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A Cross-Sectional Study of prevalence of Prostate lesions and inter-Observer Variability in Histopathological Reporting

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Abstract: Introduction: To report the prevalence of various prostate lesions in the general population through cadaver prostates and to determine the interobserver variability for reporting high-grade lesions of the prostate. Materials and Methods: The cross-sectional study was carried out on 110 autopsy specimens of healthy prostate with deceased age over 40 years. The specimens were grossed, sectioned, stained and reported independently by the primary investigator resident and the senior professor. The lesions were categorized into prostatitis, benign prostate hypertrophy (BPH), prostate intraepithelial neoplasia (PIN) further graded as low grade (LGPIN) and high grade (HGPIN) and prostate cancer (PCa). Inter-rater kappa agreement was used to find the strength of agreement between the pathologists. Results: Among 110 prostate specimens, only 8(7.27%) cases had normal prostate with 72 (65.4%) having BPH and 12(10.9%) cases having prostatitis. There were 17 cases of PIN with 11 cases of HGPIN and 6 cases of LGPIN. Malignancy was seen in only a single case (95% Confidence Interval: 0% - 2.71%). The primary resident missed 4 cases of HGPIN and 2 cases of LGPIN. Interobserver agreement between the resident and senior pathologist was fair (Kappa 0.282, p value=0.335). Conclusion: In conclusion, prostate lesions remain latent and show high prevalence in general population without causing any symptoms. The study depicts a high interobserver variability of reporting the high-grade lesions of prostate since they cause a diagnostic dilemma with PCa. The consultation with uropathologists and use of molecular markers must be included in the diagnostic panel while reaching a final diagnosis.

Keywords: Neoplasms; Pathology; Prostate

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1. Introduction

Prostate cancer (PCa) is one of the most common malignancy in males; second only to lung carcinoma. In 2018, there were 1,276,106 new cases with 3.8% cancer-related mortality(1, 2). Studies propose the incidence of such conditions to double by the end of 2030(3-5).

In India, the incidence rate of PCa was estimated at 3.9 per100,000 men, with 25,696 new cases and 9% cancer related mortality(6). The vast majority of cases are adenocarcinoma with squamous cell, transitional cell, and small cell carcinoma accounting for only a small minority of cases. Racial differences have been found to occur in the prevalence of prostatic carcinoma with the prevalence being higher among African-Americans and lower among Asians(7).

The diagnosis of PCa involves the screening of men aged 40 years or more with serum prostate specific antigen (PSA) levels and digital rectal examination (DRE). The procedure may be followed by a biopsy for clearing a suspicion(8). PSA carries a relatively low specificity (36%)(9) and on the other hand, TRUS biopsy also misses 20–30% of patients with PCa. Imaging techniques such as Multiparametric magnetic resonance imaging (mp-MRI)(10) and Ultrasound elastogra-

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phy(11, 12) has shown a definite role in the definitive diagnosis but the gold standard still remains the biopsy(11).
High-grade prostatic intraepithelial neoplasia (HGPIN) is an acceptable precursor to PCa but its recognition may require a good expertise and correlation among two or more pathologists(13). The accurate diagnosis of PIN may depend on a variety of factors including the specimen type, grossing, sections, tissue preparation and inconsistent reporting among different pathologists(14). In prostate gland several lesions with some of the histological features simulating adenocarcinoma have been described, but it has not been established that any of these patterns represent biological precursor of invasive carcinoma(15).
It is difficult to assess the malignant potential of the histological abnormality in the solid organ like prostate as it is not possible to follow clinically the evolution of questionable lesions found at biopsy. The original biopsy site cannot be located subsequently with an accurate degree of precision, and if carcinoma develops later the tumor is usually too large by the time of its detection to allow determination of its exact point of origin. Similarly, the organ cannot be sampled as repeatedly and early as can be done with organs like cervix.
It is probably because of these limitations, that the significance of the pre-malignant state or intraepithelial neoplasm in prostate was appreciated quite late. In spite of potential significance of identification of pre-malignant phase in natural history of prostatic carcinoma, very little attention has been given in detecting any such possibility by means of alternate modalities.
This calls for a standard following of College of American Pathologists (CAP) protocol for patients undergoing Prostate biopsy(16). Also, it becomes pertinent to understand the prevalence of various prostate lesions in different age groups in general population for a rough prediction or the high grade lesions of the prostate.
The present study was undertaken to report the prevalence of various prostate lesions in the general population through cadaver prostates and to determine the interobserver variability for reporting high grade lesions of the prostate.

2. Materials and Methods

A cross-sectional study was carried out in the medical institute attached to the government general hospital in Pune over a period of 15 months. This study was approved by the Institutional ethical committee. Since the cadaver was autopsied in the hospital, it was considered an applied consent for the present study. No further consent was obtained from the patient's relatives for the study. The sample size calculation of the study was based on the study of Aldaoud et al.(13), who observed that prevalence of high-grade prostate intraepithelial neoplasia was 34%. Taking this value as reference, the minimum required sample size with 9% margin of error and 5% level of significance is 107patients. To reduce margin of error, total sample size taken is 110. The 110 cadaver specimens were consecutively analysed for inclusion in the study as per the eligibility criteria.

2.1. Inclusion criteria

Cadaver specimens of prostate, which underwent routine full-body autopsy in the hospital; Age of Deceased 40 years and above; Healthy prostate of the deceased.

2.2. Exclusion criteria

Any cadaver with previous or recent history of prostatic complaints. All these specimens were processed in the surgical pathology and autopsy sections of the same institute. The tissues were processed as routine procedures, that is, by preparing paraffin blocks and taking 5-micron thick sections with manual microtome. These sections were stained with Haematoxylin and Eosin (H&E). After primary examination of these tissues, few of them showing evidence of PIN were treated with special stains like PAS. This was done to demonstrate intact basal lamina in cases of high grade PIN. All specimens of prostate were subjected to thorough gross examination. These specimens were fixed in 10% formalin before submitting for processing. A total four sections at first trimming were submitted for processing. These sections were taken from different areas of the gland in an attempt to get tissues from all zones of the entire prostate gland.
The trimmed tissues were kept in 10% formalin overnight and then taken for further processing - i.e., dehydration with ascending grades of alcohol embedding with paraffin and cutting with microtome. The sections were cut at 5-micron thickness and stained with Ehrlich's hematoxylin and eosin solution for primary reporting of the tissues.
The lesions were categorized into prostatitis, benign prostatic hyperplasia (BPH), prostate intraepithelial neoplasia (PIN) further graded as low grade (LGPIN) and high grade (HGPIN) and PCa. The glands with evidence of HGPIN or suspicious of malignancy were re-sectioned and multiple sections were taken from different areas of the gland other than the previously trimmed areas. This was done to find out the possible foci of malignancy in the other parts of the gland. The final reporting was blindly reviewed by two independent pathologists (resident doctor and senior professor) and labeled accordingly. Inter-rater kappa agreement was used to find the strength of agreement between the pathologists with the report of the senior professor being taken as the final. BPH was defined by increase of glandular and stromal tissue with papillary buds, infoldings and cysts. The basal layer was continuous which differentiated it from PIN. PIN was considered to be characterized by proliferation and dysplasia of cells lining prostatic ducts and acini with nuclear

crowding, pleomorphism, nucleomegaly, presence of nucleoli, basal cell layer disruption, loss of polarity and stratification(17, 18). It was divided into two grades, low grade (grade-I) and high grade (Grade-II and Grade-III). Malignant transformation was characterised by loss of basal cells, with glands being(19) too many, too small, and too crowded.

2.3. Statistical analysis

The presentation of the Categorical variables was done in the form of number and percentage (%). On the other hand, the presentation of the continuous variables was done as mean ± SD values. The association of the variables, which were qualitative in nature, were analysed using Chi-Square test/Fisher's exact test. Inter-rater kappa agreement was used to find the strength of agreement between the pathologists.

The data entry was done in the Microsoft EXCEL spreadsheet and the final analysis was done with the use of Statistical Package for Social Sciences (SPSS) software ver 21.0.

For statistical significance, p value of less than 0.05 was considered as significant.

3. Results

A total of 110 prostate specimens of cadavers were included in the study which were characterized by mean cadaver age of 52.64 ± 8.32 years. The prevalence of various prostatic lesions has been shown in Table 1. It was interesting to note that only 8(7.27%) cases had normal prostate (95% Confidence Interval: 2.34% - 12.2%) with 72 (65.4%) having benign prostate hypertrophy (95% Confidence Interval: 56% - 73.9%) and 12(10.9%) cases having prostatitis (95% Confidence Interval: 5% - 16.7%). There were 17 cases of PIN with 11 cases of HGPIN (95% Confidence Interval: 4.3% - 15.6%) and 6 cases of LGPIN (95% Confidence Interval: 1.1% - 9.6%). Malignancy was seen in only a single case (95% Confidence Interval: 0% - 2.71%).

Among the 11 cases of HGPIN, 6 were seen in association with BPH, 3 were along with BPH and prostatitis while 2 had no other pathology. Among the 6 cases of LGPIN, 4 were seen in association with BPH, while 2 had no other pathology.

The age wise distribution of the prostate lesions has been shown in Table 2. Statistically there was no difference in the occurrence of the lesions in varied age groups (p>0.05).

The primary resident missed 4 cases of HGPIN and 2 cases of LGPIN. Interobserver agreement between the resident and senior pathologist was fair (Kappa 0.282, p value=0.335)

4. Discussion

The continuous research about PIN has shifted the management of PCa from surgical treatment towards surveillance(20). The study results show the prostate lesions remains silent and is not detected up to the late fifties. The exact causation of the lesion is not yet known and hence it is important to detect its occurrence as early as possible, to reduce mortality and morbidity. Hence overall the study of prevalence of benign and premalignant changes in prostate, that is PIN, becomes important.

The considerate attention has been paid to the prostate lesions especially PIN because it forms the link of continuum from normal prostate to PCa. Since it seldom increases size of the prostate or PSA levels, its detection relies solely on the biopsy. As against the reported incidence of 4-16% of PIN(21), we report a prevalence of 15.4% PIN. The significance lies in the fact that it demands repeated biopsies to see the progress and risk of PCa over the next 10 years(21). In our case, that was not feasible since we included the prostate specimens of the cadavers, but it provided us the opportunity to biopsy the whole of the prostate even to the minor sections to see the presence of PCa(22, 23). With PIN showing high-grade changes in BPH cases, however even after re-sampling from various other areas of the gland, there was no evidence of malignancy in the present study.

The prevalence of HGPIN was minimum in the 5th decade, and increased progressively thereafter though it failed to reach a statistical significance (p>0.05). This is in accordance with the literature Davidson et al.(22), which states that the process of dysplastic changes may start at third decade of age with increasing incidence with advancing age. We observed that 11 cases out of 110 showed changes of HGPIN (prevalence rate of 10%) and 06 cases showed changes of LGPIN (prevalence rate of 5.4%). Majority of the cases of LGPIN were seen in 41-50 year age group compared to HGPIN which was seen maximally in older age groups - i.e., 6th decade onwards. It was found that prevalence of LGPIN declined after the 5th decade and no case of LGPIN was seen among the specimens from the 71-80 age group. This is in contrast to the observations of McNeal JE et al.(24), who described similar age distribution for both LGPIN and HGPIN. The findings of our study therefore indicate that with advancing age the changes of low grade PIN progressed to high grade group in general population.

Interestingly we found that PIN lesions were more associated with BPH (fibromuscular or glandular hyperplasia) or prostatitis (chronic inflammation) and not simultaneous PCa. This correlates with the previous studies(23, 25, 26). The lesions of PIN showed histopathologic characteristics intermediate between normal prostate and PCa including loss of normal architecture, cell differentiation, stratification and nuclear changes. The architectural patterns has been described in the literature(27, 28). Two cases showed the classical micropapillary pattern. In addition, one of them showing the presence of epithelial trabecular bars with epithelial structures traversing glandular lumen and inserted into opposite wall. While in nine cases typical tufting pattern was

shown. These findings correlate well with studies by Bostwick et al(29). Special stains were done on two cases among which PAS was used to delineate basement membrane where difficulty was encountered in ruling out stromal invasion on routine H&E.

Surprisingly, there was a single case of carcinoma of prostate which was present in more advanced age (71-80 years). This shows that men in eighties can have latent PCa which may not present itself with symptoms. It concurs with the fact that men over 50 can have a latent prostate disease which may progressively develop into PCa(30). The targets of the continuing research have been to innovate newer therapeutics to intervene in the cycle and prevent the neoplastic disease progression. "Androgen deprivation therapy" has shown good results to decreases the prevalence PIN, indicating that it may play an effective role in prevention (29).

4.1. Interobserver variability

From the overall diagnostic point of view, the current three tier system for PIN24 holds inconsistency in reporting among various pathologists (based on years of experience) and uropathologists; based on which it was converted to two a two tier system(31). Though there are theoretical differences in terms of nuclear morphology, nucleoli, and basal cell disruption, the distinction can be erroneous because of certain mimics such as metaplasia, PCa and overt benign proliferations(17, 18, 32-34).

Despite this, there exists interobserver variability while diagnosing and reporting PIN. It poses a concern for the prognosis of the patients. The primary reporting pathologist missed 6 cases of PIN and diagnosed them as normal prostate or PCa among which 2 were LGPIN and 4 were HGPIN. Among other studies missing of HGPIN was 75% in Tan et al. (35), 45% in Aldaoud N et al.(13), and 34.5% by Kronz et al(19).

Overall, the Kappa agreement in the present study was just fair (Kappa 0.282, p value=0.335) as opposed to the study of Aldaoud N et al.(13), where among the 65 cases of HGPIN, the lesion was correctly recognized in 36 (55%) cases and missed in 29 (45%) cases. (Kappa 0.53, p value>0.05) The causes of variation include the section of slide examined, the unfamiliarity in mind of all the different permutations and combinations and the continuously changing reporting system. Different approaches such as consultation with a uropathologist, examination of multiple sections, special stains and use of molecular markers such as ETV4(36) have come into play for a better differentiation. Besides, there has been a changing terminology in concordance with Gleason grading where florid HGPIN are labelled as intraductal cancer (IDC). Due to the marginal risk of PCa with HGPIN, the term is being thought to be omitted(37).

The results of the present study hold importance in terms of providing the prevalence of the prostate lesions in the healthy population. The results may be validated in the future studies on a larger sample size to gain more insight into the prostate changes with age.

The study results must be interpreted in view of certain limitations. Firstly, the interobserver variability was between two pathologists with a difference in the experience and not between a pathologist and uropathologist. Second, PSA levels were not obtained from the cohort. Third, as this study was done on cadavers, the relevant data about the patients was restricted only to age as there was no one to provide the additional data of the patients and this can be a source of potential bias. Lastly, the age distribution in this study mostly included the middle age range and older people were less. Therefore, there might be an age bias in the reporting of the data.

5. Conclusion

We report a high prevalence of BPH and PIN lesions in healthy prostate though the cadaver autopsies. There was a fair agreement between the resident and senior pathologist in diagnosing the PIN lesions.

In conclusion, prostate lesions remain latent and show high prevalence in general population without causing any symptoms. The microscopic presence of HGPIN from as early as fifth decade prompts us to recommend regular prostate screening programs to make the general population aware about it. The consultation with senior pathologists seems to be a better option while reaching a final diagnosis for prostate lesions.

6. Appendix

6.1. Ethics and Publishing consent

This study was approved by the Institutional ethical committee.

Patient consent: Since the cadaver was autopsied in the hospital, it was considered an applied consent for the present study. No further consent was obtained from the patient's relatives for the study.

6.2. Conflict of interest

None.

6.3. Funding and support

None.

6.4. Author's contributions

All the authors have shared the same workload and thereby are entitled to equal contribution.

6.5. Acknowledgement

None.

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Table 1: Prevalence of Prostatic Lesions (n= 110).

Lesion	n (%)	95% C)
Normal	8(7.27%)	2.34% - 12.20%
BPH	72(65.4%)	56% - 73.9%
HGPIN	11(10%)	4.3% - 15.6%
LGPIN	6(5.4%)	1.1% – 9.6%
Prostatitis	12(10.9%)	5% - 16.7%
Malignancy	1(0.9%)	0% - 2.71%

Table 2: Prevalence of various prostatic lesions with respect to age (n = 110).

Age (years)	Total Cases	Normal	BPH	HGPIN	LGPIN	Prostatitis	Malignancy	P value	Test
41-50	38	4	25	2	3	4	Nil	0.675	
51-60	38	2	26	4	2	4	Nil	0.996	Fisher's Exact test
61-70	20	0	13	3	1	3	Nil	0.664	
71-80	14	2	8	2	Nil	1	1	0.165	
Total	110	8	72	11	6	12	1		
P value		0.266	0.901	0.557	0.935	0.917	0.127		
Test performed		Fisher Exact test	X^2 test	Fisher Exact test	Fisher Exact test	Fisher Exact			
Mean ± SD				52.64 ± 8.32					