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Original Research Article

STUDY OF BIOPSY OF PROSTATIC LESIONS

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Abstract
Prostatic pathology is deceptively simple. Benign prostatic Hyperplasia, prostatitis and prostatic carcinoma are the three principal conditions involving the prostate accounting for more than 95% of lesions. Though the morphologic diagnosis of prostatic lesions, separating benign from malignant is relatively straight forward, there are several benign proliferations and normal histo-anatomic structures of prostate which mimic malignancy and their awareness is essential to avoid diagnostic pit falls.

Keywords: Biopsy, BPH, Malignancy, Prostate

Introduction

The prostate is an amazing challenge to the pathologist and urologists alike. The history of prostate gland dates back to 300 B.C., when Herophilos of Chalcedon, the father of anatomy coined the word PROSTATE-Pro-status-meaning to stand before-indicating that the gland stands before or guards the bladder.

The incidence of prostatic lesions, both benign and malignant increases with age and are rare before 40 years of age. Though BPH is an almost universal ageing process, prostatic carcinoma, demonstrates ethnic and racial variations. Africans and Americans have higher incidence than Japanese and Asians [1]. As on date the incidence of prostatic carcinoma is 0.13% in Americans and 0.09% in Japanese and 0.10% in other Asian Countries. In India, the prostate malignancy is 6 times higher when compared to other communities. The incidence of malignancy is higher among Gujarati.

The diagnosis of prostatic carcinoma is usually too late because there are no signs and symptoms specific to malignancy other than those for BPH. As a result, patients present with a locally advanced cancer or with metastasis where in little could be done in the way of cure. The biological behavior of prostatic carcinoma is also peculiar. Some tumors behave in a very indolent fashion while others behave very aggressively. Latent, occult and incidental malignancies are also well documented in prostate all these facts in the background, there are currently two main issues in prostate pathology

1. Early detection of prostatic carcinoma in the pre-invasive phase.
2. Identification of the prognostic factors that predict the outcome of individual patients with

in situ carcinoma.

Advances in the field of biochemistry that have brought out PSA and other markers are valuable diagnostic tools, advances in the field of radiodiagnosis that have provided Transrectal ultrasound, advances in the field of instrumentation and biopsy procedure, TURP and prostatectomy that have led to the minimally invasive procedures like Needle biopsy, ongoing research in prostate pathology that led to the documentation of premalignant lesions like PIN & AAH that predate malignancy by at least 10 years. Invention of newer treatment options including androgen ablation, radiotherapy, chemotherapy-all these have helped us to resolve the problems in diagnosis and management of prostate malignancies. However much remains to be understood in the way of increased disease free survival. The present study aims at highlighting on all these issues.

Aim

1. To study the lesions of prostate to identify the incidence of the premalignant and malignant conditions.
2. To study the most important precursor lesion of prostatic cancer, i.e., prostate intraepithelial neoplasia (PIN) and its diagnostic value in pathological analysis.
3. To correlate the PIN with clinical, radiological, biochemical and immunohistochemical findings wherever possible.

Materials and Methods

The study of prostatic lesions was done from January 2016 to December 2016. This includes 75 prostate biopsies of prospective study. For all the prospective cases, clinical history regarding various putative aetiological factors and presenting symptoms were taken. PSA values, transrectal ultrasound findings and details for evidence of metastasis were taken whenever possible.

Results

Table 1: Prostate lesions

Benign	68
Premalignant	3
AAH	1
HGPIN	2
Malignant	4

Table-1 shows about prostatic lesions. Out of 75 prostatic biopsies, there were 68 (90.7) benign lesions, 3(4%) premalignant lesions and 4 (5.3%) malignant lesions.

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Percentage distribution of prostatic lesions

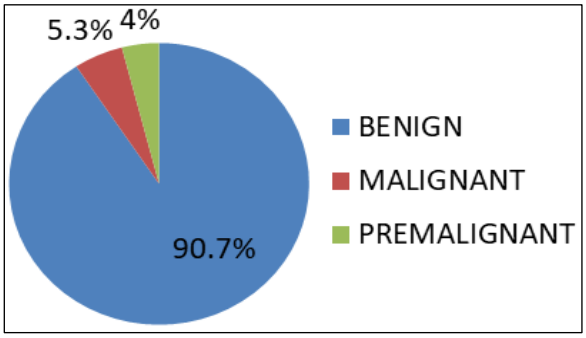

Table 2: Age-Wise Distribution

Premalignant				
Age group	**Benign**	**AAN**	**HGPIN**	**Malignant**
41-50	7	0	0	0
51-60	20	1	1	2
61-70	28	0	1	0
71-80	12	0	0	2
81-90	1	0	0	0

Table 2-shows age wise distribution of various prostatic lesions. The maximum incidence of benign lesions was in the 6th decade, premalignant lesions was in the 5th decade and malignant lesions was in the 6th decade.

Age wise distribution of prostatic lesions

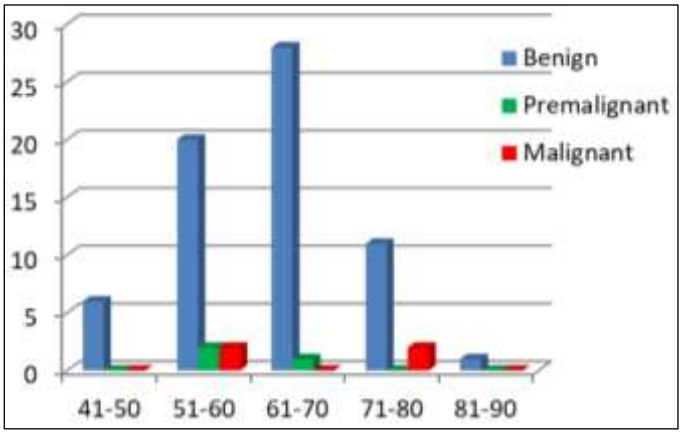

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Table 3: Analysis of Risk factors in malignant lesions

Sl. No.	Risk factor	Positive	Negative
1	Hereditary H/O Prostate cancer	1(25%)	3(75%)
2	H/O Androgens intake	0	4(100%)
3	Meat consumption	3(75%)	1(25%)
4	Cigarette Smoking	3(75%)	1(25%)
5	Alcohol use	2(50%)	2(50%)
6	Obesity	1(25%)	3(75%)

Out of several risk factors analysed in prostate cancer patients, a positive history of cigarette smoking is observed in maximum number of cases (75%) and none of the cases have the history of androgen intake.

Table 4: TRUS findings in malignant lesions

Sl. No.	Finding	No. of Cases
1	Hypoechoic	3(75%)
2	Isoechoic	1(25%)
3	Hyperechoic	0

Transrectal ultrasound (TRUS) findings were available for all cases of prostatic carcinomas, and premalignancy. 3 showed Hypoechogenicity and 1 showed Isoechogenicity.

Table 5: PSA levels in malignant lesions and PIN

Sl. No.	PSA values	No of Malignant lesions	No. of PIN lesions
1	0 - 4 ng/ml	1(75%)	1(50%)
2	4 - 10 ng/ml	0(0%)	1(50%)
3	>10 ng/ml	3(75%)	-

Three cases of prostatic carcinoma, for which PSA values have > 10 ng/ml, and one case of prostatic carcinoma have < 4 ng/ml. The mean PSA in two men with isolated high-grade PIN was 4.34 ng/ml.

Table 6: Distribution of Gleason Scores

Sl. No.	Gleason Score	No of Cases
1	7	1(25%)
2	8-10	2(75%)

The above table shows that maximum number of acinar adenocarcinoma (75%) have Gleason score (8-10), followed closely by Gleason score 7 with (25%) of cases.

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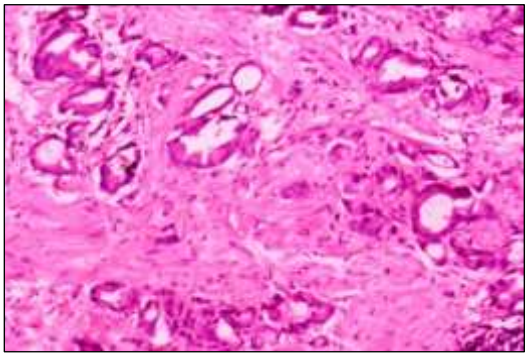
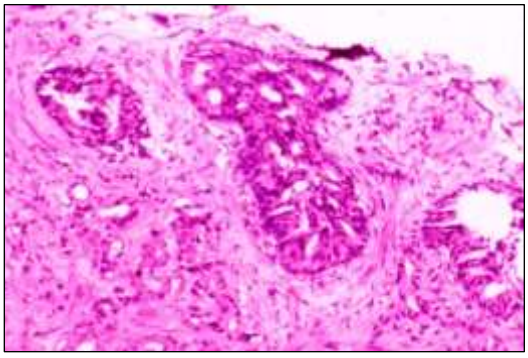
Table 7: Distribution of benign lesions

Sl. No.	Nature of lesion	No of Cases
1	Benign Prostatic Hyperplasia	49(72%)
2	Chronic prostatitis	12(17.6%)
3	Granulomatous prostatitis	1(1.4%)
4	Basal cell hyperplasia	1(1.4%)
5	Atrophy	1(1.4%)
6	Xanthogranulomatous prostatitis	1(1.4%)
7	Squamous metaplasia	1(1.4%)
8	Transitional metaplasia	1(1.4%)
	Total	68

Benign prostatic hyperplasia is the most common benign lesion encountered in the present study followed closely by chronic prostatitis.



Prostatic Adenocarcinoma, Gleason Score: 3 + 4 = 7 [Biopsy also includes Rectal Mucosa] H & E X 100.



Prostatic Adenocarcinoma-Cribriform Pattern, H & E X 400

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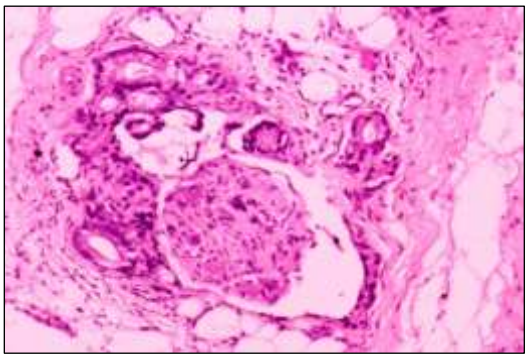

Prostatic Adenocarcinoma with Evidence of Perineural Invasion, H & E X 400 [Gleason Grade: 5 + 3, Total score = 8]

Discussion

Out of 75 biopsies, malignant lesions constituted 5.3%, premalignant lesions constituted 4 %, HGPIN constituted 2.71% and other benign lesions constituted 90.6%.

Table 8: Incidence of Prostatic Carcinomas in Various Studies

Sl. No.	Study	No. of specimens	No. of carcinomas	Incidence in %
1	Newmann *et al*. (1982) [2]	500	71	14
2	Moure *et al*. (19926) [2]	143	31	22
3	Yamabe *et al*. (1986) [2], Japan	191	24	13
4	Yamabe *et al*. (1986) [2], Netherlands	452	57	13
5	Ohori *et al*. (1994) [2]	385	68	18
6	Rubin *et al*. (1998) [2]	642	142	22
7	Present study (2013)	75	4	5.3

The incidence of prostatic carcinomas in the present study is 5.3%. The general incidence of prostatic carcinomas is increasing over years such a trend is clearly noticeable from the above mentioned studies.

The incidence is lower in studies of Japan and Netherlands. This is in agreement with the fact that the incidence of prostate cancer in Japan, China and other Asian countries is much lower when compared to White American men. The incidence of 5.3% in the present study is correlating with the incidence of prostate cancer in Asian men during the period of 1994-96.

Incidence of premalignant lesions

Prostatic Intraepithelial Neoplasia (PIN)

PIN was originally subdivided in to 3 groups which have now been combined into Low-grade (PIN 1) and HGPIN (PIN 2 and PIN3). HGPIN differs from low-grade PIN in that cytologic atypia is more apparent, particularly the presence of prominent nucleoli, as observed using a 20 x power lens (200-fold magnification). Because of its lack of clinical significance, low-grade PIN should not be included in a pathology report to avoid confusion with HGPIN which does impact clinical management.

High grade PIN (HGPIN)

Table 9: Incidence of HGPIN in various studies

Sl. No.	Study	No. of men	Isolated HGPIN
1.	Mettlin *et al*. 1991 [2]	330	5.20%
2.	Richie *et al*. 1994 [2]	163	8.60%
3.	Feneley *et al*. 1997 [2]	212	20%
4.	Hoedemaker *et al*.1999 [2]	1824	0.70%
5.	Present study 2013	75	2.70%

In the present study out of 75 prostate biopsies, 2 cases showed changes of isolated high grade PIN, constituting around 2.71% of total biopsies.
In the present study, the incidence of PIN is much lower than when compared to the western studies. In the above studies the incidence of PIN was studied in step sectioned whole prostatectomy specimens where wide tissue sampling is possible. So the likelihood of detecting associated PIN changes was much higher, but in the present study PIN changes are studied only on TURP chips biopsies where the likelihood of detecting PIN is limited by the amount of biopsy material available and the amount of material embedded. This difference may be responsible for the overall lower evidence of PIN.

Incidence of PIN

In the present study, the incidence of PIN is in the age group of 55-64 yrs. The studies of Mc. Neal & Bostwick [3] revealed that the maximum incidence of PIN was in the age group of 50-60yrs. Atypical Adenomatous Hyperplasia (AAH) In the present study, out of 75 prostatic biopsies, atypical adenomatous hyperplasia is observed in 1 case contributing an incidence of 1.3%. The reported incidence in literature varies from 1.5 to 19.6%. The common age group for this lesion is 51-60 years in the present study.

Risk Factors

Risk factors for High-grade PIN and carcinoma of prostate are same
Enquiry has been made in to the presence of any of the proposed risk factors for prostatic carcinoma. Various studies by Carter *et al*. 1993 [1]. Steinberg *et al*. 1990 [1], Pienta *et al*. 1993 [1] proposed an average of 9% of cases with familial history of prostate cancer. But in our series of cases, only 1 out of 4 men i.e. 25% have positive familial history of prostate cancer. In Indian scenario, it is highly difficult to obtain a positive familial history of prostate cancer as this is influenced by several factors including the non-detection of prostate cancer due to non-cancer deaths, Lower average survival rates in Indian men.

Meat consumption: Studies by Kolonel *et al*. [1] showed that meat consumption has a risk for prostate cancer. In the present study, 75% of patients of malignancy consume meat.

Cigarette smoking: There is little agreement over the role of cigarette smoking. 75% of patients have a history of cigarette smoking in the present study.

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Alcohol intake: Alcohol is believed to have protective effect. 50% have habit of alcohol intake in the present study.

Obesity: Obesity is proposed as a protective factor. 25% of patients are obese in the present study. (Peripheral conversation of testosterone to estrogen).

Though the present study predicts positive association with some of the proposed risk factors, the study group is smaller and a more wider community based study is needed to comment on the aetiological association of these factors.

The incidence of low grade PIN lesions is more in the transition zone whereas HGPIN lesions are more common in peripheral zone. The studies of Epstein *et al*., Bowstwick *et al*. [3] had shown that PIN was common in the peripheral zone than in the transition zone.

But in present study, PIN is studied on TURP chips. So, the biopsy material studied is mostly from transition zone and in consequence, PIN also more in frequency in the transition zone. The incidence of atypical adenomatous hyperplasia is more in the transition zone. This is in agreement with the fact documented in the literature [4] that atypical adenomatous hyperplasia is more common in the transition zone.

Trans-rectal ultrasound findings in prostate malignancies

Trans-rectal ultrasound is an important tool in identifying suspicious areas in prostate and perform needle biopsy from these targeted ares and thus increasing the diagnostic yield of malignancy but not all hypoechoic areas are malignancies and some of the malignant lesions appear as isoechoic or hyperechoic area.

Table 10: TRUS finding Malignancies in various studies

Sl. No.	Study	Hypoechoic	Isoechoic	Hyperechoic
1.	Ellis *et al*. 1994 [5]	63%	37%	0
2.	Carter *et al*. 1989 [6]	53%	47%	0
3.	Egawa *et al*. 1992 [7]	73%	25%	2%
4.	Present study 2013	75%	25%	0

The present study results are consistent with the results reported by Egawa *et al*. 1992 [7].

In the present study the proportion of Hypoechoic is higher than isoechoic lesions when compared with other western studies. Hypoechoic lesions present as nodules on digital rectal examination and mostly seen in the peripheral zone whereas the malignancies in the central and transitional zones appear as iso-echoic lesions and these cannot be picked up by ultrasound. These lesions picked up with systematic needle biopsy based on PSA screening. Even digital rectal examination these lesions are not always palpable. In Indian scenario, where the screening programmes are hardly done. It is very difficult to pick up these TZ and CZ malignancies.

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PSA values in Benign and Premalignant lesions PSA values between 4-10 ng/ml is considered as a gray zone where maximum overlap occurs between benign and malignant lesions. PSA value in lesions with HGPIN is2.2-6.4ng/ml. HGPIN by itself does not elevate PSA in significant level. Any associated prostatitis or malignancy may be responsible for elevation. But malignancy is not detected in this case even on repeat biopsy and periodical follow up is advised for this patient.

Table 11: PSA values in Malignancies

Sl. No.	Study	PSA Values		
		0-4ng/ml	4-10ng/ml	>10ng/ml
1.	Catalona *et al*. 1990 [1]	18%	31%	51%
2.	Brawer *et al*. 1992 [1]	25%	36%	39%
3.	Androile *et al*. 1993 [1]	15%	25%	60%
4.	Present study 2013	25%	0%	75%

In the present study, three malignancies have PSA >10ng/ml and one malignancy have <4ng/ml. The percentage of lesions with PSA>10ng/ml is also much higher when compared with the western studies. The cause for the disparity is probably the late identification in symptomatic phase by malignancies in Indian scenario at which the cancer has already spread locally to increased volume of cancer tissue which in turn leads to increased PSA.

Table 12: Distribution of variants of prostatic carcinoma

Sl. No.	Study	Small acinar variant	Other variants
1	Amin *et al*. 1993 [4]	90%	10%
2	Present study 2013	100%	0%

Histopathology of prostatic carcinoma

In our study, out of 4 malignancies, all are constituted by small acinar variant of adenocarcinoma.
The present study almost correlates with the studies of Amin *et al*.

Features Specific for Malignancy [8]

1. Glomerulations
Consists of glands with a cribriform proliferation that is not trasluminal, rather these cribriform proliferations are attached to only one edge of a gland resulting in a structure superficially resembling a glomerulus. Studies by Varma *et al*. [9] had reported an incidence of 3% to 15% of biopsies. The incidence in the present study is 33.3%. The glomeruloid pattern is best considered as Gleason`s primary pattern 3 cancer [9]. The pattern can be focal or extensive and is associated with other primary pattern. In our study, the glomeruloid pattern is focal and is associated with primary Gleason pattern 3.

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2. Mucinous fibroplasias (Collagenous micro nodules)

Collagenous micronodules are a specific but infrequent and incidental finding. These nodules are formed when the intraluminal mucinous secretions become extensions and become focally organized. The lesion is verified by very delicate loose fibrous tissue with an ingrowth of fibroblasts resulting in formation of microscopic nodules of paucicellular eosinophilic fibrillar stroma that impinges on acinar lumens. However these are not observed in the present study.

3. Perineural invasion (PNI)

Perineural invasion serves as a diagnostically specific criterion only when the glands in question completely encircle the nerve. However in some cases even benign glands may be seen adjacent to peripheral nerves. In contrast to malignant glands, these benign glands only indent the nerve (perineural indentation) and do not completely the nerve (perineural invasion).

Table 13: PNI in various studies

Sl. No.	Study	% of cases with PNI
1.	Rubin *et al*. [9]	18%
2.	Bastacky *et al*. [9]	20%
3.	Varma *et al*. [9]	22%
4.	Tallie *et al*. [9]	24%
5.	Merrick *et al*. [9]	25%
6.	Bostwick *et al*. [9]	38%
7.	Present study	25%

The incidence of PNI in present study is correlating with that of Merrick *et al*.

There are conflicting reports regarding the prognostic ability of PNI. Studies by Bostwick *et al*., Bastacky *et al*. [10] had suggested that PNI was predictive of extra prostatic extension but studies by Rubin *et al*., Merrick *et al*. [11] had shown that PNI had no predictive value after Gleason score, serum PSA and amount of cancer on biopsy were considered. Nonetheless as PNI is readily identifiable, it is a reasonable to report this finding.

Most common Gleason grade

The studies of pre-PSA era by VACURG headed by Donald F. Gleason had shown that grade 3 is the most common grade encountered [12]. The studies of PSA screening era by Hymphrey *et al*. [13] had also shown that grade3 is the most common grade encountered. In the present study grade 3 is present in 68% of cases forming the most common encountered grade followed closely by grade found in 56% of cases. This is in agreement with Western studies.

Most common Gleason Score:

Pattern 3 + pattern 5 = Score 8

Pattern 3 + pattern 4 = Score 7

In the original Gleason series, a composite of pattern 3 with pattern 5 producing a score of 8 was more common than a composite of pattern 3 with pattern 4 producing a score of 7 [12].

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But in the recent series of cases by Humphrey *et al*. [14], Gleason scores of 5-7 with pattern 3 embedded was the most common presentation of prostatic adenocarcinoma.
In the present study, 75% of cases have score of 8, with score 7 alone contributing to around 25% of cases. This is in close agreement with studies of Humphrey *et al*.

Benign lesions
Benign prostatic hyperplasia

Benign prostatic Hyperplasia is the most commonly encountered codition constituting 71% all the biopsies and 78% of all the benign lesions the present study. The term nodular hyperplasia proposed by Moore is a exact designation. The disease represents a nodular enlargement of the gland caused by hyperplasia of both glandular and stromal components. The reported incidence of this disease was only8% during the fourth decade [15]. The highest incidence of BPH is in the Sixth decade [40%] followed closely by the fifth decade (30%) in the present study.

Basal cell Hyperplasia (BCH)

The incidence of basal cell hyperplasia is 1.4% of all the benign lesions. It is seen as part of the spectrum of nodular hyperplasia in samples from transition zone.

Clear cell cribriform hyperplasia

Benign nodular hyperplasia demonstrates areas of prominent cribriform glands. The cells comprising the central cribriform areas are cuboidal to low columnar secretory type cells with uniform round nuclei and clear cytoplasm. Cribriform hyperplasia constituted 1.5% of all benign lesions.

Atropy

Atropy of prostate glands is a common process and is seen as a massive lesion in 1.5% of benign lesions and is seen focally in 15% of BPH lesions.
4 main patterns of atropy are seen-Lobular (simple), Sclerotic, Elastic and Linear or streaming.
Squamous metaplasia: Squamous metaplasia can be seen at the periphery of infarct, after TUR, hormonal therapy. In our study squamous-metaplasia constituted 2.6% of benign lesions and in all the cases is associated with infract. Transitional cell hyperplasia or metaplasia Transitional cell hyperplasia is seen in 1.5% benign lesions in our study.

Prostatitis

Prostatitis is the second most common condition involving the prostate, next to BPH. Prostatitis has constituted has 15.71% of all lesions affecting the prostate and 17.18% of all the benign lesions involving the prostate in the present study.
Chronic nonspecific prostatitis is the most common form of prostatitis (nearly 96% of prostatitis lesions). Apart from chronic prostatitis, one case of granulomatous prostatitis and one case of Xanthogranulomatous prostatitis are reported in the present study. One case of

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Xanthogranulomatous prostatitis [16] has caused diagnostic difficulty as it is closely resembling Gleason`s 4B patterns (Hypernephroid pattern) of adenocarcinoma.

Summary and Conclusions

The incidence of prostatic lesions is 0.5% among the various specimens received in the department during the period of one year. Benign lesions constitute 91.8%, premalignant lesions constitute 4.1% and malignant lesions constitute 4.1% of all the prostatic lesions.
Among the premalignant lesions, high grade prostatic intraepithelial Neoplasia is seen in 66.6% of cases and atypical adenomatous hyperplasia is seen in 33.3% of cases.
The peak age incidence of premalignant lesions is in the 5th and 6th decade.
The peak age incidence of prostatic carcinomas is in the 6th decade.
High-grade PIN is considered as a premalignant condition based on morphologic, epidemiologic and genetic features. High-grade PIN precedes carcinoma by 10 years.
Currently, high-grade PIN is associated with adenocarcinoma on rebiopsy in 25% of patients; significantly less than the 50% association reported in patients biopsied in the late 1980.

The decreasing association between high-grade PIN and carcinoma is due to

Increased number of cores performed per biopsy procedure with lower prevalence or lower volume of adenocarcinoma; Bayesian reasoning dictates that the positive predictive value of any test result (high-grade PIN on biopsy) is a function of the prevalence of disease (carcinoma) in the population being tested.
Presence of high-grade PIN mandates rebiopsy; however it is unclear that chasing PIN has any benefit (i.e. it simply results in the detection PIN has any benefit (i.e. it simply results in the detection of clinically insignificant prostate cancers.
Small acinar (usual cancer) variant is the most common prostatic malignancy.
Among the prostatic carcinomas for which transrectal ultrasound (TRUS) findings are available, 66.6% have Hypoechogenicity confirming the corroborative role of TRUS in dealing with a case suspicious of malignancy.
The awareness of several benign lesions that mimic premalignant and malignant lesions is essential. Meticulous observation of light microscopic features will help in the differential diagnosis in most of the cases.
Failure to recognize HGPIN in prostate cancer research will lead to inaccurate conclusion. Which may impede the clinical diagnosis, treatment and prevention of prostate cancer.

References

1. Cambell’s urology 8th Edn, edited by Walsh, Retick, Vaughan, Wein, 2002, 4.
2. John N Eble, Jonathan. Epstein-Stage a carcinoma of prostate-contemporary issues in surgical pathology edited by David. G. Bostwick 3rd edition.
3. Diagnostic surgical anthology 2nd edition; edited by S.S Sternberg, 1994, 2.
4. Anderson’s Pathology 10th edition; Edited by Ivan Damajanov James Linder, 1996, 2.
5. Ellis, *et al*.: Diagnosis of prostatic carcinoma. The yield of serum PSA, digital rectal examination and transrectal ultrasonography. J Urol. 1994;52:15-20.
6. Carter, *et al*.: Evaluation of transrectal ultra sound in diagnosis of prostate cancer. J Urol. 1929;142:1008.

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7. Egawa, *et al*. Hyperechoic appearance of prostate cancer Br. J Urol. 1992:69:1697-74.
8. Baisden, Epstein, Kahane, *et al*. Diagnostic features of limited cancer on prostate needle biopsy Am J Surg. Pathol. 1999;23:918-924.
9. David G Bostwick, Qian J. Cory Schlesinger-contemporary pathology of prostate cancer-Urol. Clin. N Am. 2003;30:181-207.
10. Bostwick, *et al*. Am. J Surg. Pathol. 1997;21(12):1496-1500.
11. Rubin, *et al*. Hum pathol. 2003:31(4):504-12.
12. Gleason DF. Histological grading of prostatic carcinoma-pathology of prostate-contemporary issues in surgical pathology edited by David. G. Bostwick 3rd edition.
13. Humphrey, *et al*. prospective characterization of pathological features of prostatic carcinoma detected via serum prostate specific antigen based screening. J Urol. 1996;155:816-820.
14. Humphrey, *et al*. Gleason grading and prognostic factors in carcinoma of the prostate. Modern Pathology. 2004;17:292-306.
15. Ackermans surgical pathology 9th edition, Juan Rosai, 2004, 2.
16. Srigley JR, *et al*. -Benign mimickers of prostatic adenocarcinoma Modern pathology. 2004;17:28-348.