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Study of Expression of P53 in Prostatic Lesions

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Authors' contributions

This work was carried out in collaboration among all authors. All authors read and approved the final manuscript.

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Original Research Article

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ABSTRACT

Prostate gland is an accessory gland of the male reproductive system.Prostate begins development from the mesenchymal tissue, surrounding the urogenital sinus in the 3 rd month of gestation. Epithelial buds invaginate from the posterior sinus on either side of verumontanum. Concurrently, Wolffian ducts develop into seminal vesicles, epididymis, Vasdeferens and ejaculatory ducts that are stimulated by fetal testosterone. Histologically all malignant lesions encountered were Conventional Adenocarcinoma of Prostate. The commonest pattern seen was acinar followed bycribriform and fused glandularpattern. Conventional Adenocarcinoma forms the most commontype of prostatic carcinoma and they are moderately differentiated byGleason's microscopicgrading. Serum Prostate Specific Antigen (PSA) levels increases proportionately with advancing clinical stage. Studies have shownthat serial increase in serum PSA is associated with incidence of occult carcinoma.In the present study, the TURP specimen received was ranged in the volume from 8 to 20cc. Every tissue was carefully examined for the presence of yellow and firm or gray hard areas and necrotic areas. After fixation and processing, 4 -5µ sections were cut and Hematoxylin and Eosin staining was done. In the present study all the benign lesions stained negative except for cases were the PSA value is more than >50ng/ml with p53 IHC and in prostate carcinoma positive indicating epithelial marker positive for prostate gland. In coclusio, the IHC expression of p53 is significantly up- regulated in malignant lesions and have importance in prognostic factors and disease survival.

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Keywords: Prostate gland; prostate carcinoma; serum Prostate Specific Antigen (PSA), Gleason's score.

1. INTRODUCTION

Ageing is an inevitable phenomenon with both structural and functional changes in the organs of human body. One of the organ undergoing these senile changes is prostate gland. Because of its location at bladder neck, enlargement of the gland leads to problems related to urinary obstruction. Incidence of prostatic disease like Benign Nodular Hyperplasia and Carcinoma Prostate increases with age 1.A recent American Urological Association (AUA) guidelines [1] suggest an increase in the incidence of Benign Nodular Hyperplasia worldwide and predicted by the age of 60 yrs, more than 50% of men will have microscopic evidence of disease 2..Very few studies conducted on prostate carcinoma patients in India suggest Benign Nodular Hyperplasia and Prostatic Carcinoma as the most common pathological condition with an incidence of 82.97% and 17.03% 3.

Globally Carcinoma of Prostate is the 5th cause of cancer and ranking 4th in cancer mortality in men. Incidence is highest among black men in United States. Prostatic Carcinoma is more common in India compared to other Asian Countries and its incidence is increasing by 3.5% every year due to the westernization.

The combination of Digital rectal examination (DRE), Transrectal Ultra sonogram, Serum Prostate Specific Antigen (SPSA) estimation, supplemented with biopsy procedures represents a powerful diagnostic tool in the diagnosis of various prostatic lesions4. Histopathological examination of prostate biopsy remains the gold standard for diagnosing all lesions including inflammatory, benign and malignant conditions 6,8,9.

The unrelenting challenge encountered in differentiating limited volume of prostatic carcinoma and sometimes subtle variants from its many morphologic mimics has increased the use of ancillary immunohistochemistry in prostate biopsies. The availability of prostate cancer-associated and epithelial cell- associated markers has been an invaluable addition to diagnostic surgical pathology5, 10, 13, 15

2. MATERIALS AND METHODS

During the study period between August 2015 to September 2017, 100 TURP specimens were received in the department of pathology, Sree Balaji Medical College and Hospital, Bharath University. Relevant clinical data including age, the presenting complaints, digital rectal examination were recorded and S.PSA values were considered in selected cases.

In our cases the TURP specimen received was ranged in the volume from 8 to 20cc. Every tissue was carefully examined for the presence of yellow and firm or gray hard areas and necrotic areas. Fixation was done by neutral buffered 10% formalin for 12 hrs and then specimen was submitted for processing. After processing, 4 -5µ sections were cut and Hematoxylin and Eosin staining was done.

2.1 Inclusion Criteria

1. Prostate TURP specimen received from urology department were included in thestudy.

2.2 Exclusion Criteria

1. Patients not willing for the study wereexcluded.
2. All females were excluded in the study because prostate is not present.
3. Patientwith congenital abnormalitieslike prune bellysyndrome, prostatepolyps.

2.3 Hematoxylin and Eosin Stains

Sections were deparaffinised and Stained with hematoxylin for 5 minutes and rinsed well in running tap water. Dehydrated with 1% acid alcohol for 3 to 4 times, wash and then stained with 1% aqueous eosin for 2 minutes, then Washed in running tap water for 2minutes. Sections were dehydrated with graded ethanol, cleared and mounted with DPX (dextrenepolysterene xylene).

3. RESULTS

Among 100 cases of Prostatic biopsies, 77 cases were benign lesions, 10 malignant cases and 13 inflammatory conditions observed.

Benign lesions of prostate was the most common histopathological lesion encountered (77cases) with maximum incidence in the age group of 50 -70 yrs. Inflammatory lesions in prostate (prostatitis, prostatitic abscess) was the

s econd most common type of lesions encountered (13 cases) of inflammatory lesions was encountered in the present study. Prostatic carcinoma was the third most common type of lesions encountered (10 cases).

3.1 Age Incidence

In present study, the youngest patient was 40 years old and the eldest was 81 years and above old. The Mean age and the Median age of the patients with benign prostatic disorder were 58. 2 and 59.9 years, whereas the mean age and median age of the patients with malignant neoplasm of prostate was 62.5 and 68 years. In the present study both the benign and malignant lesions were common in sixth decade.

In the present study 60 -70 years age group was the common age group having 47% followed by 51 - 60 years (27%) age group, 71- 80 years (17%) and above 80 years (5%) in age group.

3.2 Clinical Presentation

In the present study following symptoms was noted, among that difficulty in micturition (86 cases) was the most common presentation followed by frequency of micturition (65 cases). 54 cases presented with hesitancy as chief complaint while 32 cases presented with other complaints like burning micturition, retention of urine and hematuria.

3.3 Digital Rectal Examination

Out of 100 cases, benign cases 60 were firm, 3 in malignant cases, 5 in inflammatory cases, 2 were hard in inflammatory cases, 6 in malignancy and 10 in benign cases and 7 were cystic in benign, 6 in inflammatory and 1 in malignant cases.

3.4 Rostatic Disorder and Serum Psa Level

Among the Benign Nodular Hyperplasia patients, serum PSA was obtained for 100 cases out of which 30 were noted to have the PSA value in the range of above 50ng/ ml, remaining cases less than 40 ng/ ml. The lowest value of serum PSA among the carcinoma prostate patient was 45 ng/ml and the highest value noted was 398ng/ ml serum PSA level. Serum PSA level obtained for adenocarcinoma patient was in the range of 250 -300ng/ml with a P value <0. 008. In inflammatory lesion out of 13 cases 3 had serum PSA value above 50ng/ml with p value <0.010. In benign lesions out of 77 cases 10 cases had serum PSA value above 50ng/ ml with P value <0.006.

3.4.1 p53 IHC expression in prostatic carcinoma

In our study out of 10 prostatic carcinoma cases, the p53 expression is seen by the brown color on the epithelial nuclei on immunostaining with p53 antigen. T hese cells are taken as positive. The number of positive stained nuclei compared to the negative stained nuclei (unstained) was evaluated for IHC scoring .

- ✓ It was observed that all carcinoma cases were positive for p53 expression.
- ✓ IHC score 1 (< 10% nuclei stained) was seen in nil cases, IHC score 2 (10- 33% nuclei stained) in 2 cases (30.3%), IHC score 3 (>33% nuclei stained) was in 6 cases (70.7%).

3.4.2 p53 expression and serum psa level

In our study out of 100 cases 30 have increase in PSA level more than 40 ng/ml. IHC P53 staining was done for cases with increase in PSA value, showed positive for P53 staining with varying intensity of expression in IHC stain. Scoring was done depending upon the percentage of IHC stain intensity and number of positive stained nuclei.

3.5 Histopathalogy Images

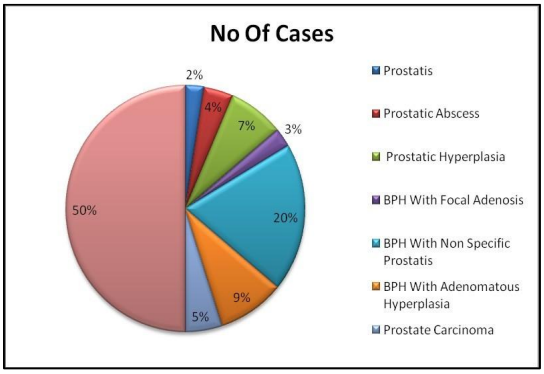

Fig. 1. Incidence of prostatic lesions

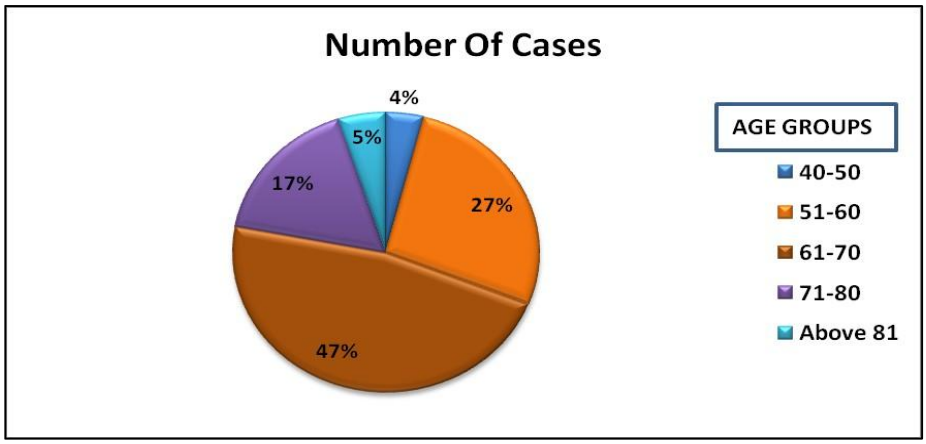

Fig. 2. Age distribution and prostatic disorder chart

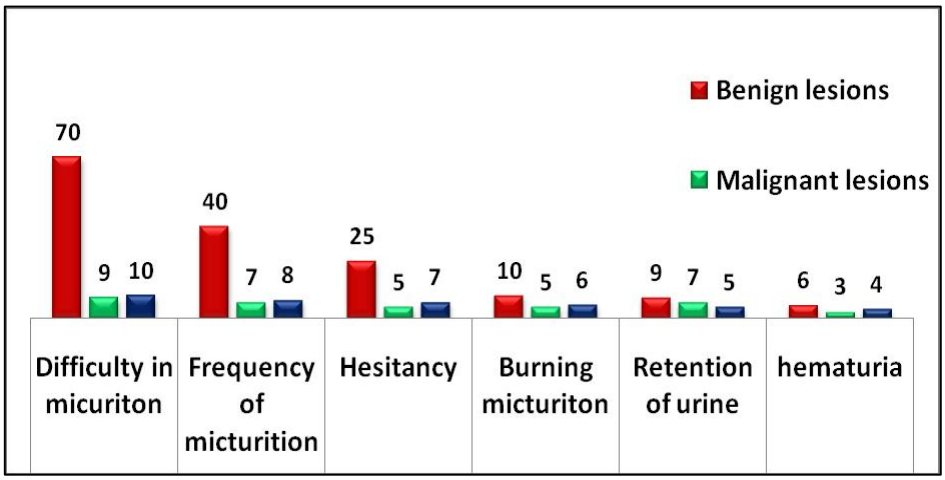

Fig. 3. Incidence of clinical presentation in prostatic lesions

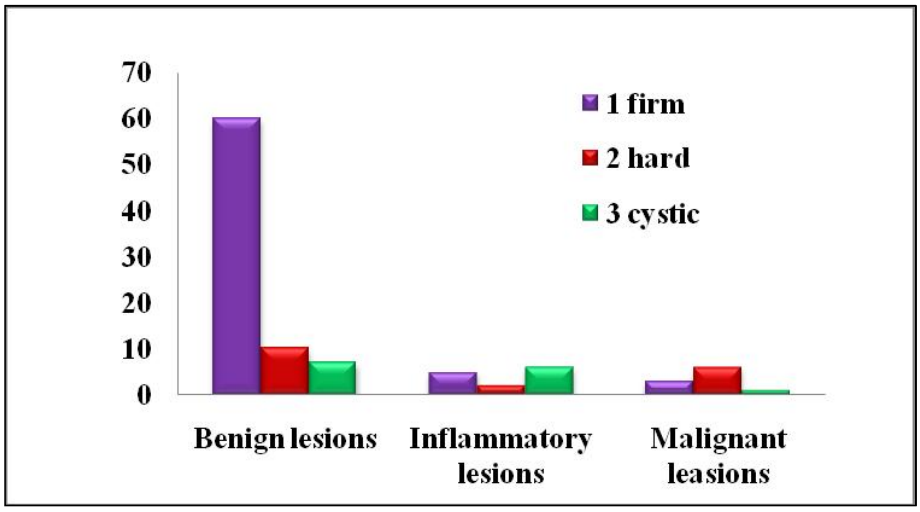

Fig. 4. Clinical presentations in prostate lesions

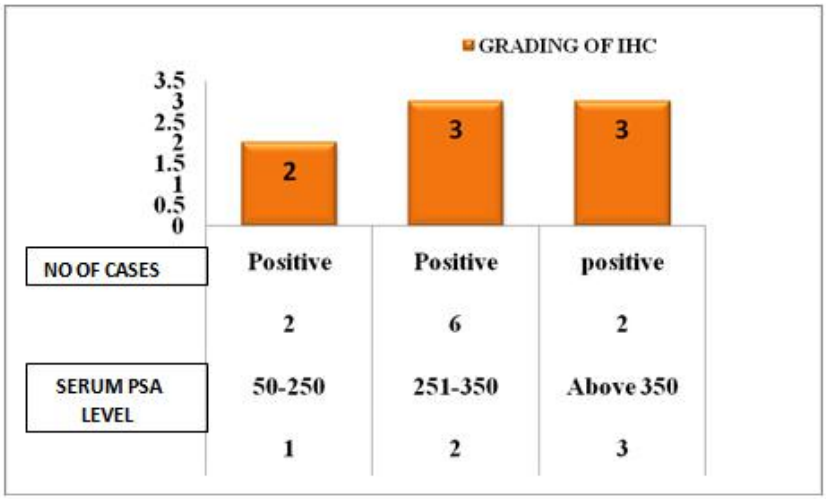

Fig. 5. Grading of IHC

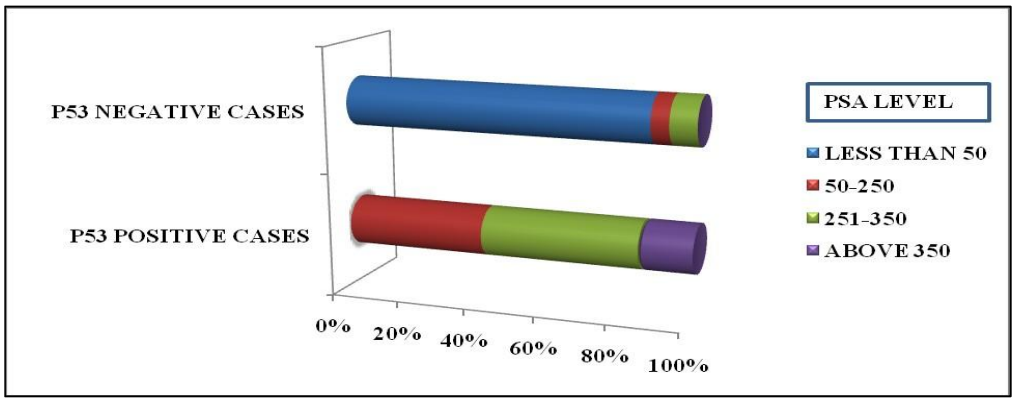

Fig. 6. Correlation of prostatic lesions with p53 and PSA level

Malignant Lesions

Case no: 1

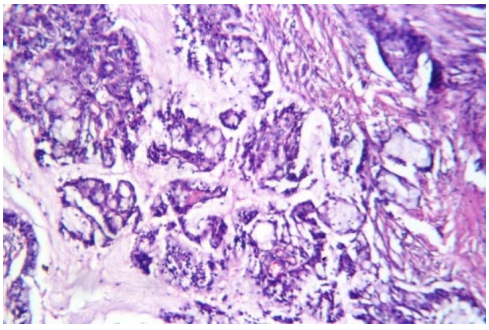

Fig. 7. LPF (100x) H228/16 prostatic carcinoma with individual irregular small glands and presenting as nodule with Gleason's score 3+3=6

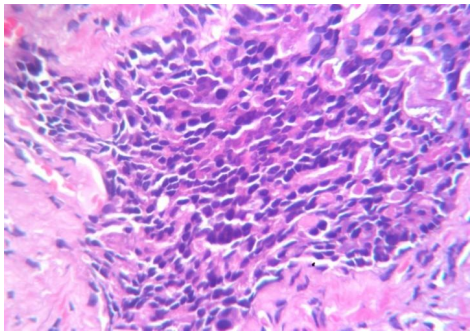

Fig. 8. HPF (400x) H228/16 prostatic carcinoma shows tumor cells infiltrating the stroma with adjacent prostatic glands

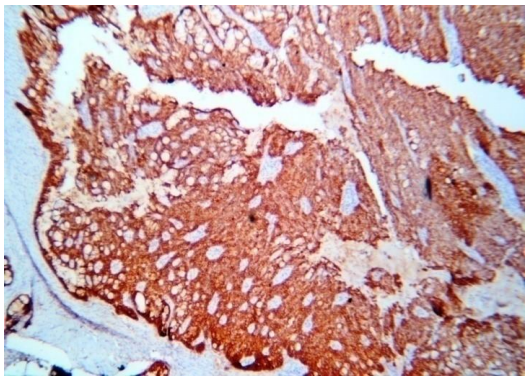

Fig. 9. LPF (100x) H228/16 Prostatic carcinoma shows positive for p53 epithelial marker

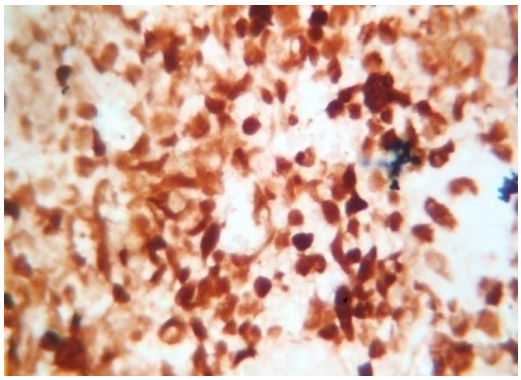

Fig. 10. HPF (400x) H228/16 Prostatic carcinoma positive for p53 epithelial marker with low intensitystaining

Case no:2

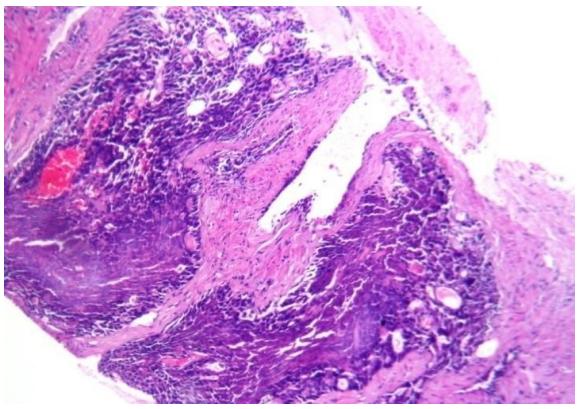

Fig. 11. LPF (100x) H188/16 prostatic carcinoma shows compressed glands and malignant cells infiltrating the stroma with Gleason's score 4+4=8

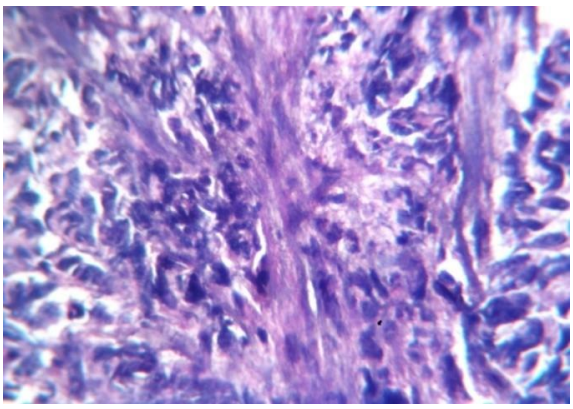

Fig. 12. HPF (400x) H188/16 prostatic carcinoma shows malignant cells infiltrating the stroma

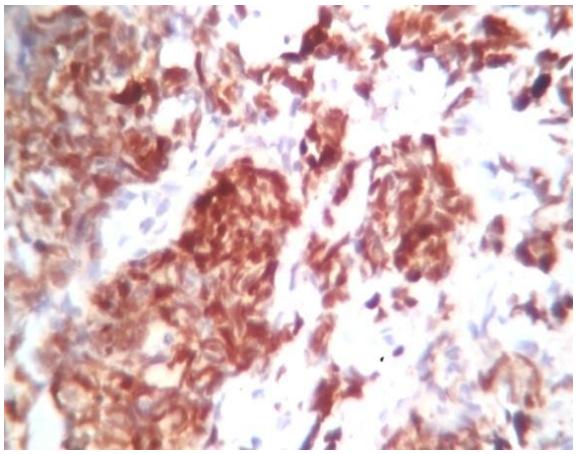

Fig. 13. HPF (400x) H188/16 prostateic carcinoma show P53 positive epithelial cell involving more than 50% of the tissue with high

Case No:3

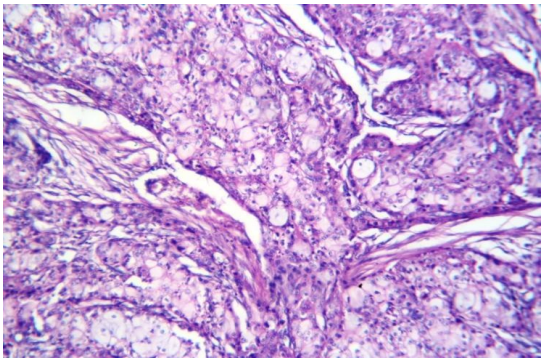

Fig. 14. LPF (100x) H984 / 16 Prostatic carcinoma shows hypernephroid cells and small acinar cells infiltrating the stroma with gleasons score 4+4=8

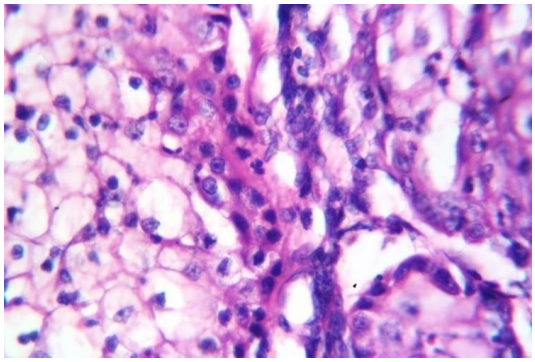

Fig. 15. HPF (400x) H984 / 16 Prostatic carcinoma shows tumour cells infiltrating the stroma

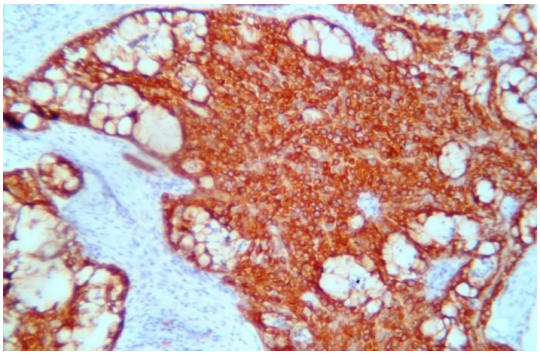

Fig. 16. LPF (100x) H984/16 prostatic carcinoma show P53 positive epithelial cell involving more than 50% of the tissue with high intensity

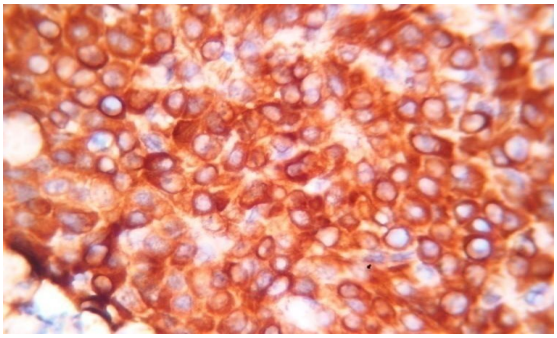

Fig. 17. HPF (400x) H984/16 prostatic carcinoma show P53 positive epithelial cell with high intensity staining

4. DISCUSSION

Lower urinary tract symptoms (LUTS), previously known as Prostatism, is a common malady in the geriatric age group. Benign nodular hyperplasia and carcinoma of the prostate are increasingly frequent with advancing age and are uncommon before the age of forty years. A careful examination of the prosta te in an unselected series of autopies disclosed nodular hyperplasia in approximately 20% of men in 40 yrs of age, a figure that increase to 75% by the age 60 yrs and to 90% by 80 yrs of life. In India the incidence of benign prostatic hyperplasia is est imated to be 29.97%.Carcinoma of prostate is the most common malignant tumour in men over the age of 65 years. In patients with clinically detected nodules, raised PSA; needle biopsy / tru- cut needle biopsy is an established tool to confirm the diagnosis. It is currently estimated that in United States of America approximately 241, 740 (29%) new cases are detected every year, of which approximately one fifth prove to be lethal. In India the incidence of carcinoma of prostate is estimated at 28/ 100, 000 persons 3.

Incidence of prostatic disorders increases with increasing age in male population in this study comprising of 185 biopsies reported Benign Nodular Hyperplasia in 172 (92.97%) cases and carcinoma prostate cases in 13 (7.02%) cases 24.

Study of 15753 prostatic biopsy reported highest incidence for benign lesions (55.5%) followed by carcinoma (33.4%) 79. In the study by Mohammed and Alhasan 2009 they reported 235

(77.6%) cases of Benign Nodular Hyperplasia and 68(22.4%) cases of carcinoma of prostate80, 82,84. series of 142 prostatic biopsy reported Benign Nodular Hyperplasia in 61(42.9%) patients and carcinoma prostate in 31 (21.8%) cases. There were 19 cases of atypical small acinar proliferation and 31 cases of prostatic intraepi thelial neoplasia 81.

Study comprising of 749 prostate biopsies, noted an incidence of 60.6% for benign prostatic lesions and 35.2% for malignant neoplasm 82.In this study comprising of 106 prostate biopsies with result of incidence of 88.67% for benign prostatic lesions and 10. 4% for malignant neoplasm.

4.1 Atypical Adenomatous Hyperplasia

Study reported the incidence of atypical adenomatous hyperplasia ranged from 2.2% to 19.6% in TURP specimen 26. In the present study AAH was seen in 3 cases (1.50%). These lesion seen in TURP specimen, were small, multifocal and associated with NH. All cases were in the age group of 68 - 74 years incidence of prostatic carcinoma in different studies 26,28.
In the present study peak incidence of prostatic carcinoma was seen in age group of 61 -70 years which was similar to many studies. The mean age and median age of patient with malignant neoplasm of prostate are 70.5 and 70 years.

4.2 Carcinoma Prostate and Gleason' s Score

Numerous grading systems have been designed for the histopathological grading of prostate cancer. The Gleason's grading system named after D. F. Gleasons grading system. In prost ate biopsy Gleason's score correlates with tumour aggressiveness, tumour volume, serum PSA levels, prognostic and influence of the treatment policy. The Gleason score is also often used to determine eligibility of clinical trials including those for watchf ul waiting 63.

Murthy et al. [2] in their study estimated that majority of carcinomatous prostate (49%) had Gleason' s score 2 -4 ie) well differentiated to moderately differentiated tumors (27%) with GS 5-78. In the study done there were 46% of carcinoma prostate patients presenting with GS 5 -7 with 33%. reported 34.8% of carcinoma prostate patients with a GS 8 -10. Majority of the cases (63.35%) presented with GS 5 -7 82. In the present study 63.63% of carcinoma cases presented with GS 5 - 7 and 36. 40% with GS 8 - 10.

In the present study majority of the adenocarcinoma of prostate (54.54%) were moderately differentiated with GS 5 - 7 followed by poorly differentiated tumors (36.40%) with GS 8 -10. this was closely similar to that of study. 81 where in 63.95% of carcinoma patients presented with moderately differentiated GS 5 -7 and 34.88% presented with poorly differentiated tumors GS 8 - 10.

4.3 Serum Psa Values

Normal level of PSA are usually <4ng/ml but they vary according to the age of the patient.PSA levels <4ng/ml of 60 yrs or less and levels <6.5ng/ml in mean age of 60 -80 years are normal. PSA is elevated by any change that destroys the normal architecture of the prostate which allows diffusion of prostate into the microvascular circulation. 8. In the present study only 70 cases had serum PSA level estimated. It is observed that not all the cases of surgical resection of the prostate, serum PSA level estimation is required .14,15, 3.

Out of 100 cases, 77 cases were benign. A total of 30 cases showed elevation of PSA level and 70 shows PSA <40ng/ml. This is because these cases of Benign Nodular Hyperplasia was associated with prostatitis, abscess, infracts and granulomatous prostatitis. In the present study 13 cases of prostatic carcinoma showed PSA level >50ng/ml, however this is attributed to study in which prostate cancers detected at lower are more likely to have a small volume and are of low grade27,28,.

In the present study all the benign lesions stained negative except for cases were the PSA value is more than >50ng/ml with p53 IHC and in prostate carcinoma positive indicating epithelial marker positive for prostate gland. Study observed that epithelial cell stain more with intensity in prostate carcinoma cases. This observation suggested that staining for p53 have poor prognosis in high intensity % cell staining, moderate intensity % cell staining and low intensity % cell staining. It differentiate benign lesions from malignant lesions. Study proved that p53 immunostaining was diagnostically reliable and sensitive in identifying epithelial cells in prostate needle biopsies and TURP specimens. TURP specimens in which cautery artifact can

impair the ability to detect high molecular weight cytokeratin, staining for p53 appears superior. 26

The results of p53 staining is prostate adenocarcinoma in this study supports the results who performed on p53 on 130 cases of invasive prostate cancer and found p53 positive 126(97%) cases 34. noted that 50 prostatic adenocarcinoma expressed p 53 in his study. Positive p53 expression of the malignant lesions in the present study correlates with studies done. The rate of p53 alterations increases with prostate cancer progression [3]. Patients given targeted treatment can increase their survival period through the association of immunoreactivity of p53 marker with increased tumor grade.

5. CONCLUSION

Benign Nodular Hyperplasia and Adeno carcinoma of prostate are the most common disease encountered in the aging population. Screening protocols and awareness programs over the year significantly reduced the morbidity and mortality. Use of immunohistochemistry p53 marker helps to differentiate the benign from malignant prostatic lesions in diagnosticall y challenging cases effectively. The mutation in p53 gene (a tumor suppressor gene) is an important IHC marker in malignant cells. So the IHC expression of p53 is significantly up-regulated in malignant lesions and have importance in prognostic factors and disease survival. More research and developments is to be done in this area of tumor suppressor genes and cancer cell biology [4-34].

CONSENT

As per international standard or university standard, patients' written consent has been collected and preserved by the author(s).

ETHICAL APPROVAL

The study was approved by the Institutional Ethics Committee

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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