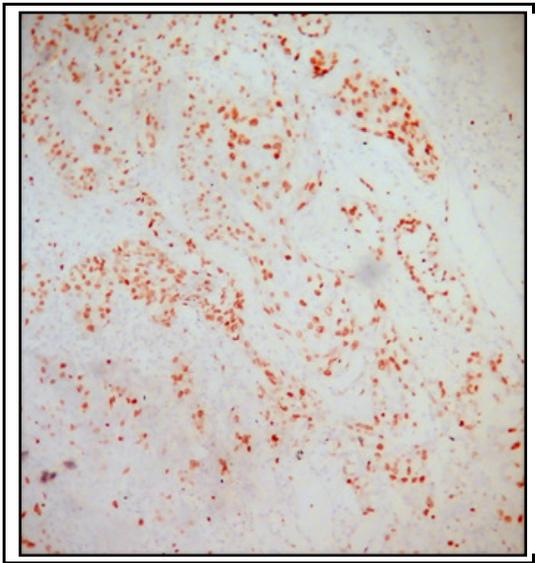


**Fig-2:** PCa with trabecular pattern & Gleason's pattern 5 (H&E, x100). Inset shows squamous differentiation (H&E, x400)

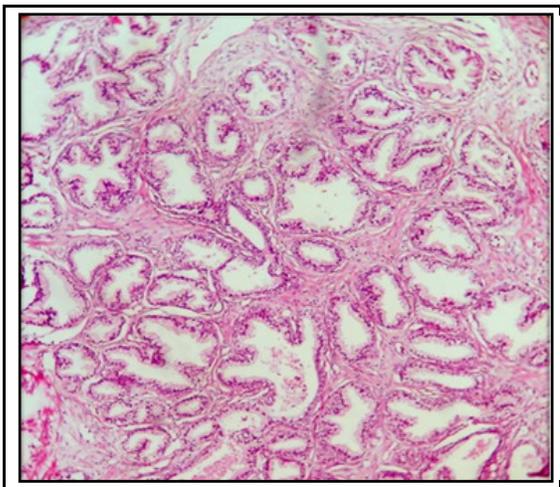


**Immunohistochemistry:** It was done using primary antibody Ki-67(Biogenex,USA) in all the cases. In immunostained sections hot spots were identified under low power then focused under x40 and number of brown stained nuclei was counted in stroma and glands for every 500 cells seen in each. The numbers were added and percentage derived to get the immunoscore (Figure-3).

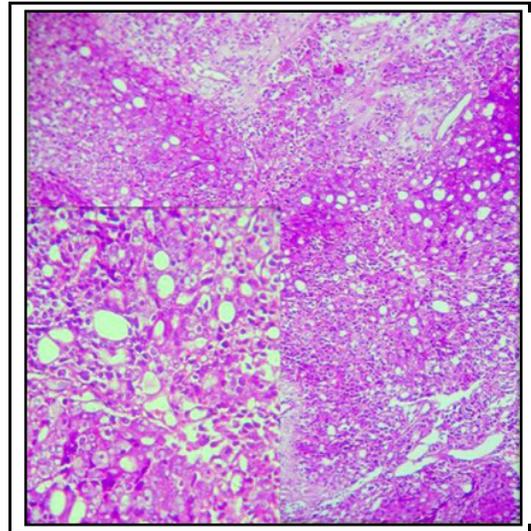
**Fig-3:** Ki-67 labelling in PCa with PI=42% (IHC, x100)



**Fig-4:** NH with more glandular hyperplasia (H&E, x100)



**Fig-5:** PCa in cribriform pattern & Gleason's pattern 4 (H&E, x100; Inset x 400)



**Analysis of Data:** Analysis was done by using SPSS 11 (Statistical package for social sciences version 11), USA. Descriptive statistics like frequencies, proportions, mean, and standard deviation were calculated for qualitative and quantitative data respectively. Chi Square test was the test of significance for categorical data.  $p$ -value  $< 0.05$  was considered statistically significant.

## Results

Out of 90 cases studied, commonest pathology encountered was benign lesion constituting 88.7% and malignant lesions were 12.3%. The commonest clinical presentation in both benign and malignant lesions was difficulty in micturition, followed by urgency. NH, HPIN and PCa were common in age group of 61-70 years, where as LPIN was more common between 71-80 years (Table-1). Majority of the benign cases (74.4%) show a predominantly glandular component. 11.2 % of the cases had equal amount of glandular and fibroamascular component. 71.1 % of cases show a papillary hyperplasia followed by BCH in 14.4%.

Squamous metaplasia was seen in 38 cases (31.3%), atrophy in 33 cases (36.7%), Calcification in 11 cases (12.2%), stromal nodule in 8 cases (8.8%), myxoid change in 7 cases ( 7.7%), granulomas in 3 cases (3.3%) and infarction in 2 (2.2%). Out of 33 cases of

atrophy, Cystic atrophy comprised of 81.8% of all atrophies, followed by simple and partial atrophy (9.1%) each. In 72 % of NH, 65.6% of LPIN, and

57.1% of HPIN the Sr PSA was in the range of 4.1-10 ng/dl. 81.8% of PCa had a PSA > 20ng/ml (Table-2).

Age Distribution (years)	No. of cases		NH		LPIN		HPIN		Malignant	
	No.	%	No.	%	No.	%	No.	%	No.	%
40-50	5	5.5	3	7	2	6.9	0	0	0	0
51-60	19	8	8	18.6	8	27.6	2	28.6	1	9.1
61-70	41	45.5	24	55.8	8	27.6	2	28.6	7	63.6
71-80	20	22.2	7	16.3	9	31	2	28.6	2	18.2
>80	5	5.5	1	2.3	2	6.9	1	14.3	1	9.1
<b>Total</b>	90	100	43	100	29	100	7	100	11	100

Sr PSA (ng/ml)	NH		LPIN		HPIN		PCa	
	No.	%	No.	%	No.	%	No.	%
0-4	6	14	1	3.4	0	0	0	0
4.1-10	31	72	19	65.6	4	57.1	0	0
10.1-20	3	7	1	3.4	1	14.3	2	18.2
>20	3	7	8	27.6	2	2.9	9	81.8
<b>Total</b>	43	100	29	100	7	100	11	100

The association between Sr PSA levels (>20ng/ml) and PCa was found to be highly significant. The Mean Sr PSA levels in PCa is  $71.1 \pm 34.4$  ng/ml, much higher than the mean Sr PSA of NH ( $8.3 \pm 8.6$  ng/ml). 62.8% of NH and 55.1% of LPIN had a PI between 2.1-25, whereas 71.2% of HPIN and 72.7% of PCa had higher index between 25.1-50. A significant association was found between the PI >25 and PCa with a chi-square of 38.77 and degree of freedom = 3. The association between Sr PSA levels and PI was found to be highly significant. The mean PI of PCa is  $42.1 \pm 11.9$  and NH is  $7.6 \pm 9.9$  %. Out of the 11 PCa, the Gleason's score of 9 was seen in majority of the 5 cases (45.5%), Gleason score of 7 was seen in 3cases (27.3%)

### Discussion

Most of the patients (45.5%) affected in our study group were in sixth decade of their lives and the this finding was consistent with the results of

other studies (Table-3) in the Indian subcontinent, except the study of Ghartimagar et al [8], whose findings relied on autopsy samples, hence the majority of cases were in their fourth decade. According to American estimates 50% of males experience prostatitis during their lifetimes and PCa is responsible for largest number of cancer related deaths in men after lung cancer in the globe. Patients with prostatic disorders present with a wide range of complaints, many times non-specific. Hence, we investigated for the most common presentation, which was difficulty in passing urine seen in 69.6 % of the benign cases and 90.9% of cancers. Urgency was the second most common complaint in patients with benign lesion followed by urinary retention. Aslam et al reported urinary retention in 95.5% of NH, followed by hematuria (83.3%) [9].

<b>Histopathological Diagnosis</b>	<b>Present study</b>	<b>Aslam et al [9] (2013)</b>	<b>Ghartimagar et al [8] (2012)</b>	<b>Sinha et al [13] (2011)</b>	<b>Mohammed et al [31] (2005)</b>	<b>Talukder et al [38] (2008)</b>	<b>Gupta et al [12] (2005)</b>
PCa	11 (12.3%)	6 (12.5%)	-	29 (24%)	121 (24.6%)	19 (20.4%)	34 (24%)
NH	43 (47.7%)	42 (87.5%)	55 (55%)	50 (42%)	372 (75.4%)	72 (77.4%)	59 (41.5%)
PIN	36 (40%)	-	16 (16%)	10 (8%)	69 (18.6%)	-	03 (2.1%)
<b>Total</b>	90	48	71	89	562	91	96

In India the incidence of PCa is about 6.8/100000 (Anil Mandhani et al) [10], and an upward trend has been observed of late (B Yeole et al) [11]. In our study, out of 90 cases, malignancy was noted in 11 cases comprising 12.3% of our cases and consistent with findings of Aslam et al [9]. However, the number of cancers in other studies is relatively higher and this could be attributed to the diversity in races and their habits. For example increased dietary fat is a risk factor, whereas fruits and vegetables reduce the risk of PCa. The most common lesion in prostate in all studies including our study has been NH comprising 47.7% of cases. The percentage is higher in a few studies because they have not segregated NH from those associated with other preneoplastic conditions like PIN. However, the frequency of NH in our study correlates well with the findings of other Indian authors like Gupta et al [12] and Sinha et al [13]. The incidence of PIN in our study (40%) was much higher than those in other studies, simply because others have reported only HPIN and even in our study HPIN is only 7.7%. (Table-3)

Prostate-specific antigen (PSA) assay is an important tool in screening for PCa. However, biopsy-detected PCa, including high-grade cancers, has been found among men with normal PSA levels of 4.0 ng per milliliter or less. 15 percent of men with a "normal" PSA level had prostate cancer [14]. However in our study none of the PCa had a PSA below 4ng/ml. The American Cancer Society estimates the risk of PCa at 1 in 4 for men with PSA between 4 and 10 ng/ml and 50% for men with PSA above 10 ng/ml. These values are far higher than reported by Sinha et al [13] and Dublin et al [15]. Dublin

found cancer in 10% of men with PSA of 4.1–20 ng/ml. In a study from Mumbai, Chavan et al [16] found cancer rates of 0.6%, 2.3%, 2.5%, 34.1%, and 54.9% in Indian men with PSA values among 0–4 ng/ml, 4–10 ng/ml, 10–20 ng/ml, 20–50 ng/ml, and >50 ng/ml, respectively. The number of men with cancer was much higher in patients with a PSA of >20 ng/ml (52% versus 7%) as compared to those with a PSA less than 20 ng/ml. In our study, out of the 11 PCa, only 1 case had a PSA below 20ng/ml, yet our sample size is too small to suggest 20 ng/ml as a cut-off in the Indian males and we should keep in mind that by raising the cutoff we do not miss latent PCa or negatively impact the stage at diagnosis and eventually, the disease-specific mortality outcome.

Haid et al [17] reported an accuracy rate of 68% with Sr PSA. In the present study, the accuracy rate was 95.6%. Richie et al [18] studied the efficacy of Sr PSA in the early detection of prostatic carcinoma in men who were aged >50 yrs and found that the sensitivity of PSA was 75% and that its specificity was 87%. Babaian et al [19] suggested that PSA levels of < 4ng/ml conferred a low cancer risk, that PSA levels of >4 ng/dl but of <10ng/dl suggested an intermediate risk and that PSA levels of >10 ng/dl conferred a high risk. In the present study, all the cases of cancer had PSA levels which were above 10ng/ml. In another study the authors did not find any case with raised PSA levels which were due to any inflammation or any other cause apart from malignancy, which could be attributed to a

difference in the sample size [20]. Bains et al [21] found a significant association between the PSA levels and the glandular proliferation. Chronic prostatitis and glandular proliferation contribute to the Sr PSA elevation in hyperplastic prostates. In our study, among the 27 patients who had an elevated PSA (above 10ng/ml) 81.4 % patients showed a predominantly glandular proliferation and only 3.7% a predominantly fibromuscular proliferation. Inflammation had no significant association with PSA levels in our study.

Alexander et al demonstrated that PIN does not increase PSA levels [22]. Our study, shows an rise in the mean Sr PSA across the spectrum from NH (8.3ng/ml), LPIN (13.2), HPIN (18.8ng/ml) and PCa (71.1ng/ml). Gerstenbluth et al [23] reported that a Sr PSA level of 20 ng/ml or greater, independent of digital rectal examination findings was 87.2% accurate in predicting the cancer and a Sr PSA level of 50 ng/ml or greater had a positive predictive value of 98.5%. Chavan et al [16] showed 80.6% accuracy in detection of prostate cancer at the PSA cutoff of 10 ng/ml whereas at 20 ng/ml 91.3% specificity was observed. In our study, taking 10ng/ml as the cutoff the specificity becomes 100 % and diagnostic accuracy was 82.2 %. On increasing the cutoff as 20ng/ml the diagnostic accuracy and sensitivity rises to 47.6% and 86.7% respectively, but specificity falls to 98.6%.

The prevalence of PIN in malignant prostate samples is 33-100%, while in benign prostate it ranges from 4-18%. In our study HPIN was seen in 9 cases where in 2 cases were associated with PCa and 7 cases associated with NH. HPIN reportedly is detected in 33–100% of malignant prostates compared with benign prostates (range, 4–18%) [26]. Borges et al [27] reported 85.24% HPIN in a majority of PCa. Conversely, none of the benign prostate samples were found to have HPIN. On the contrary, in a study from Sri Lanka, 4.39% of samples were found to contain HPIN in the absence of adenocarcinoma [28].

The morphology of HPIN (flat vs tufting vs micropapillary vs cribriform) does not determine which HPIN lesions are at greater risk of being associated with carcinoma on repeat biopsy. In our study out of the 7 cases of HPIN, 42.9% showed a tufting pattern. Other patterns observed were micropapillary (28.6%), cribriform (28.6%)

and flat (14.3%). The prevalence of HPIN in radical prostatectomy specimens is remarkably high; it was present in 85-100% of specimens, reflecting the strong association between the lesion and PCa [22]. There is marked variation in the literature on the incidence of isolated HPIN on needle biopsy, ranging from 0 to 24.6%, the mean incidence being 7.6% with a median value of 4.7%. The most likely explanation for the observed variation in the incidence of HPIN relates to the vague definition of HPIN. Although one study has reported that African-American men have a higher incidence of HPIN than Caucasian men, this by itself is an unlikely explanation for the marked variation seen in the literature [24]. The importance of sampling can be seen in the study by Eskicorapci et al, where the risk of cancer after an initial sextant biopsy showing HPIN was 56.5% and was significantly more than that after a benign diagnosis. By contrast, Eskicorapci found that the risk of cancer after an extended biopsy (10 cores) showing HPIN was only 22.9% and was not statistically different from that seen after a benign diagnosis [25].

Studies have reported AAH in at least 20% of TURP specimens, but its occurrence in the general population is unknown [29]. In our study, 4 cases of AAH were reported most of them in the seventh decade of life, comprising 4.4 % of total cases consistent with the findings of Ghartimagar et al [8], yet much lesser than the number reported by Rekhi et al [30] and Mohammed et al [31]. In none of our cases AAH was associated with PCa. The PI was relatively higher in these cases than exclusive NH. Gaudin et al [32] studied AAH in 44 cases, inferred that a high percentage of AAH could be diagnosed, by a number of histologic features and confirmed with the use of antibodies to high molecular weight cytokeratin. Ghartumagar et al [8] observed 23% cases with metaplastic changes, transitional metaplasia being the commonest (21%) followed by mucinous metaplasia (2%). We reported 31.3% of squamous metaplasia, 7.7% of myxoid change, 8.8% of stromal nodule. Basal cell hyperplasia (BCH) is a benign lesion that is often misdiagnosed as PCa. Ghartimagar et al observed 25 cases

(25%) of BCH, where as we saw 14 cases (15.55%). We report 11 cases of calcification in prostate comprising 12.2% of our cases.

In the study by Munoz et al the correlation between the immunolabeling for Ki-67 and the histological diagnosis showed statistically significant differences between NH and PCa ( $p < 0.001$ ), LPIN and PCa ( $p < 0.001$ ) and HPIN and PCa ( $p < 0.001$ ). Even our findings were consistent with the above findings showing a statistically significant association between the immunoscore and the diagnosis. The mean PI increases across the spectrum – NH (7.6%), LPIN (22.7%), HPIN (37.5%) and PCa (42.5%) [33]. This expression was more intense in HPIN lesions and similar to that observed in invasive adenocarcinoma (Montironi et al., 1993). This supports the hypothesis that HPIN represents an intermediate stage in the neoplastic transformation of the prostate epithelium. Equally, in studies of cell kinetics, a rank order among NH, AAH, low grade carcinoma, PIN and high grade carcinoma has been established, considering PIN as a pre-neoplastic lesion (Helsap, 1995) [34].

The presence of Ki-67 in an epithelial layer where the cells should be differentiated (the luminal layer) could be useful as a prognostic factor. There is an evident increase in the number of immunopositive cases in accordance with the increase of grade of histological lesion, the greater percentage being found in the HPIN lesions [33]. Theodoropoulos et al [35] showed a significant relationship between Ki-67 index and Gleason's grading of tumors with low- to high-

grade differentiation. Nilson et al [36] showed a significant correlation between positive cases of Ki-67 and also tumoral cell differentiation. All poorly differentiated tumors, fewer than half of the moderately differentiated tumors and only one of well-differentiated tumors were positive for Ki-67 in their study. In addition, all cases of NH were negative for Ki-67. In cases of NH less than 2% of cells were shown to be positive for Ki-67 marker. So Madani's study also showed a statistically significant correlation between the Ki-67 marker and increased Gleason's grading with increased number of stained cells ( $P = 0.001$ ) [37]. Neither Munoz et al nor did we find any significant difference between the immunolabeling for Ki-67 and Gleason's score. In our study, we observed increasing mean PI from a score of 7 to 10. With the exception of Gleason score 8, which had a higher PI. This disparity could be attributed to our small sample size, since we had only one case of Gleason score 8.

### Conclusion

The elderly age group is most commonly afflicted with prostatic diseases. In morphological spectrum of prostatic lesions majority of the cases are benign. NH comprised of almost half the total number of cases, followed by LPIN (32.3%) and HPIN (7.7%). Sr PSA is a reliable parameter to differentiate between benign and malignant diseases of prostate. PI bears a highly significant association with malignancy and is a independent parameter to indicate PCa.

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