"STUDY OF MORPHOLOGICAL SPECTRUM OF PROSTATIC LESIONS"

By

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IN

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DEDICATED

TO
MY BELOVED PARENTS

LIST OF 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

ABSTRACT

Background: There is a paucity of literature regarding the prevalence of neoplastic and non-neoplastic lesions of prostate in India. The current study attempts to document the occurrence of prostatitis, hyperplasia, prostatic intraepithelial neoplasia(PIN), prostate carcinoma in patients operated at the study institution.Correct diagnosis of prostatic lesions goes a long way in the treatment and prognosis of the patient.

Objective: To study the morphological spectrum and evaluate the proliferative index by Ki-67 antibody in neoplastic and non-neoplastic lesions. To correlate histopathological findings with serum PSA levels.

Materials and Methods: Cross-sectional study comprising of 90 patients who underwent transurethral resection of prostate from January 2012 to June 2013 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, USG prostate size and clinical diagnosis was noted. Histological studies were done by 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 using SPSS 11 software.

Results: Out of 90 cases , 88.7% were benign and 12.3% malignant lesions. 69.3% of benign and 90.9% of malignant lesions had difficulty in micturition. NH, HPIN and PCa were common in age group of 61-70 years, where as LPIN was more common between 71-80 years. 74.4% of NH, 75% of LPIN, 71.4% of HPIN and 72.7 % of PCa had high inflammation (Grade

2 & 3). 62.8% of NH, 79.3% of LPIN, 57.1% of HPIN and 63.6% of PCa show a lower inflammatory aggressiveness (Grade 0 & 1). 71.1 % of cases show a papillary hyperplasia followed by BCH in 14.4%. 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/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. The association between Sr PSA levels and inflammatory aggressiveness was found to be 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. Out of the 11 PCa, the Gleason's score of 9 was seen in 5 cases (45.5%), Gleason score of 7 was seen in 3cases (27.3%).

Conclusion: NH comprised 48% of the total number of cases, followed by LPIN (32.3%) and HPIN (7.7%). The elderly age group is most commonly afflicted with prostatic diseases. A high grade of inflammation was seen in three-fourths of the cases and it bears as significant association with increase in prostatic size. Inflammatory aggressiveness is significantly associated with increase in Sr PSA levels and also prostatic size. 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.

KEY WORDS: Nodular hyperplasia, Prostate cancer, Inflammation, PSA, Proliferative index

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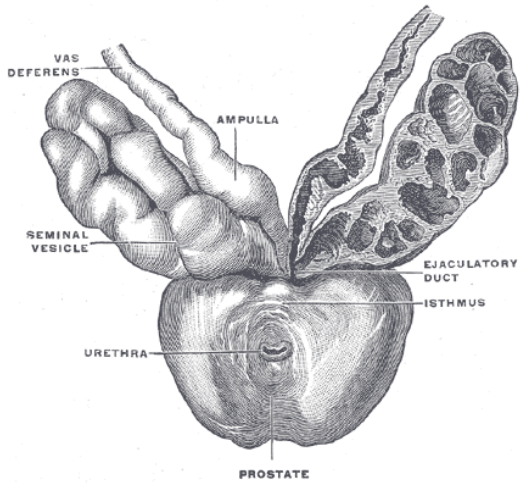

INTRODUCTION

The three main pathologic processes that affect the prostatic gland are inflammation, nodular enlargement and tumors. The benign nodular enlargement is the most common, followed by Prostatic carcinoma (PCa). [1]

Recent reports have hypothesized histological inflammation to be the third component in the progression of nodular hyperplasia (NH).[2] Therefore, inflammation is a therapeutic target for NH.[3] The aggressiveness of glandular inflammatory infiltration in NH also elevates prostate specific antigen (PSA) levels.

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.

Atypical adenomatous hyperplasia (AAH; also termed adenosis), is a localized proliferative lesion consisting of small amounts of atypical epithelial cells arranged in

irregular glandular patterns. It is a putative precursor of transition zone adenocarcinoma and even mimics it in needle settings.[5]

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.[6]

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%).[7,8]

There is a paucity of literature regarding the prevalence of neoplastic and non-neoplastic lesions of prostate in India. The current study attempts to document the occurrence of prostatitis, hyperplasia, prostatic intraepithelial neoplasia (PIN), PCa in patients operated at the study institution. Correct diagnosis of prostatic lesions goes a long way in the treatment and prognosis of the patient.

1) To study the morphological spectrum of neoplastic and non-neoplastic lesions of prostate.

2) To evaluate the proliferative index in neoplastic and non-neoplastic lesions by immunohistochemistry using Ki-67 antibody.

3) To correlate histopathological findings with serum PSA levels **.**

REVIEW OF LITERATURE

ANATOMY

Prostate is a pear shaped organ with the base located closer to the bladder neck and the apex towards the penile urethra. The portion of the urethra that traverses through the prostate is known as prostatic urethra and exits the prostate at its apex, where it is continuous with membranous urethra. Grossly, McNeal's model is often simplified such that the central inner periurethral aspect of the prostate is termed the "transition zone," and the outer peripheral aspect is referred to as the "peripheral zone" and includes the "central zone," which is located toward the base of the prostate has 3 zones.[9] (Figure.1)

1. Central zone – Urethra and ejaculatory ducts course through this zone
2. Transition zone – site of benign prostatic hyperplasia
3. Peripheral zone – where most carcinoma arises [10]

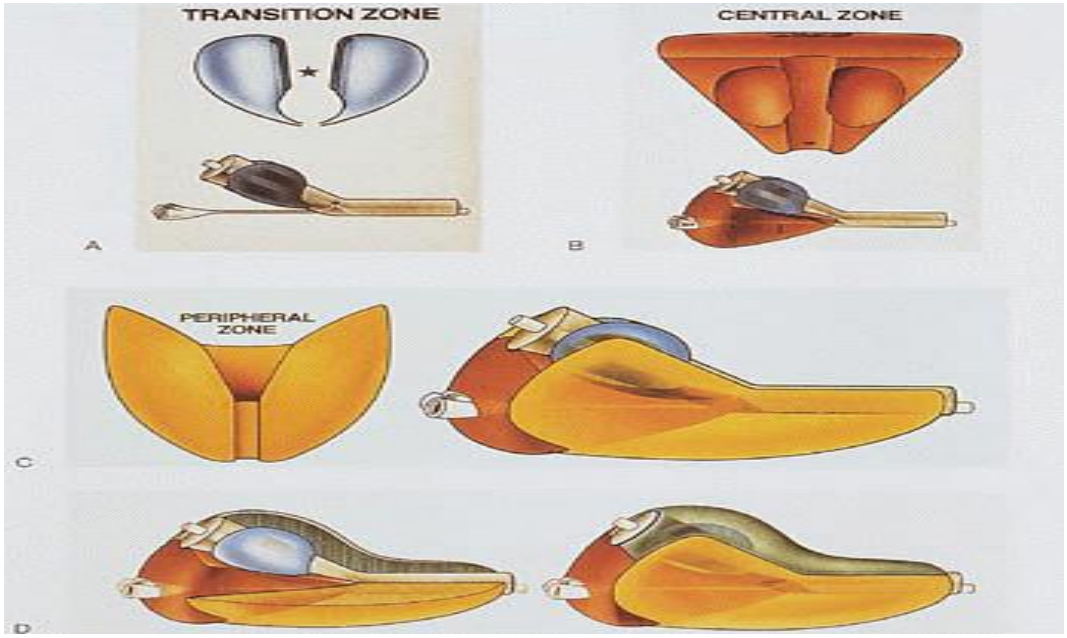

Figure-1: McNeal's model of zonal anatomy of the prostate

The prostate gland is a functional conduit that allows urine to pass from the urinary bladder to the urethra and adds nutritional secretions to the sperm to form semen during ejaculation. The prostate gland secretions contain hydrolytic enzymes (like PSA, prostate-specific acid phosphatase [PSAP]) functioning to increase sperm motility.

Age-Related Changes

Significant prostatic growth occurs after puberty. It achieves an average weight of 20 ±6 g at age 25 years to 30 years. In the next 2 decades prostatic growth is minimal and around 50 years of age, the prostate undergoes progressive atrophy.

HISTOLOGY

Microscopically, the prostate is composed of glandular epithelium and fibromuscular stroma. In the central zone, the glandular epithelial cells are dense with an epithelial stromal ratio of 2:1 compared to 1:1 at the transitional and peripheral zone. The duct and glandular system is arranged in a complex architectural pattern. These glands are lined by three distinct epithelial cell populations:

1) The luminal secretory cells stain positively with PSA and prostatic acid phosphatase. Strong α-methyl acylcoA racemase (AMACR) positivity indicates malignancy.
2) Basal cells which are cigar shaped are peripherally located in the gland between the secretory cells and basement membrane. Presence of basal cells confirms the diagnosis of benign condition and absence of basal cell marker does not imply

malignancy. Basal cells are thought to represent the stem cell compartment within the prostate.[11,12]

3) Neuroendocrine cells are irregularly distributed throughout the ducts and acini. Positive staining with neuron-specific enolase (NSE), chromogranin, and synaptophysin is observed. They regulate adjacent cells by paracrine action.

INFLAMMATORY DISORDERS

Clinical prostatitis is classified into three broad categories including acute, chronic, and granulomatous prostatitis.

Bacterial Prostatitis

Acute and chronic prostatitis comprises a significant portion of urologic practice.

Acute prostatitis characteristically presents with intense discomfort on voiding, associated with fevers, chills, and perineal pain. Clinically apparent acute prostatitis, is rarely biopsied, and commonly diagnosed by examining smears and cultures of prostatic fluid. Most studies have reported gram-negative bacteria, especially Escherichia coli, as the most common etiologic agent. Acute bacterial prostatitis is characterized by sheets of neutrophils within and around acini, intraductal desquamated cellular debris, and stromal edema and hyperemia.[13] It is difficult to distinguish histologically chronic infectious prostatitis from nonspecific chronic inflammation seen in hyperplasia

Most patients with chronic prostatitis are symptomatic and report suprapubic, perineal, or low back discomfort of gradual onset. Schaeffer and associates concluded that ten or

more white blood cells per high-power field in prostatic fluid supported the diagnosis of prostatitis. The pathogenesis of chronic prostatitis involves reflux of infected urine into prostatic ducts, with associated factors such as infected prostatic calculi and local prostatic duct obstruction contributing to the perpetuation of the infection.[14]

Granulomatous prostatitis

The term granulomatous prostatitis, sometimes preceded by qualifiers such as *nonspecific* or *idiopathic*. The clinical triad of high fever, symptoms of prostatitis, and a hard prostate on palpation is present in one-fifth of cases and should suggest the diagnosis. A preoperative diagnosis of carcinoma is made in about 30% of cases because of the firmness of the lesion, caused by the dense fibrosis.[15]

Grossly, the gland is firm to stony hard. The cut surface shows obliteration of the architecture, with formation of yellow granular nodules. Microscopically, large nodular aggregates of histiocytes, epithelioid cells, lymphocytes, and plasma cells are seen. Characteristically, these granuloma-like formations are centered in the lobules. A tubercle-like reaction with multinucleated giant cells, as well as collections of neutrophils, eosinophils, and detritus within the ducts, also may be seen. Microorganisms and caseation necrosis are absent. The microscopic changes can simulate carcinoma in needle biopsy specimens.

Prostatitis with eosinophils

1) **(Nonspecific) granulomatous prostatitis** : Eosinophils would be diffusely admixed with the other inflammatory components.[16]

2) **Eosinophilic prostatitis** is characterized by small stellate necrobiotic nodules surrounded by palisading epithelioid histiocytes and eosinophils, resembling rheumatoid nodules. Vasculitis may be found. There is a history of allergy and asthma and exhibits peripheral eosinophilia. Elevation of Sr PSA levels may occur in this disorder.[17]

3) **Iatrogenic granulomas**: The granulomas may represent a reaction to collagen altered as a result of the surgery or to metal deposition from the instruments themselves. Some of these granulomas are elongated and tortuous, whereas others are wedge shaped, with their base facing the cauterized tissue.

4) A **parasitic infestation** resulting from metazoa.

Other inflammations

Tuberculous Prostatitis

The incidence of prostatic involvement in systemic tuberculosis ranges from 3% to 12%, with more than 90% of these cases also showing lung involvement. More commonly, seen following Bacillus Calmette-Guérin (BCG) immunotherapy for superficial transitional cell cancer of the bladder. The granulomas may be small to large and noncaseating. The large ones can result in an abnormal rectal examination or increased Sr PSA level. Most patients remained asymptomatic and require no specific therapy.[18]

Miscellaneous Infections

Other rare infections involving the prostate, some of which are more commonly seen in developing countries, include: brucellosis; schistosomiasis; amebic prostatitis; syphilis;

actinomycosis; infection by atypical mycobacteria; echinococcosis; cytomegalovirus infection; and herpes zoster infection.[19]

Prostatic Infarct

Abeshouse in 1933 first described prostatic infarcts. In 1951, Mostofi and Morse reported 50 cases confirmed the potential danger of misinterpreting these changes as neoplastic. Moore (1943) reported infarcts in 25% and Baird (1951) reported infarcts in 18.7% of cases of prostatic hyperplasia. Trauma from previous catheterization or extrinsic pressure on regional vascular tributaries by enlarging hyperplastic nodules may result in infarcts. It has also been attributed to cholesterol emboli in prostatic arteries and aortic aneurysm. Histologically, prostatic infarcts vary in size and age. Recent infarction of the ductal and acinar epithelium and surrounding stroma is associated with interstitial hemorrhage and variable numbers of neutrophils at the margin. Stewart et al and others reported the occurrence of elevated serum PAP in a patient with prostatism and recent infarction. The serum PAP level declined following TUR of the area of infarction.[20,21]

TUMOR LIKE CONDITIONS

The microscopic appearance of prostatic malignancy can be simulated by a bewildering number of benign conditions and some normal structures in an unexpected place.[22]

Lobular atrophy is an age-related phenomenon that occurs exclusively in the peripheral zone of the prostate. A Working Group has proposed the following subtypes: (1) *simple atrophy*; (2) *simple atrophy with cyst formation*; (3) *postatrophic hyperplasia*; and (4) *partial atrophy.*[23] Postatrophic hyperplasia may simulate carcinoma because of its

complex arborization and surrounding fibrosis; however, the cytoplasm is scanty, and the lobular architecture is retained. Gland size and shape are typically variable, including round, oval, elongated, slitlike, and stellate forms. The nuclei are regular and devoid of hyperchromasia, but the nucleoli may be prominent. Spermatozoa may be found within the dilated lumina of the atrophic glands.[24] The stroma may show elastosis in addition to fibrosis. Partial atrophy is the most common benign mimicker of PCa has crowded glands, irregular nuclei, and visible but not prominent nucleoli; keys to the diagnosis include scanty cytoplasm, distinct wrinkled nuclei, pale cytoplasm, and association with fully developed atrophic changes of the simple or postatrophic hyperplasia type.[25]

Basal cell hyperplasia (BCH) is seen in the transition zone aswell as peripheral portion of the gland.[26] It appears as small, generally solid nests of benign-appearing epithelial cells with a somewhat clear cytoplasm. They are always in association with NH. In *florid* BCH, the proliferation is unduly complex. Nuclear enlargement, hyperchromasia, and nucleolar prominence are seen in the variant designated as *atypical BCH*. Other variations include the presence of intracytoplasmic globules, psammomatous calcification, squamous changes, and a pseudocribriform pattern of growth.[27] BCH may be the progenitor of the so-called 'adenoid basal cell tumor'. The proliferating basal cells are immunoreactive for high molecular weight keratin (34ßE12) and p63 but not for actin. The lesions are consistently negative for racemase.[28]

Transitional cell hyperplasia shows stratified epithelium composed of oval to spindle cells perpendicularly oriented to the lumina, and having scanty pale eosinophilic to clear

cytoplasm. The nuclei are elongated, vesicular, often with longitudinal grooves and inconspicuous nucleoli.[29]

Cribriform hyperplasia: The cytoplasm of the hyperplastic glandular cells often has a clear appearance, hence designated as *clear cell* cribriform hyperplasia. Differentiated from carcinoma by the presence of basal cells, which are highlighted by the 34ßE12 keratin stain. Nuclei are small, nucleoli are inconspicuous, and mitotic figures are absent.[30]

Sclerosing adenosis has an appearance similar to the homonymous lesion in the breast. It is a well-circumscribed nodule composed of variably sized and shaped glands and small clusters of epithelial cells embedded in a cellular, often myxoid stroma. The clusters contain both a continuous basement membrane and a layer of basal cells. The latter are immunoreactive for keratin, S-100 protein, and smooth muscle actin, suggesting myoepithelial differentiation.[31] There can be significant cytologic atypia (*atypical sclerosing adenosis*) mimicking carcinoma.[32]

Radiation changes are characterized by cytologic atypia associated with retention of the lobular architecture, squamous metaplasia, stromal fibrosis, atypical fibroblasts, and vascular alterations. These changes can be very long-lasting (up to 72 months in one series).[33]

Postoperative spindle cell nodules resembling sarcomas can develop as a result of an exuberant stromal reaction after a TUR procedure. They present as friable reddish nodules in the prostatic bed and may bleed postoperatively. The proliferating cells, which

are myofibroblastic, show immunohistochemically a strong and unexpected reactivity for keratin.[34]

Inflammatory myofibroblastic tumor: Microscopically there is a proliferation of spindle cells of myoid (myofibroblastic) appearance in a well-vascularized and myxoid background. It is thought to be a reactive pseudoneoplastic condition (as its original name *inflammatory pseudotumor* implies).[35]

NODULAR HYPERPLASIA (Benign Prostatic Hyperplasia)

Incidence and Epidemiology

Three factors—geography, race, and age—appear to be related to the incidence of clinical prostatic hyperplasia. In recent years, the influence of family history on the risk of development of this disorder has been recognized.[36,37]

Age

The peak age of patients with clinical prostatism is the seventh decade. It shows progressive increase in the frequency with age. Most reports indicate 75% of men aged 80 years or older have prostatic hyperplasia. The studies of Berry et al show men younger than 30 years are also affected.[38]

Familial NH

Sanda et al suggested that familial NH is caused by a gene with Mendelian-dominant transmission and they present clinically at an earlier age than in sporadic cases.[39]

Pathogenesis

Although the pathogenesis is not yet completely understood, the role of chronic inflammation is emerging as an important factor in NH development and progression.[40] NH is frequently associated with inflammatory infiltrates mainly composed of T and B lymphoid cells and macrophages. The Medical Therapy of Prostate Symptoms (MTOPS) trial showed that about 40% of baseline biopsy specimens had chronic inflammatory infiltrates—in particular, in men with higher PSA values and larger prostate volumes.[2] Furthermore, patients with inflammation were at a higher risk of NH progression and acute urinary retention when compared with patients without inflammatory infiltrates at baseline. The Reduction by Dutasteride of PCa Events (REDUCE) trial also confirmed it.[41] Inflammation is a possible target for NH and PCa prevention; different anti-inflammatory agents have been tested in vitro and in vivo for the management of both conditions.[42,43]

Earlier, prostatic enlargement had been variously interpreted to reflect a neoplastic process (Virchow, 1862–1863), compensatory hypertrophy (Guyon, 1888), a response to inflammation (Ciechanowski, 1901), or arteriosclerosis (Loeschke, 1920), as outlined in the historical reviews by Walker et al.

Jores (1894), LeDuc and Moore et al , reported hyperplasia of the periurethral glands to be the primary underlying event. Pure stromal hyperplasia with nodule production was first reported by Resichauer in 1925. Deming and associates, and Newmann, and Moore confirmed this observation. Investigators regarded the glandular component of prostatic

nodules as an event secondary to a stromal stimulus to epithelial proliferation within adjacent ducts, which then infiltrate the hyperplastic nidus. Evidence of prostatic stromal–epithelial interaction (first suggested by Deming and Newmann in 1939) is supported by the in vitro experiments of Cunha and associates, who demonstrated an inducing effect of urogenital mesenchyme on epithelial gland formation. The role of testosterone in the hormonal regulation of prostatic growth is well documented. However, the role of testosterone in the pathogenesis of prostatic hyperplasia is less clearly understood. Castration before puberty apparently prevents it. In addition, patients with inherited deficiency of 5α-reductase do not develop prostatic nodular hyperplasia. The efficacy of castration in treating established prostatic hyperplasia has produced inconclusive results. Noteworthy is the patient reported by Marinello et al—a 69-year-old phenotypical male with an XX karyotype, and essentially no circulating testosterone, who nonetheless had "severe prostatic hyperplasia." Exogenous testosterone has no observable effect on the histology of hyperplastic prostatic nodules or in areas of the prostate evidencing senile atrophy. Advancing age is associated with a reduction of circulating testosterone in both normal controls and men with prostatic hyperplasia. However, no reduction in serum DHT level is noted. Siiteri and Wilson have reported increased levels of DHT in specimens of prostatic hyperplasia compared with normal tissue from the same prostate specimen. Isaacs et al has reported elevated levels of activity of the enzyme-converting testosterone to DHT, offering partial explanation for the observation of Siiteri and Wilson.

Serum levels of estrogen are reported to increase with advancing age in men. Exogenous estrogens are reported to produce squamous metaplasia of the urethra and distal prostatic

ducts but no significant histologic change in nodules of prostatic hyperplasia. The role of estrogens in the production of prostatic hyperplasia is not understood. These observations suggest that testosterone and its more active metabolite, DHT, may have a role in the origin of human prostatic hyperplasia.[21]

Clinical Features

The clinical manifestations of NH reflect a spectrum of severity and duration of urinary bladder outlet obstruction. Most patients are usually asymptomatic. In symptomatic patients, the initial manifestation is reflected in diminished urinary stream. Progressive obstruction leads to enlargement and diminished muscular strength of the urinary bladder wall. If this progresses untreated, bilateral hydronephrosis and renal failure are the result, a complication rarely observed currently except in developing countries. The enlarging gland elevates the Sr PSA. The PSA elevation resulting from inflammation is transient and amenable to appropriate antibiotic therapy.[44]

Pathologic Features

The nodular expansion of the transition zone is evident in whole-mount prostatectomy specimens. Medially, the expanding nodules distort and compress the urethral lumen. Laterally and posteriorly, the nodules eventually compress the non-hyperplastic prostate tissue into an attenuated rim of tissue beneath the prostatic capsule. The nodules may expand distally toward the apex again with compression of the peripheral zone prostate glands in this region. Uncommonly, NH may be identified in the peripheral zone.

Grossly, appears as well-defined clustered nodules typically with variable solid and cystic composition. Focal hemorrhage, calcification, and macrocystic change may be present.

Microscopically, NH is the result of proliferation of epithelial cells in acini, smooth muscle cells, and fibroblasts in variable proportions. On this basis, Franks has described five types of nodules: stromal (fibrous); fibromuscular; muscular; fibroadenomatous; and the most common type, fibromyoadenomatous.

The epithelium lining the ducts and acini within the fibromyoadenomatous nodules generally comprises tall columnar cells over a basal cell layer. Characteristic of the epithelium and stroma of the nodules is the absence of cytologic atypia. This epithelium lines the acini of varying sizes, some of microcystic proportions. Intraglandular papillary hyperplasia is characteristic. The epithelium of the fibroadenomatous nodules comprises low cuboidal cells with frequent foci of urothelial or squamous cell metaplasia of the intranodular ducts. The ultrastructural features of the acinar epithelium of hyperplastic nodules and normal prostate are not significantly different.

The stroma of each type of nodule differs in composition, as suggested in their descriptive names. Common to all types of nodules is the absence of elastic tissue in the stroma. Franks describes wide stromal septa separating lobules of large hyperplastic nodules in contrast to the more common interacinar stromal septa within the lobules. Some nodules are composed exclusively of stromal elements.[21]

Associated Lesions Accompanying NH

Associated features of hyperplastic nodules include: (1) cystic dilatation of ducts; (2) chronic inflammatory cell infiltration comprising lymphocytes, plasma cells, and histiocytes within the stroma of the nodule; (3) corpora amylacea within glandular acini; and (4) intranodular infarcts of varying size and vintage, commonly showing squamous and urothelial metaplasia at the interface of the infarct and the viable nodular stroma.

Stromal Nodule

The stromal nodule represents the tissue component—exclusively stromal, variously composed of fibroblastic, fibromuscular, muscular, or immature mesenchymal cells in order of decreasing frequency (62%–4%). This histologic variety of NH is most commonly found as a well-circumscribed nodule in the periurethral tissue proximal to the verumontanum. Microscopically, the nodule comprises spindle cells, fibroblasts, and/or smooth muscle cells in a hyalinized or myxoid stroma. Scattered thick hyalinized blood vessels are common. The utilization of a panel of immunostains including vimentin, desmin, smooth muscle actin, CD117, CD34, and myosin allows characterizing the spindle cell population present.

Atypical Adenomatous Hyperplasia (Adenosis, Microacinar Hyperplasia)

Atypical adenomatous hyperplasia (AAH), was originally described by McNeal in the 1960s. AAH was defined as a “localized proliferation of small glands within the prostate that may be mistaken for carcinoma”. The acini tend to be closely packed, preponderantly small, and lined by uniform cuboidal or columnar cells with clear

cytoplasm. The nuclei are not enlarged and nucleoli are generally small. The periphery of shows an expansile edge with only minimal foci of stromal invasion present. Basal cells are present and basal cell–specific immunostains disclose a discontinuous basal cell population in the acini of AAH. Corpora amylacea is common, and crystalloids are reported in 40% of cases.[21,45]

It is mostly seen within the transition zone and is frequently multifocal. The frequency of identification of AAH is highest in prostatectomy specimens (23%), intermediate in TURP specimens, and lowest in needle biopsies (1%) that sample the peripheral zone. In all specimens AAH is an incidental microscopic finding. The results of cell kinetic studies are mixed, two studies showing lower proliferative rates in AAH than in PCa, and one study reporting a similar labeling index with Ki67 and MIB-1.[46]

Multilocular Cystadenoma of the Prostate

This rare benign prostatic neoplasm presenting with bladder outlet obstruction, a pelvic mass detected on physical examination and confirmed by ultrasonography or computed tomographic (CT) scan. The mass is a multilocular cystic lesion, most commonly extending superiorly from the base of the prostate. Microscopically, it has benign cuboidal-columnar lining cells, and an intervening fibromuscular stroma. The epithelial cells are PSA and PSAP-positive with immunostains.[47]

WHO histological classification of tumors of the prostate[48]

Epithelial tumors

Glandular neoplasms

Adenocarcinoma (acinar)

Atrophic

Pseudohyperplastic

Foamy

Colloid

Signet ring

Oncocytic

Lymphoepithelioma-like

Carcinoma with spindle cell differentiation

(carcinosarcoma, sarcomatoid carcinoma)

Prostatic intraepithelial neoplasia (PIN)

Prostatic intraepithelial neoplasia, grade III (PIN III)

Ductal adenocarcinoma

Cribriform

Papillary

Solid

Urothelial tumors

Urothelial carcinoma

Squamous tumors

Adenosquamous carcinoma

Squamous cell carcinoma

Basal cell tumors

Basal cell adenoma

Basal cell carcinoma

Neuroendocrine tumors

Endocrine differentiation within adenocarcinoma

Carcinoid tumor

Small cell carcinoma

Paraganglioma

Neuroblastoma

Prostatic stromal tumors

Stromal tumor of uncertain malignant potential

Stromal sarcoma

Mesenchymal tumors

Leiomyosarcoma

Rhabdomyosarcoma

Chondrosarcoma

Angiosarcoma

Malignant fibrous histiocytoma

Malignant peripheral nerve sheath tumor

Haemangioma

Chondroma

Leiomyoma

Granular cell tumor

Haemangiopericytoma

Solitary fibrous tumor

Hematolymphoid tumors

Lymphoma

Leukaemia

Miscellaneous tumors

Cystadenoma

Nephroblastoma (Wilms tumor)

Rhabdoid tumor

Germ cell tumors

Yolk sac tumor

Seminoma

Embryonal carcinoma & teratoma

Choriocarcinoma

Clear cell adenocarcinoma

Melanoma

Metastatic tumors

PROSTATIC INTRAEPITHELIAL NEOPLASIA (PIN)

Historical Background

Andrews initially reported prostatic intraductal foci with cytologically atypical hyperplasia in 1949. Subsequent studies of "atypical hyperplasia" in the prostate or PIN suggest that these foci may be premalignant, and histogenetically function as the source of invasive PCa. Three grades of cytologic atypia with descriptive criteria were introduced—low, intermediate, and high grade (PIN 1, 2, and 3). Later it was graded as low grade and high grade, compressing the former grades 2 and 3 into HPIN. The histogenetic link is multifaceted, and includes genetic, clinical, morphologic, and immunohistochemical observations.[21,49]

Epidemiology

The frequency of HPIN in autopsy study was observed in the third decade, progressively increasing with age. The frequency exceeds 60% in men aged 60 years and older. The lesion was consistently and significantly more frequent in African Americans in each of the corresponding decades. Whole-mount studies from cystoprostatectomies report a frequency of 49% to 85%.[21]

The frequency of PIN in TURP specimens is reported between 2% and 3%, reflecting the predilection of this lesion for the peripheral zone. In addition, the frequency of HPIN identified in needle biopsies ranges from 1% to 16% with a mean of approximately 7%.[50]

Clinical Features

PIN is a non–mass formative lesion, and therefore is not identified by diagnostic clinical symptoms or digital rectal examination (DRE). Transrectal ultrasound (TRUS) hypoechoic foci are characteristic, but not diagnostic of PIN.[51] Sr PSA is not elevated by PIN, and any elevation is attributable to the accompanying lesions such as NH or carcinoma.[52]

Histologic Features

In low grade PIN, there is proliferation and "piling up" of secretory cells of the lining epithelium with irregular spacing. Some nuclei have small, usually inconspicuous nucleoli while a few may contain more prominent nucleoli.

High grade PIN is characterized by a more uniform morphologic alteration. Cytologically, the acini and ducts are lined by malignant cells with a variety of architectural complexity and patterns. The individual cells are almost uniformly enlarged with increased nuclear/cytoplasmic ratio, therefore showing less variation in nuclear size than that seen in LPIN. Many cells of HPIN contain prominent nucleoli and most show coarse clumping of the chromatin that is often present along the nuclear membrane. HPIN can be readily appreciated at low power microscopic examination by virtue of the darker "blue" staining of the lining that reflects the expanded nuclear chromatin area.

Basal cells are present in normal quantities in acini with LPIN, but are discontinuous and reduced in numbers in HPIN. This is demonstrated best with the basal cell–specific immunostain 34βE12.[53]

Common to both LPIN and HPIN is a limited spectrum of histologic patterns. These patterns, in order of decreasing frequency, include tufted, micropapillary, flat, cribriform,

solid, and the least frequent, inverted pattern. Sometimes PIN arises from atrophic acini and may show focal budding or microinvasion of prostatic stroma from PIN lesions.

The cribriform pattern of HPIN shows small, less hyperchromatic nuclei in the center of the cribriform bridging with smaller, or no nucleoli compared to the nuclei in the PIN population closer to the peripheral basement membrane.[21]

The second consideration is that differentiating cribriform PIN from intraductal spread of acinar or ductal adenocarcinoma and invasive Gleason pattern 3 is difficult in needle biopsies. In summary, if basal cells are absent, the most probable diagnosis is invasive carcinoma with a cribriform Gleason pattern 3. If basal cells are identified with appropriate immunostaining, and multiple duct segments are involved by a proliferation with a high nuclear grade, the focus is interpreted as intraductal spread of adenocarcinoma. HPIN with a cribriform pattern would also be expected to have basal cells, however few, and involve one or only a few duct segments, and possibly be accompanied by other PIN patterns.[54] Shepherd et al reported 36% of malignant lesions on the side opposite the original PIN site.[55]

Some rare cytologic variants have been reported including small cell neuroendocrine, mucinous, foamy cell, clear cell, pigmented cell, and signet-ring cell.

Clinical Significance and Follow-up Studies of Prostatic Intraepithelial Neoplasia

In contrast to LPIN, there is an increased risk of identifying carcinoma on rebiopsy following the diagnosis of HPIN.

ACINAR ADENOCARCINOMA

An invasive malignant epithelial tumor consisting of secretory cells.

Epidemiology

PCa is now the sixth most common cancer in the world (in terms of number of new cases), and third in importance in men. The estimated number of cases was 513,000 in the year 2000. This represents 9.7% of cancers in men.[48]

Age distribution

The risk of PCa rises very with age. Incidence of clinical disease is low until after age 50. Worldwide, about three-quarters of all cases occur in men aged 65 or more

Etiology

The marked differences in risk by ethnicity suggest that genetic factors are responsible. The change in rates with time, and on migration, implies that differences in environment or lifestyle are also important. There is a strong positive association with intake of animal products, especially red meat and fats.[56]

There is a 5-11 fold increased risk among men with two or more affected first-degree relatives. It is clear that male sex hormones play an important role in the development and growth of prostate cancers. Testosterone diffuses into the gland, where it is converted by the enzyme steroid 5-alpha reductase type II (SRD5A2) to the more metabolically

active form dihydrotestosterone (DHT). DHT and testosterone bind to the androgen receptor (AR), and the receptor/ligand complex translocates to the nucleus for DNA binding and transactivation of genes which have androgen-responsive elements, including those controlling cell division. Role of polymorphisms of SRD5A2 and AR genes in regulating this process and how inter-ethnic variations in such polymorphisms might explain the higher risk of PCa in men of African descent. Studies suggest that men with a lower number of AR CAG repeat lengths are at higher risk of PCa.

Genetic changes show differences between the sporadic and hereditary PCas, but there is significant overlap and differences within cases of both types such that the two cannot be distinguished on the basis of genetic analysis alone. In inherited prostate cancer, chromosomal gains at 7q, 8q, and 19q are common and chromosomal losses involving 5q, 7q, 8p, 10q, and 16q are the most common. Petrovics et al (2005) described frequent overexpression (~70%) of the ETS related gene (ERG), a proto-oncogene in an analysis of 110 prostate cancers. This discovery was followed by the identification of recurrent gene fusions of the 5' untranslated region of TMPRSS2 to ERG or ETV1 in 23 of 29 prostate cancers. Although subsequent studies have described rare TMPRSS2-ETV4 fusions and other ETV1 fusion partners, the TMPRSS2-ERG fusions are predominant. In numerous recent studies, 50–70% frequency of this fusion has been confirmed. The presence of this fusion could be correlated with histological features of PCa, and to date is one of the most common genetic rearrangements in human cancer. In multifocal disease, the fusion status and type of fusion can vary between tumors. Recently, the TMPRSS2-ERG fusion associated with duplication of the fusion and interstitial deletion of sequences 5' to ERG identified a subset of prostate cancers with poor prognosis.[57,58]

Histogenesis

Clinical Features

The patients have been categorized into incidental cancers, clinically symptomatic cancers, and occult cancers, respectively.

Detection of Incidental PCa in Asymptomatic Patients

Multiple studies reported the frequency of incidental PCa in simple prostatectomy and TURP specimens obtained for clinically benign disorders (NH) to range from 3% to 24% with an average of 9.2% in 16 studies. The "eight-block protocol" has been recommended to identify virtually all examples of T1b and importantly, the smaller T1a cancers.[59]

Local and Systemic Symptoms of PCa

Sr PSA helps in early diagnosis. Hence, reducing the frequency of patients who present with urinary bladder outlet obstruction, rectal bleeding, and pelvic pain. Systemic manifestations of PCa reported in rare cases include hypercalcemia, leukemoid reaction, thromboembolism, and Eaton-Lambert syndrome.

Clinical Presentation with Distant Metastases

The initial presentations in PCa are rarely related to symptoms of distant metastases and were termed occult carcinomas. Studies have reported a decrease in frequency of clinical presentation from 4.2% to 1.6% during the years 1990 to 2003.[60] Examples of patients initially presenting with metastases to supraclavicular lymph nodes, lung, brain, intraorbital, skin, abdominal and retroperitoneal sites, pleura, and esophagus are recorded

in literature. In this clinical context, the application of immunostains for PSA, PSAP, and AMACR, and a high index of suspicion, will contribute to a definitive diagnosis.[21]

Diagnostic Procedures

Digital Rectal Examination

The utility of DRE remains as an integral component of the urologist's diagnostic armamentarium, currently combined with Sr PSA and radiologic procedures, especially ultrasound. Approximately 50% of palpable nodules represent carcinoma and the remainder attributable to peripheral nodular hyperplasia, granulomatous prostatitis, and prostatic infarcts. The limits of DRE sensitivity are associated with tumor size, and the smallest examples are not identified by palpation. Stamey et al report that the smallest PCa detected by DRE measures 0.3 cm to 1.3 cm.[61]

IMAGING

Transrectal ultrasound imaging (TRUS) with high frequency transducers enables the operator to evaluate gland volume, measure focal lesions and help in image biopsies. Due to lack of specificity, it has of limited value in detection of PCa and its extraglandular spread. Newer color flow techniques such as power Doppler US may be helpful. Intravenous contrast agents, harmonic imaging and 3-D US helps to delineate subtle PCa.[62]

Computed tomography (CT) and magnetic resonance imaging (MRI) have not proven valuable because of low sensitivities to detect and stage PCa. MRI is reserved for staging of patients with biopsy proven PCa.[63]

Plain film radiography and nuclear medicine

Skeletal radiography (bone survey) is reserved to confirm skeletal abnormalities in patients with positive bone scintigraphy. Bone scintigraphy (radionuclide bone scans) is the most sensitive method for detecting bone metastases.

Monoclonal antibody radioimmunoscintigraphy

(Prostate specific membrane antigen-PMSA) chelated to Indium111(Prostacint®, Cytogen Corporation, Princeton, N.J.) even detects microscopic metastatic deposits in regional and distant sites. Positron emission tomography (PET), which allows in vivo-characterization of tumors, may have implications for the evaluation of patients with PCa in the future.

LABORATORY TEST

Prostate specific antigen (PSA) is produced by the epithelial cells lining the prostatic ducts and acini and is secreted directly into the prostatic ductal system. The PSA gene is located on chromosome 19. Its androgen-regulated transcription results in the synthesis of a 261 amino acid PSA precursor, that is activated by the proteolytic liberation of a small amino-terminal fragment. Different molecular forms of PSA exist in serum. These result from complex formation between free PSA and two major extracellular protease inhibitors that are synthesized in the liver. As PSA is a serine protease, its normal mode of existence in the serum is in a complex with α-1-anti-chymotrypsin (ACT), a 67 kDa single chain glycoprotein, and α-2-macroglobulin (AMG), a 720 kDa glycoprotein. Only

a small percentage of the PSA found in the serum is free. Subfractions of free PSA include: mature single-chain, and multichain, nicked free PSA forms.[64]

Serum total PSA and age specific reference ranges

Sr PSA is determined with immunoassay techniques. Monoclonal antibodies have been designed to detect the free form of PSA (29kDa), the complex of PSA and the total PSA. Total PSA correlates well with advancing age. Based on the 95th percentile values in a regression model, white men under age 50 have PSA values <2.5 ng/ml, under age 60 have PSA values <3.5 ng/ml, under age 70 have PSA values <4.5 ng/ml, and under age 80 PSA levels were <6.5 ng/ml. It has been suggested that these age-related values be used as the upper limit of normal in PSA-related diagnostic strategies. PSA is elevated beyond the arbitrary cutoff point of 4.0 ng/ml in the majority of patients with PCa. It may also be greater than 4.0 ng/ml in some benign conditions, including NH. PCa may also be present in men with Sr PSA values lower than the above quoted cutoff points. This may be specifically true for men considered at higher risk (i.e.family history; men with faster doubling time; and in the United States African American men). Therefore, Sr PSA lacks high sensitivity and specificity for prostate cancer. This problem has been partially overcome by calculating several PSA-related indices and/or evaluating other serum markers. PSA tests are also useful to detect recurrence and response of cancer following therapy. The exact value used to define recurrence varies depending on the treatment modality.

Free form of PSA occurs to a greater proportion in men without cancer and, by contrast, the α-1-chymotrypsin complex PSA comprises a greater proportion of the total PSA in men with malignancy. The median values of total PSA and of the free-to-total PSA ratio are 7.8 ng/ml and 10.5% in PCa patients, 4.3 ng/ml and 20.8% in patients with NH, and 1.4 ng/ml and 23.6% in a control group of men without NH.

Complex PSA value may offer better specificity than total and free-total PSA ratio.

PSA density

This is the ratio of the Sr PSA concentration to the volume of the gland, which can be measured by transrectal ultrasound (total PSA/prostatic volume = PSA density, PSAD). The PSAD values are divided into three categories: normal (values equal or lower than 0.050 ng/ml/cm3), intermediate (from 0.051 to 0.099 ng/ml/cm3) and pathological (equal to or greater than 0.1 ng/ml/cm3). The production of PSA per volume of prostatic tissue is related to the presence of NH and PCa and to the proportion of epithelial cells and the histological grade of the carcinoma. PSA density of the transition zone. NH is the main determinant of Sr PSA levels in patients with NH . Therefore, NH volume rather than total volume is used when trying to interpret elevated levels of Sr PSA. PSA density of the transition zone (PSA TZD) is more accurate in predicting PCa than PSA density for PSA levels of less than 10 ng/ml.

PSA velocity (or PSA slope) refers to the rate of change in total PSA levels over time. Rate of increase over time is greater in men who have carcinoma as compared to others.

This is linked to the fact that the doubling time of PCa is estimated to be 100 times faster than NH. Given the short term variability of Sr PSA values, Sr PSA velocity should be calculated over an 18-month period with at least three measurements. PSA doubling time (PSA DT) is closely related to PSA velocity. Patients with NH have PSA doubling times of 12± 5 and 17 ± 5 years at years 60 and 85, respectively. In patients with prostate cancer, PSA change has both a linear and exponential phase.[65]

Prostatic acid phosphatase (PAP) is produced by the epithelial cells lining the prostatic ducts and acini and is secreted directly into the prostatic ductal system. Serum PAP may be significantly elevated in patients with NH, prostatitis, prostatic infarction or PCa. The sensitivity and specificity of this tumor marker is very low.

Human glandular kallikrein 2 (hK2) and PSA exhibit different proteolytic specificities, but show similar patterns of complex formation with serum protease inhibitors. The serum level of hK2 is relatively high, especially in men with diagnosed PCa and not proportional to total PSA or free PSA concentrations.

Prostate specific membrane antigen (PSMA) is a membrane-bound glycoprotein with high specificity for benign or malignant prostatic epithelial cells. This is a novel prognostic marker that is present in the serum of healthy men, according to studies. An elevated concentration is associated with the presence of prostate cancer. PSMA levels correlate best with advanced stage, or with a hormone refractory state.[66]

Reverse transcriptase-polymerase chain reaction (RT-PCR) is an extremely sensitive assay, capable of detecting one prostate cell diluted in 10^8 non-prostate cells. Because of the high sensitivity of RT-PCR, low-level basal transcriptions of prostate-specific genes from non-prostate cells will also result in a positive RT-PCR signal.[67]

Adenocarcinoma of peripheral ducts and acini

Most PCas arise in the peripheral zone, whether posteriorly, laterally, or anteriorly, with sparing of the periurethral region except for the late stages of the disease. However, a small percentage of tumors do actually arise in the prostatic transition zone. Grossly, the tumor can be identified as a gray or yellowish, poorly delineated and firm area.

Microscopically, PCa exhibit a wide spectrum of appearances, ranging from anaplastic tumors to highly differentiated neoplasms that are distinguished from the non-neoplastic gland only with great difficulty. Four major cytoarchitectural patterns are: medium-sized glands, small glands, diffuse individual cell infiltration, and cribriform. Carcinomas composed of *medium-sized glands* are detected on low-power examination by virtue of the closely spaced arrangement of those glands, irregular outline, smooth inner surface, and scanty intervening stroma. Tumors made up of *small glands* appear as expansive nodules on low power, the individual glands having a regular round configuration and small size. Both of these architectural patterns (but particularly the latter) are accompanied by cytologic abnormalities in the form of nuclear enlargement, irregularity of contour, hyperchromasia, and – most important – prominent nucleoli (‘macronucleoli’, defined as measuring >1 μ in diameter). These nucleoli tend to be marginated and are often multiple. Mitoses are also of significance, but they are rarely found in well-

differentiated tumors composed of either medium-sized or small glands. The pattern of *diffuse cell infiltration* resembles somewhat that of invasive lobular carcinoma of the breast, whereas the *cribriform* pattern represents intraductal carcinoma, as evidenced by the preservation of the epithelial basal layer. The gland-forming types of PCa are usually lined by a single cell layer but occasionally they exhibit a stratified epithelium that may simulate PIN. An additional pattern of growth that has recently been described is that referred to as *glomeruloid*. It is characterized by the presence of intraluminal ball-like clusters of tumor cells and is regarded by many as a pathognomonic sign of malignancy.[48,68]

Squamous metaplasia may also be associated with PCa (especially of the high-grade type). It is often seen with hormonal or radiation therapy, and is associated with a poor prognosis.

The presence of prostatic glands within perineurial spaces is common in these tumors. This finding is a strong indicator of malignancy but is not pathognomonic.

The stroma surrounding the neoplastic glands may show a combination of hypercellularity and deposition of a basophilic ground substance (‘*mucinous fibroplasia*’ or ‘*collagenous micronodules*’). Both intraluminal and stromal calcification may be seen in association with PCa, but the incidence of the latter is much lower than in benign prostates.

Protein crystalloid structures morphologically and immunocytochemically similar to Bence Jones crystals are seen in the glandular lumina and are particularly common in tumors composed of medium-sized glands. Their presence usually indicates malignancy.

In benign cases, it is a significant risk factor for the subsequent development of cancer. Electron probe x-ray microanalytic studies have shown that they are predominantly composed of inorganic sulfur. Exceptionally, these crystalloids are also found in metastatic foci. The intraluminal secretion of malignant glands often has a bluish hue ('wispy blue mucin'), indicative of a mucinous composition.[69]

The variations of PCa include:

1) **Foamy gland carcinoma**. The cytoplasm of the carcinoma cells have finely granular appearance, but on occasionally it is clear or foamy ('xanthomatous') because of the massive accumulation of lipids. Grossly, it is bright yellow and soft in consistency. The voluminous tumor cells are cuboidal to columnar, and the nuclei are small and hyperchromatic. The nucleoli are not particularly conspicuous. Foamy gland carcinomas is often aggressive, even in the presence of deceptively innocuous microscopic features.[70]
2) **PCa with atrophic features**. It is composed of tumor cells with an attenuated cytoplasm, such that the nuclei occupy almost the entire cell height. They have a infiltrative pattern of growth, nuclear enlargement, macronucleoli, and sometimes the presence of adjacent carcinoma of the ordinary type.[69]
3) **Pseudohyperplastic PCa**. It resembles hyperplastic glands at the architectural level, including papillary infoldings, branching, and corpora amylacea. On low power, the tumor has a bland microcystic appearance. There is nuclear enlargement, macronucleoli, mitoses, intraluminal crystalloids, and sometimes the presence of adjacent PIN.[71]

4) **Colloid & signet ring variant:** Some have a signet-ring-cell appearance, yet the vacuoles do not contain intracytoplasmic mucin. These vacuolated cells may be present as singly invasive cells, in single glands, and in sheets of cells. It has lakes of mucin lined by tall columnar epithelium with goblet cells showing varying degrees of nuclear atypia. These tumors have been negative immunohistochemically for PSA and PAP

5) **Mucinous PCa** behave aggressively. Although the tumors are not as hormonally responsive as their nonmucinous counterparts, some respond to androgen withdrawal. Mucinous PCa have a propensity to develop bone metastases and increased Sr PSA levels with advanced disease.[72]

6) **Oncocytic variant :**. Tumor cells have round to ovoid hyperchromatic nuclei, and are strongly positive for PSA. Numerous mitochondria are seen on ultrastructural examination. A high Gleason grade, elevated Sr PSA and metastasis of similar morphology have been reported.[48]

7) **Lymphoepithelioma-like variant:** This undifferentiated carcinoma is characterized by a syncytial pattern of malignant cells associated with a heavy lymphocytic infiltrate.

8) **Sarcomatoid carcinoma of the prostate** is a rare neoplasm composed of both malignant epithelial and malignant spindle-cell and/or mesenchymal elements. The gross appearance often resembles sarcomas. Microscopically, sarcomatoid carcinoma is composed of a glandular component showing variable Gleason score. The sarcomatoid component consists of a nonspecific malignant spindle-cell proliferation. Amongst the specific mesenchymal elements are osteosarcomas,

chondrosarcoma, rhabdomyosarcoma, leiomyosarcoma, liposarcoma, angiosarcoma or multiple types of heterologous differentiation. Sr PSA is within normal limits in most cases. Nodal and distant organ metastases at diagnosis are common. There is less than a 40% five-year survival.[48]

Tumor multicentricity : Multiple tumor foci have been demonstrated in 75–85% of radical prostatectomy specimens studied by step-section or whole-mount techniques.

'Minimal adenocarcinoma' and atypical small acinar proliferation (ASAP)

A foci of small atypical glands that are suspicious but not diagnostic of carcinoma. Grignon has proposed minimal criteria for the unequivocal diagnosis of malignancy. For the cases in which the recommended threshold is not reached, terms such as 'atypical gland suspicious of malignancy' and *ASAP* have been proposed. It is used for certain prostatic biopsies (about 4–6%) that cannot be confidently placed into a benign or malignant category, either with plain morphology or after immunostaining with 34ßE12 keratin and/or racemase. A patient with such a diagnosis warrants a second biopsy.[73,74]

Carcinoma of large ('primary') ducts

The other major (but numerically less significant) type of PCa originates from (or is located within) the large (primary) ducts that are normally found in a periurethral location. Cystoscopic examination often shows a polypoid villous or an infiltrative urethral component. Microscopically, the following types have been recognized:

1) **Large (prostatic) duct adenocarcinoma**. This tumor is characterized by malignant changes in large dilated ducts, with a cribriform and/or papillary architecture lined by columnar pseudostratified malignant epithelium, occasionally with a clear cell (mesonephroid) like. Sometimes the tumor is accompanied by pagetoid spread in the prostatic urethra. Positivity for PSA and PAP is the rule. The tumors tend to have a more advanced stage at presentation and a higher short-term survival rate than peripheral duct–acinar carcinomas. It is distinguished from HPIN, by the presence of cystically dilated glands, a greater predominance of flat architecture, a lesser frequency of macronucleoli, absence of basal cells on high molecular weight keratin immunostain, and higher Ki-67 index.

   Endometrial-type (endometrioid) adenocarcinoma regarded as a variant of large duct PCa. Microscopically, glands and papillae are seen, lined by tall, pseudostratified columnar epithelium.

2) **Primary urothelial (transitional cell) carcinoma** of the prostate. The existence of this tumor type is because the outer portion of the prostatic (periurethral) ducts emptying into the urethra is lined by urothelium. This variant comprises less than 2%. The microscopic appearance of this neoplasm is identical to that of the homonymous bladder tumor.
3) **Mixed adenocarcinoma–urothelial (transitional cell) carcinoma**, exhibiting a combination of types 1 and 2.[75]

Gleason's grading

The most commonly used pathologic grading system for PCa was first described in 1966 by Donald F. Gleason, a pathologist .[146] Gleason's system is based entirely on the architectural pattern of the tumor, without taking cytologic features into account. Additionally, it takes into account two most common architectural patterns. The original five Gleason pattern as follows: (Figure-2)

- Pattern 1. A well-circumscribed, tight cluster of uniform, separate, medium-sized glands with round or oval shape.

- Pattern 2. The tumor acini are present in a circumscribed nodule, with less uniformity of size and shape, and more loosely packed than observed in pattern 1. Additionally, the peripheral leading edge of the tumor focus is more irregular, and may suggest minimal stromal invasion.
- Pattern 3. Tumor acini are generally smaller, with variation of shape and size. Importantly, the tumor acini are discrete and separate, and they infiltrate the stroma accompanying benign prostatic acini. A cribriform pattern may be present, and show a smooth, round configuration.
- Pattern 4. There is fusion of tumor acini, which are poorly defined glands with equally poorly delineated gland lumina. The "hypernephroid" form of PCa, originally described by the Gleason protocol, and resembling renal cell carcinoma, is uncommonly observed and designated pattern 4.
- Pattern 5. The neoplastic proliferation comprises sheets, solid cords, or single cells devoid of gland formation, infiltrating the prostatic stroma. Alternatively,

papillary, cribriform, or solid masses with true comedonecrosis is regarded as Gleason pattern 5.[76,77]

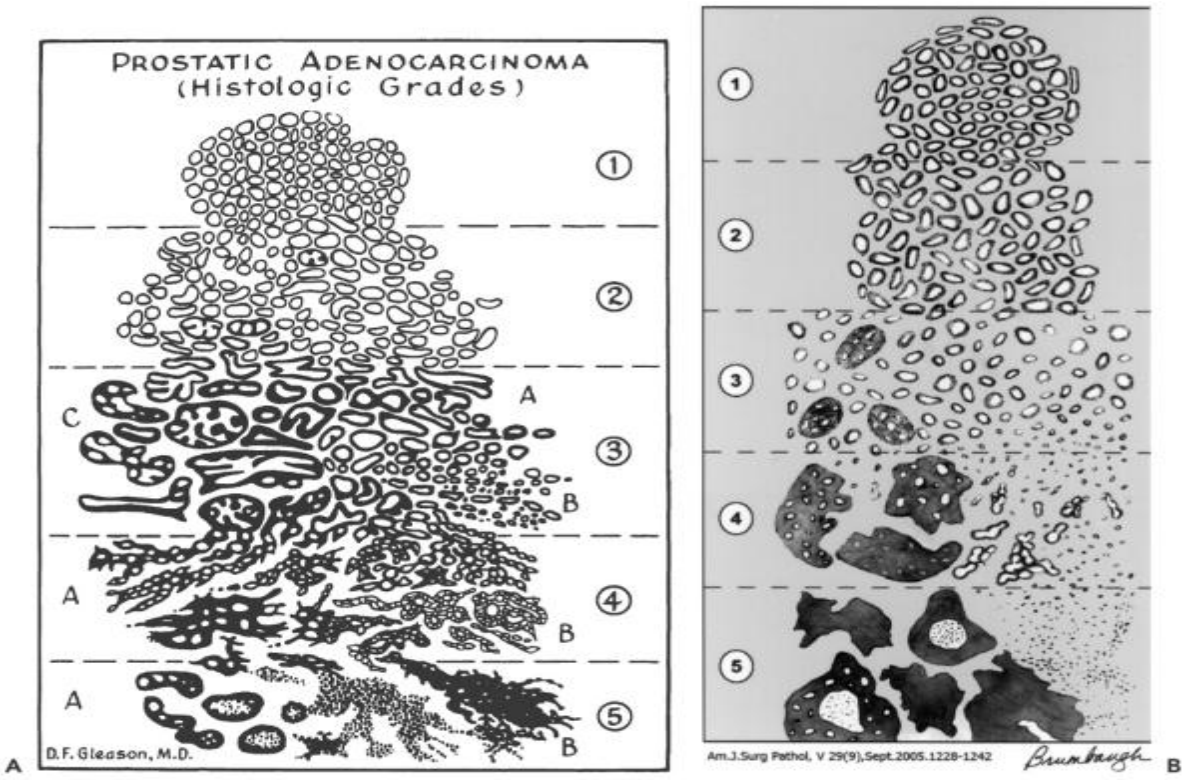

Figure-2: Gleason's grading system

Thus, under this schema the most well-differentiated tumors have a Gleason score of 2 (1 + 1), and the least-differentiated tumors merit a score of 10 (5 + 5). Gleason scores are often combined into groups with similar biologic behavior, with grades 2 through 4 representing well-differentiated cancer, 5 and 6 intermediate-grade tumor, 7 moderate to poorly differentiated cancer, and 8 through 10 high-grade tumor.

Tertiary Gleason pattern

On needle biopsies with patterns 3, 4, and 5, both the primary pattern and the highest grade should be recorded. Consequently, tumors with Gleason score 3 + 4 and

a tertiary pattern 5 would be recorded as Gleason score 3 + 5 = 8. In cases where there

are three patterns consisting of patterns 2, 3, and 4, it was the consensus of the group that one would ignore the pattern 2 and the biopsy would be called Gleason score 3 + 4 = 7 or Gleason score 4 + 3 = 7, depending on whether pattern 3 or pattern 4 was more prevalent.

For a radical prostatectomy specimen one assigns the Gleason score based on the primary and secondary patterns with a comment as to the tertiary pattern.[78]

REPORTING SECONDARY PATTERNS OF LOWER GRADE WHEN PRESENT TO A LIMITED EXTENT

It was the consensus of the group that in the setting of high-grade cancer one should ignore lower-grade patterns if they occupy less than 5% of the area of the tumor. For example, a needle biopsy core that is 100% involved by cancer, with 98% Gleason pattern 4 and 2% Gleason pattern 3, would be diagnosed as Gleason score 4 + 4 = 8.

Immunoprofile

Prostate specific antigen (PSA): A useful IHC marker of prostatic differentiation with both polyclonal and monoclonal antibodies available. PSA is localized to the cytoplasm of non-neoplastic prostatic glandular cells in all prostatic zones. Because of its relatively high specificity for prostatic glandular cells, PSA is a useful tissue marker expressed by most PCas. A minority of higher grade PCas are PSA negative, although some of these tumors have been shown to express PSA mRNA.[79]

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Prostate specific membrane antigen (PSMA) (membrane bound antigen expressed in benign and malignant prostatic acinar cells) and androgen receptor may be immunoreactive in some high grade, PSA immunonegative PCas. Extraprostatic tissues which are variably immunoreactive for PSA, include urethral and periurethral glands (male and female), urothelial glandular metaplasia (cystitis cystitica and glandularis), anal glands (male), urachal remnants and neutrophils.

Prostate specific acid phosphatase (PAP)

The polyclonal antibody is more sensitive, but less specific than the monoclonal antibody. PAP and PSA have similar diagnostic utility; since a small number of PCas are immunoreactive for only one of the two markers.

High molecular weight cytokeratins detected by 34βE12 (Cytokeratin-903)

Only basal cells express high molecular weight cytokeratins. An immunoperoxidase cocktail containing monoclonal antibodies to cytokeratins 5 and 6 is also an effective basal cell stain. Absence of a basal cell layer is suggestive of invasive carcinoma.

p63, a nuclear protein encoded by a gene on chromosome 3q27-29. p63 like high molecular weight cytokeratins helps in the diagnosis of PCa.[80]

Methyl-CoA racemase (AMACR)

AMACR mRNA was recently identified as being overexpressed in PCa by cDNA library subtraction utilizing high throughput RNA microarray analysis. However, AMACR is also present in NH (12%), atrophic glands, HPIN (>90%), and AAH (17.5%).[81]

Androgen receptor (AR) is a nuclear localized, androgen binding protein complex occurring in prostatic glandular, basal and stromal cells. AR immunoreactivity was demonstrated in HPIN and invasive PCas.[82]

TNM AJCC STAGING PROTOCOL FOR PCA (2002)

(Partin AW, Borland RN, Epstein JI, et al. Influence of wide excision of the neurovascular bundle(s) on prognosis of men with clinically localized PCa with established capsular penetration. *J Urol*. 1993;150:142.)	
CLINICAL STAGE	
Primary Tumor (T)	
TX	Primary tumor cannot be assessed
T0	No evidence of primary tumor
T1	Clinically inapparent tumor not palpable nor visible by imaging
T1a	Tumor incidental finding in 5% or less of tissue resected
T1b	Tumor incidental finding in more than 5% of tissue resected
T1c	Tumor identified by needle biopsy (eg, because of elevated PSA)
T2	Tumor confined within the prostate*
T2a	Tumor involves one half of one lobe or less
T2b	Tumor involves more than one half of one lobe but not both lobes
T2c	Tumor involves both lobes
T3	Tumor extends through the prostate capsule**

T3a	Extracapsular extension (unilateral or bilateral)
T3b	Tumor invades seminal vesicle(s)
T4	Tumor is fixed or invades adjacent structures other than seminal vesicles: Bladder neck, external sphincter, rectum, levator muscles, and/or pelvic wall
	*Tumor found in one or both lobes by needle biopsy, but not palpable or reliably visible by imaging, is classified T1c.
	**Invasion into prostatic apex or into (but not beyond) the prostatic capsule is classified not as T3 but as T2
PATHOLOGIC STAGE	
Primary Tumor (T)	
pT2*	Organ confined
pT2a	Unilateral, involving one half of one lobe or less
pT2b	Unilateral involving more than one-half or one lobe but not both lobes
pT2c	Bilateral disease
pT3	Extraprostatic extension
pT3a	Extraprostatic extension**
	**Positive surgical margin should be indicated by an R1 descriptor (residual microscopic disease).
pT3b	Seminal vesicle invasion
pT4	Invasion of urinary bladder, rectum
	*There is no pathologic T1 classification.
Regional Lymph Node Metastases (N)	

pNX	Regional lymph nodes not examined
pN0	No regional lymph node metastasis
pN1	Metastases in regional lymph node(s)
Distant Metastases (M)	
pMX	Distant metastasis cannot be assessed
pM0	No distant metastasis
pM1	Distant metastasis
pM1a	Nonregional lymph node(s)
pM1b	Bone(s) metastasis
pM1c	Other site(s) of metastasis

Histopathological grading

GX Grade cannot be assessed

G1 Well differentiated (Gleason 2-4)

G2 Moderately differentiated (Gleason 5-6)

G3–4 Poorly differentiated/undifferentiated (Gleason 7-10).[83]

Treatment

The management choices for localized PCa are radical prostatectomy, external radiation therapy, and 'deferred' ('expectant') treatment

Focal surgical therapy ('male lumpectomy') has been proposed for the treatment of unifocal low-risk PCa in order to preserve the presumably uninvolved prostatic tissue and

its surroundings. Time will tell whether this theoretically risky procedure has a real role in the therapy of PCa.

Radiation therapy has been applied in the form of external beam, interstitial implantation, or a combination. An important and difficult decision is whether there should be further therapy (usually in the form of radical prostatectomy) in patients with latent (incidental) carcinoma found unexpectedly in suprapubic enucleations or TUR specimens. This is based on two criteria: amount of tumor and microscopic degree of differentiation. Small well-differentiated tumors (Gleason combined scores of 2–4) generally receive no additional therapy.

Hormonal manipulation in the form of estrogens, luteinizing hormone-releasing hormone (LH-RH) analogs and antiandrogens has replaced orchiectomy as a palliative measure in locally advanced and metastatic tumor, particularly to relieve the severe pain sometimes associated with skeletal disease

Prognosis

In 1999, the College of American Pathologists (CAP) arrived at a consensus statement on the relative significance of several prognostic parameters.[84]

I Proven to be of prognostic importance and useful in clinical patient management:

Preoperative Sr PSA level

TNM stage grouping

Histologic grade as Gleason score

Surgical margin status

II Extensively studied but whose importance remains to be validated:

Tumor volume

Histologic type

DNA ploidy

III Not sufficiently studied to demonstrate their prognostic value:

Perineurial invasion

Neuroendocrine differentiation

Microvessel density

Nuclear roundness

Chromatin texture

Other karyometric factors

Proliferation markers

PSA derivates

Other factors (oncogenes, tumor suppressor genes, apoptosis genes, etc.).


METHODS &
MATERIALS

MATERIALS AND METHODS

MATERIALS :

***Study Design & Source of Data*:** Cross-sectional study comprising of 90 patients who underwent transurethral resection of prostate 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.

Study Duration: The study was carried out from January 2012 to June 2013.

Inclusion criteria: All the patients who underwent TURP at the study institution

Exclusion criteria: 1) Patients having recurrent prostatic adenocarcinoma.

2) Patients on chemo/ radiotherapy.

3) Inadequate biopsies and poorly preserved prostatic specimens.

METHODS:

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.

Gross Examination: 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 that weighed 12 g or less were submitted in their entirety, usually in 6 to 8 cassettes. For specimens that weighed more

than 12 g, the initial 12 g were submitted (6 to 8 cassettes), and 1 cassette was submitted for every additional 5 g. In PIN cases the entire tissue was processed.

***Tissue Processing*:** Histological studies were done by routine tissue processing, which involved dehydration, clearing, impregnation with wax, embedding with paraffin wax, trimming the tissue blocks, cutting 4-6µ thick sections using microtome and staining with Hematoxylin and Eosin (H & E).

Microscopic Examination: Each TURP specimen was examined thoroughly and diagnosis was made based on WHO criteria as mentioned in the review of literature. Inflammation was graded based on findings of Sciarra et al.[85]

Histologic Grading **Histologic Aggressiveness**

GRADE	HISTOLOGIC FINDING	GRADE	HISTOLOGIC FINDING
0	No inflammatory cells	0	No contact between inflammatory cells & glandular epithelium
1	Scattered inflammatory cell infiltrate without nodules	1	Contact between inflammation & epithelium
2	Nonconfluent lymphoid nodules	2	Interstitial infiltrate with glandular disruption
3	Large inflammatory areas with confluence	3	Glandular disruption on > 25%

Immunohistochemistry:

It was done using primary antibody Ki-67(Biogenex,USA) to know the proliferative activity in all the cases. Sections are cut at approximately 3-4µm thickness, floated on 4% organosialine coated slides and incubated at 58°C over night.

Deparaffinization using Xylene I and II for 15 minutes each.

Dexylenisation using absolute alcohol I and II for 1 minute each.

Dealcoholisation using 90% and 70% alcohol for 1 minute each.

Tap water wash for 10 minutes followed by distilled water wash for 5 minutes.

Antigen Retrieval technique: Microwave at power 10 for 6 minutes in EDTA TRIS buffer pH 9.0 for 3 cycles. Distilled water rinsing for 5 minutes. Transfer to TBS (Tris buffer solution pH-7.6) for 5 minutes washing

Peroxidase block: 10-15 min to block endogenous Peroxidase enzyme using 3% Hydrogen peroxide. TBS buffer wash thrice for 5 minutes.

Power block: 10-15 mins to block non-specific reaction with the other tissue antigen.

Primary stain: Drain and cover the sections with ready to use Biogenex primary antibody Ki-67 antibody for 2 hours, followed by TBS buffer wash for 5 minutes twice to wash unbound antibodies.

Super enhancer- 30 mins to enhance the reaction between primary and secondary antibodies. TBS buffer wash for 5 minutes thrice to wash unbound antibodies.

Super sensitive poly–horse radish peroxidase(HRP) for 30 minutes– to clongate chain and also to label the enzyme. Followed by TBS buffer wash for 5 minutes thrice to wash unbound antibodies.

Color development with working DAB solution for 5-8 minutes, which imparts color to the antigens.

TBS buffer wash for 5 minutes thrice then tap water wash for 5 minutes.

Counter stain Haematoxylin for 2 seconds followed by tap water wash for 5 minutes to wash out the excess stain.

Dehydration and clearing by Alcohol: Xylene for 2 minutes. Then the slides were mounted with DPX.

Immunohistochemical evaluation:

The immunostained sections were examined using light microscopy. 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. Ki-67 positive intensity was graded as 1+ , 2+ or 3 +.

Analysis of Data: The data was entered into Microsoft excel data sheet. 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. Multiple logistic regression was used to identify independent risk factors. p-value < 0.05 was considered statistically significant.

RESULTS

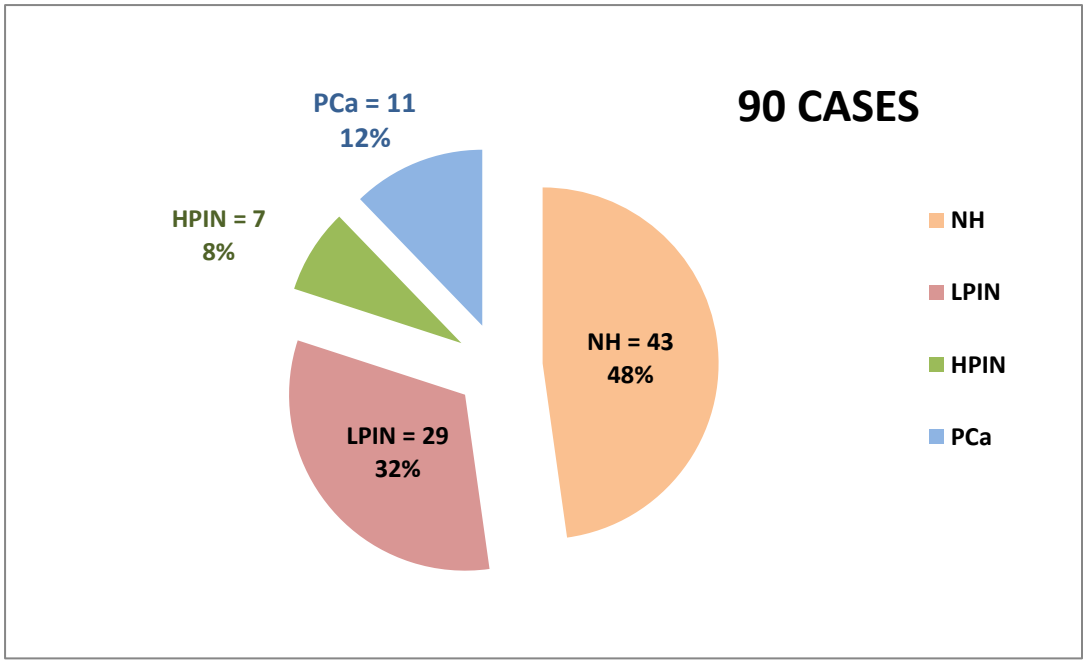
The present study deals with evaluation of various histological lesions in prostatic specimens. During the period of present study, 90 prostatic specimens were analyzed in the Department of Pathology, Sri Devaraj Urs Medical College, Kolar.

Prostatic lesions: Out of 90 prostatic specimens received, 79 cases (88.7%) were benign lesions and 11(12.3%) cases were malignant.

TABLE -1: DISTRIBUTION OF PROSTATIC LESIONS

GROSS	BENIGN LESIONS (NH + LPIN + HPIN)	MALIGNANT LESIONS (PCa)	TOTAL
TURP	79	11	90
	88.7%	12.3%	100%

CHART-1: DISTRIBUTION OF PROSTATIC LESIONS



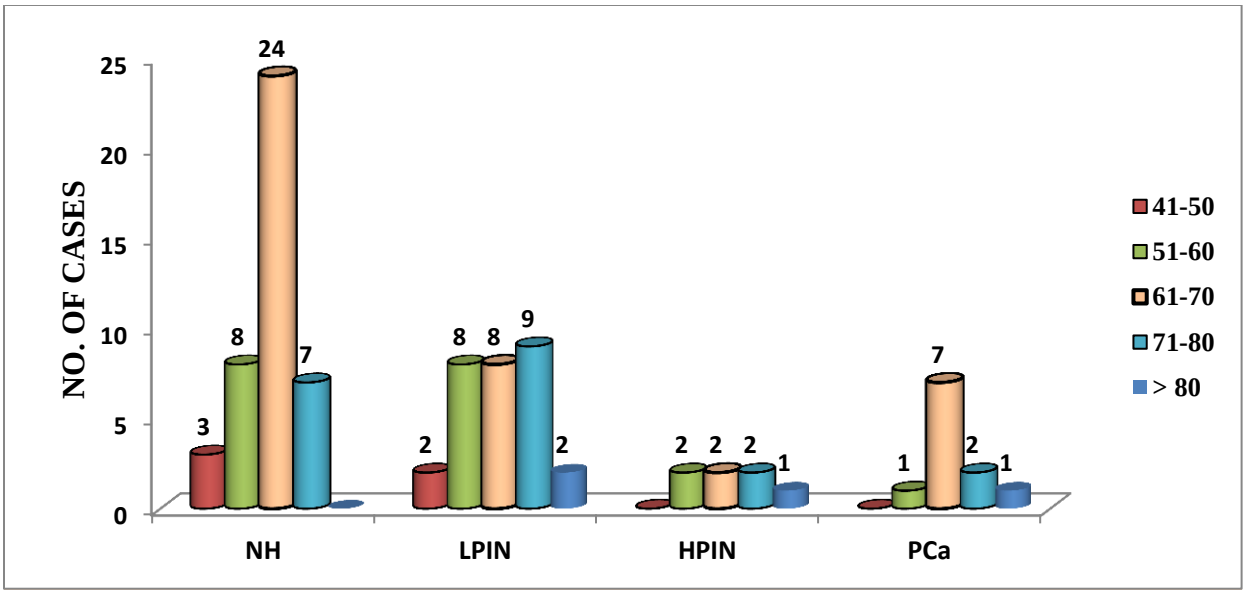
Age : Most of the patients (45.6%) were in the age group of 61-70 years. Majority of the PCa (63.6%) and benign lesions (43%) were in 61-70 years age group. Youngest case was 40 years and oldest was 94 years.

The mean age for benign lesions is 71.3 ± 9.7years and the mean age for malignant lesions is 66.5 ± 7years.

TABLE -2 : AGE DISTRIBUTION OF VARIOUS PROSTATIC LESIONS

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
TOTAL	90	100	43	100	29	100	7	100	11	100

CHART -2: AGE DISTRIBUTION OF VARIOUS PROSTATIC LESIONS



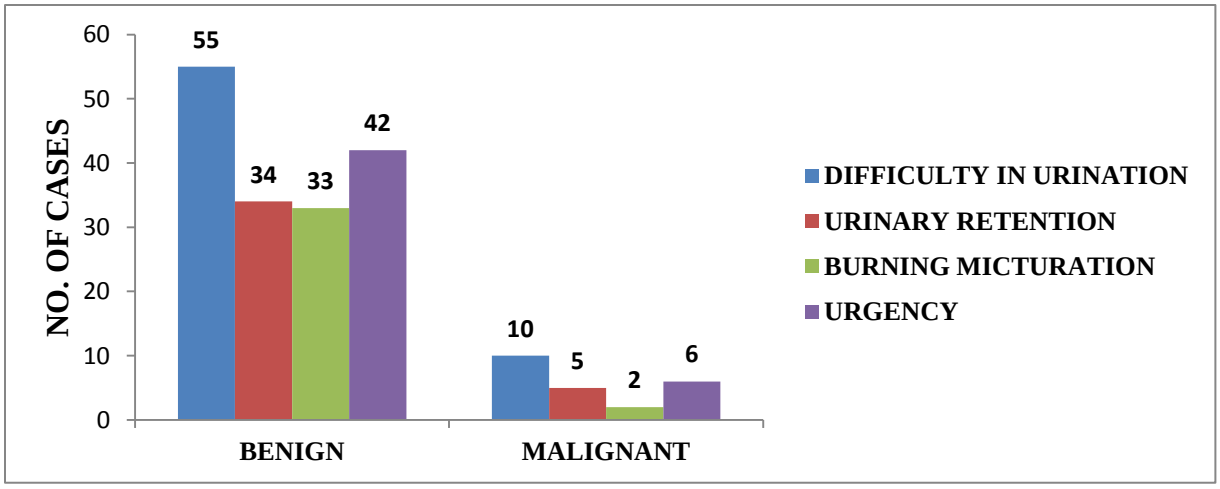
Clinical features : The majority of benign lesions presented with difficulty in urination (69.6%), followed by urgency (53.1%) and urinary retention (43%).

The most common clinical presentation in PCa is difficulty in urination (90%). Second most common symptom in carcinoma is urgency (54.5%) followed by urinary retention in 5 cases.

TABLE -3 : CLINICAL PRESENTATIONS OF PROSTATIC LESIONS

SYMPTOMS	BENIGN		MALIGNANT	
	No.	%	No.	%
DIFFICULTY IN URINATION	55	69.6	10	90.9
URINARY RETENTION	34	43	5	45.4
BURNING MICTURATION	33	41.8	2	18.1
URGENCY	42	53.1	6	54.5

CHART-3 : CLINICAL PRESENTATIONS OF PROSTATIC LESIONS



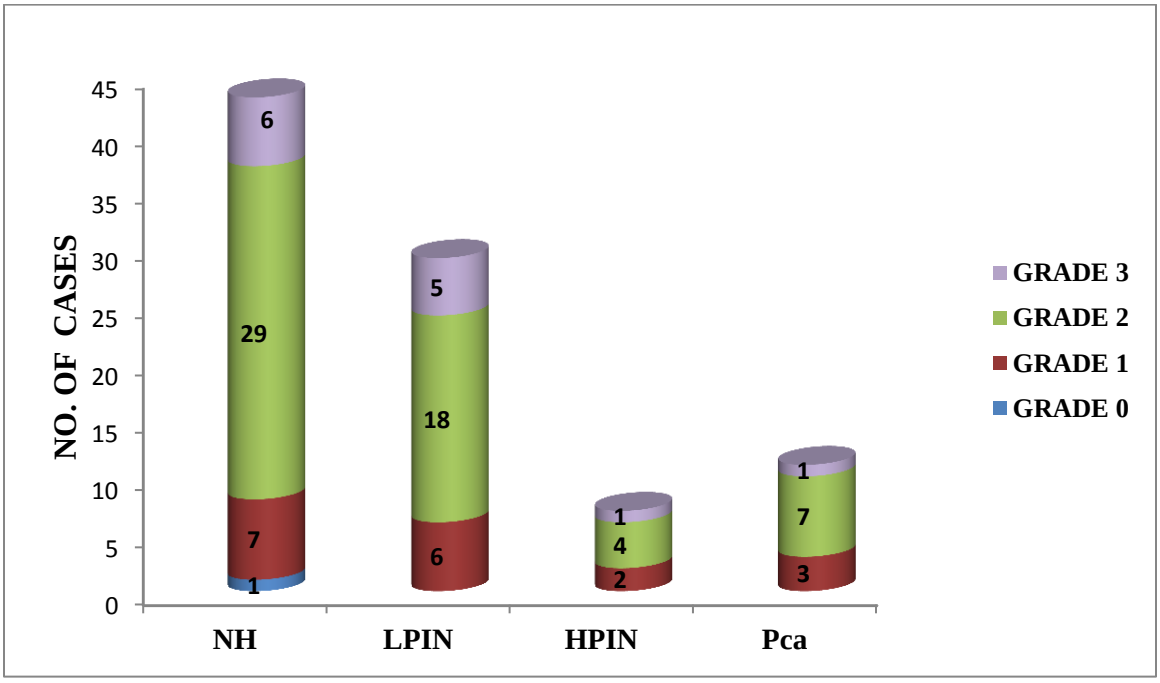
INFLAMMATION : For statistical analysis, inflammation was divided into two categories- Low (grade 0 &1) and high (Grade 2 & 3). Majority of the patients had high inflammation (Grade 2&3) comprising of 74.4% of NH, 75% of LPIN, 71.4% of HPIN and 72.7 % of PCa. However, no significant association was found between the lesions and inflammation.

TABLE-4: DISTRIBUTION OF INFLAMMATORY GRADE

INFLAMMATORY GRADE	NH		LPIN		HPIN		PCa	
	No	%	No	%	No.	%	No.	%
GRADE 0 & 1	11	25.6	7	24.1	2	28.6	3	27.3
GRADE 2 & 3	32	74.4	22	75.9	5	71.4	8	72.7
TOTAL	43	100	29	100	7	100	11	100

Chi-square=0.081 ; Degree of Freedom= 3 ; *p*-value= 0.99

CHART-4: DISTRIBUTION OF INFLAMMATORY GRADE



INFLAMMATORY AGGRESSIVENESS: For statistical analysis, inflammatory grade was clubbed into two categories- Low (Grade 0 &1) and high (Grade 2 & 3).

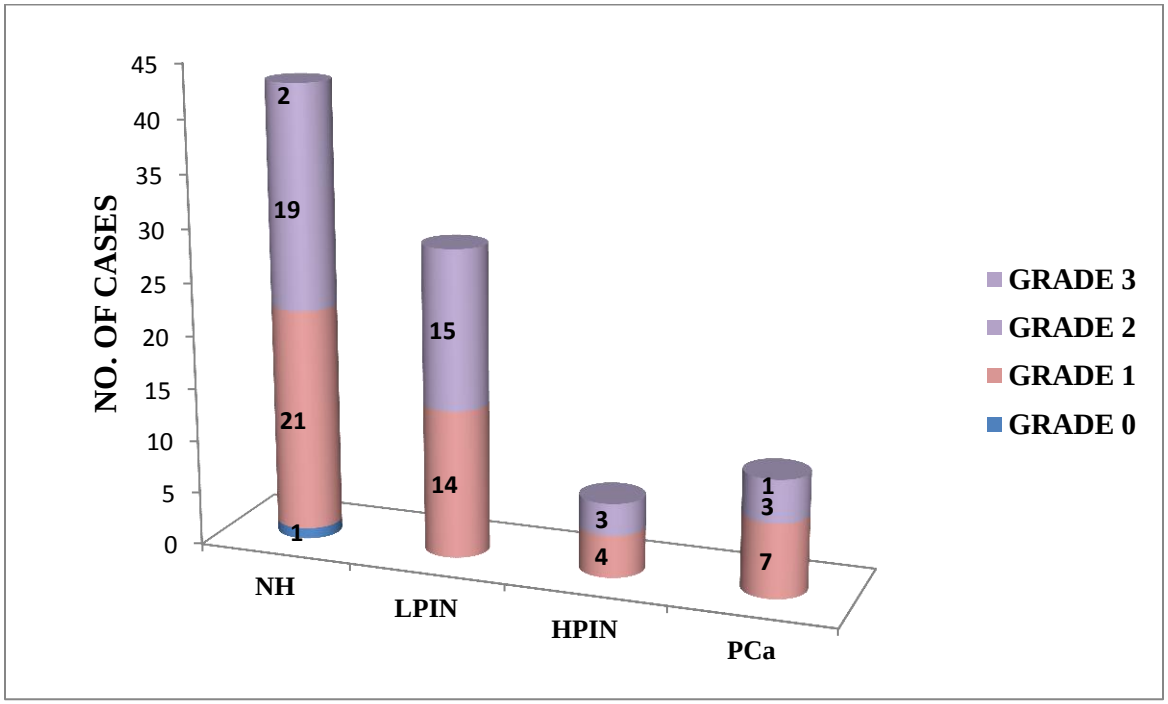
62.8% of NH, 79.3% of LPIN, 57.1% of HPIN and 63.6% of PCa show a lower inflammatory aggressiveness (Grade 0 & 1). There is no significant association of the lesions with the inflammatory aggressiveness.

TABLE-5: DISTRIBUTION OF INFLAMMATORY AGGRESSIVENESS

INFLAMMATORY AGGRESSIVENESS	NH		LPIN		HPIN		PCa	
	No.	%	No.	%	No.	%	No.	%
GRADE 0 & 1	27	62.8	23	79.3	4	57.1	7	63.6
GRADE 2 & 3	16	37.2	6	20.7	3	42.9	4	36.4
TOTAL	43	100	29	100	7	100	11	100

Chi-square= 2.7 ; Degree of Freedom= 3 ; *p*-value= 0.44

CHART-5: DISTRIBUTION OF INFLAMMATORY AGGRESSIVENESS



TISSUE EOSINOPHILS :

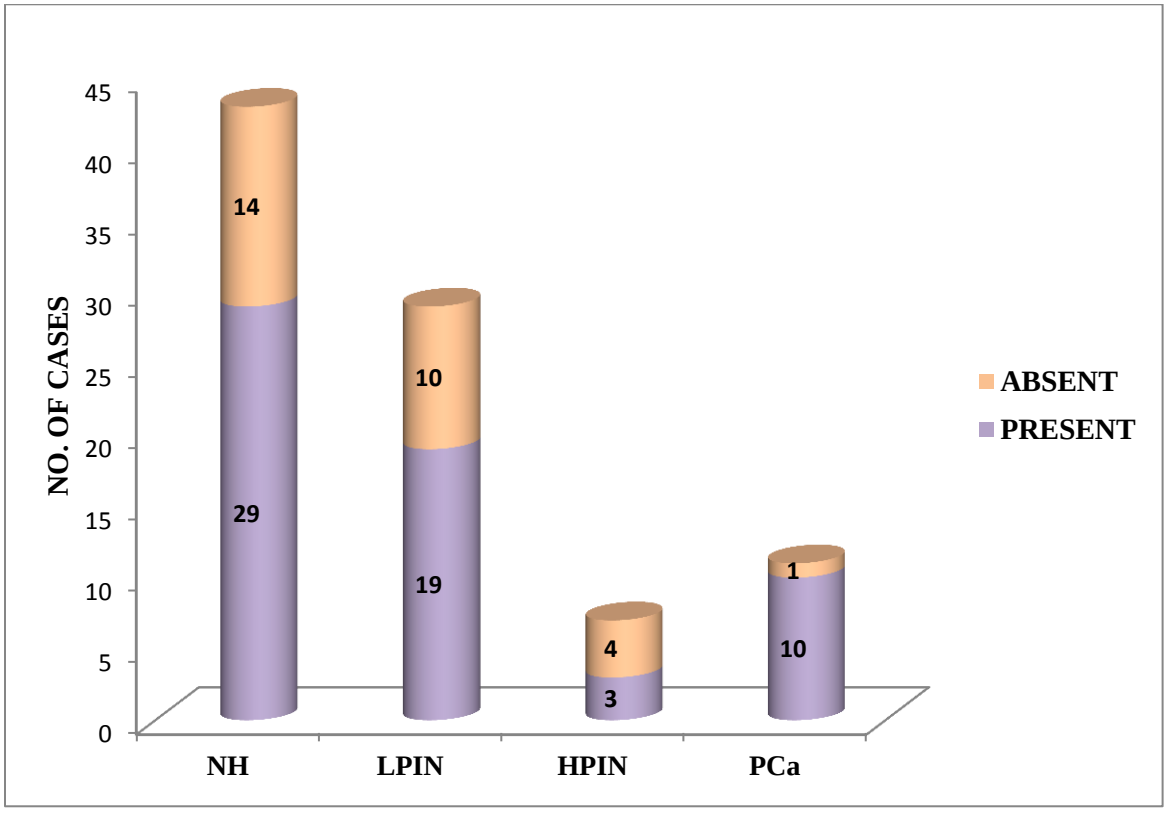
Histological eosinophilia was present in 90.9% of PCa, 67.4% of NH, 65.5% of LPIN and 42.9% of HPIN. No significant association was found between eosinophilia and the histopathological diagnosis.

TABLE-6 :DISTRIBUTION OF EOSINOPHILS IN PROSTATIC LESIONS

EOSINOPHILIA	NH		LPIN		HPIN		PCa	
	No.	%	No.	%	No.	%	No.	%
PRESENT	29	67.4	19	65.5	3	42.9	10	90.9
ABSENT	14	32.6	10	34.5	4	57.1	1	9.1
TOTAL	43	100	29	100	7	100	11	100

Chi-square= 4.75 ; Degree of Freedom= 3 ; *p*-value= 0.19

CHART-6 : DISTRIBUTION OF EOSINOPHILS IN PROSTATIC LESIONS

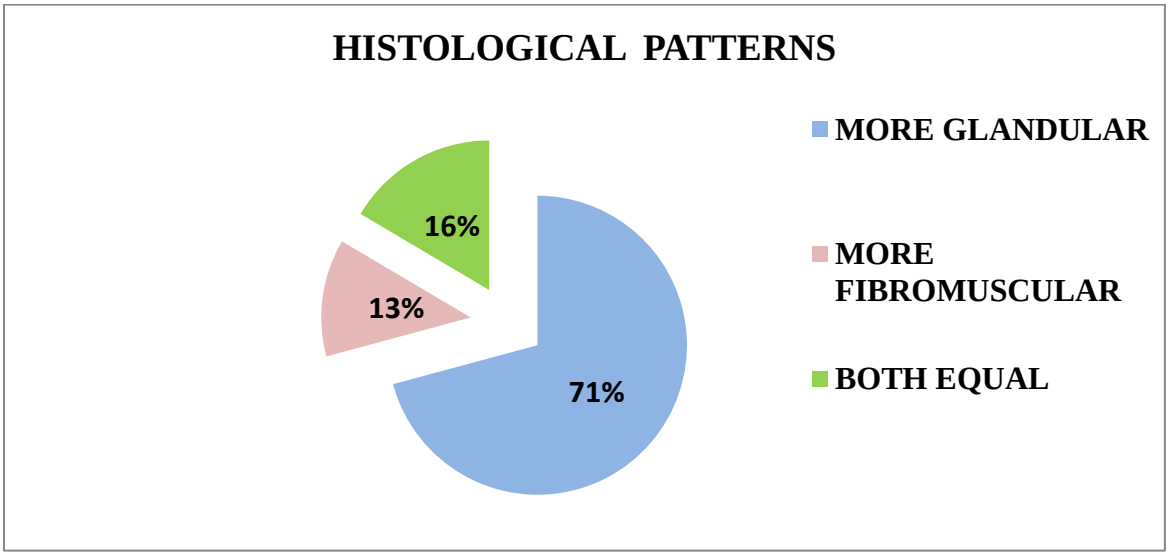


HISTOLOGICAL PATTERNS: Majority of the benign cases show a predominantly glandular component (70.8%). 16..5 % had equal components.

TABLE-7 : HISTOLOGICAL PATTERNS OF BENIGN LESIONS

	NUMBERS	PER CENTAGE
PREDOMINANTLY GLANDULAR	56	70.8
PREDOMINANTLY FIBROMUSCULAR	10	12.7
BOTH EQUALLY	13	16.5
TOTAL	79	100

CHART-7 : HISTOLOGICAL PATTERNS OF BENIGN LESIONS



Cystic atrophy comprised of 81.8% of all atrophies, followed by simple and partial atrophy (9.1%).

TABLE-8 : DISTRIBUTION OF ATROPHY

ATROPHY	NUMBERS	PER CENTAGE
CYSTIC	27	81.8
SIMPLE	3	9.1
PARTIAL	3	9.1

HYPERPLASIA : 71.1 % of cases show a papillary hyperplasia followed by basal cell hyperplasia in 14.4%.

TABLE-9 : DISTRIBUTION OF VARIOUS HYPERPLASIAS

HYPERPLASIA	NUMBERS	PER CENTAGE
PAPILLARY	64	71.1
BASAL CELL	14	15.6
CRIBRIFORM	13	14.4
CLEAR CELL	8	8.9
AAH	4	4.4

Atrophy was seen in 36.7 % of the cases and 31.3% of cases showed squamous metaplasia. ZN and PAS stain in granulomatous areas showed no organisms.

TABLE-10 : MISCELLANEOUS LESIONS IN THE PROSTATE

LESION	NUMBERS	PER CENTAGE
SQUAMOUS METAPLASIA	38	31.3
ATROPHY	33	36.7
CALCIFICATION	11	12.2
STROMAL NODULE	8	8.8
MYXOID CHANGE	7	7.7
GRANULOMAS	3	3.3
INFARCTION	2	2.2
TRANSITIONAL CELL DYSPLASIA	1	1.1

SERUM PSA:

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/ml. 81.8% of PCa had a PSA > 20ng/ml. For statistical analysis taking cut-off value of PSA as10 ng/ml, we find a highly significant association between raised Sr PSA and PCa. When we take 10 ng/ml as the cut-off value of PSA for malignant lesions, the Sensitivity is 40.7%, Specificity = 100 %, Positive predictive value = 100 % , Negative predictive value = 79.8% and diagnostic accuracy = 82.2 %.

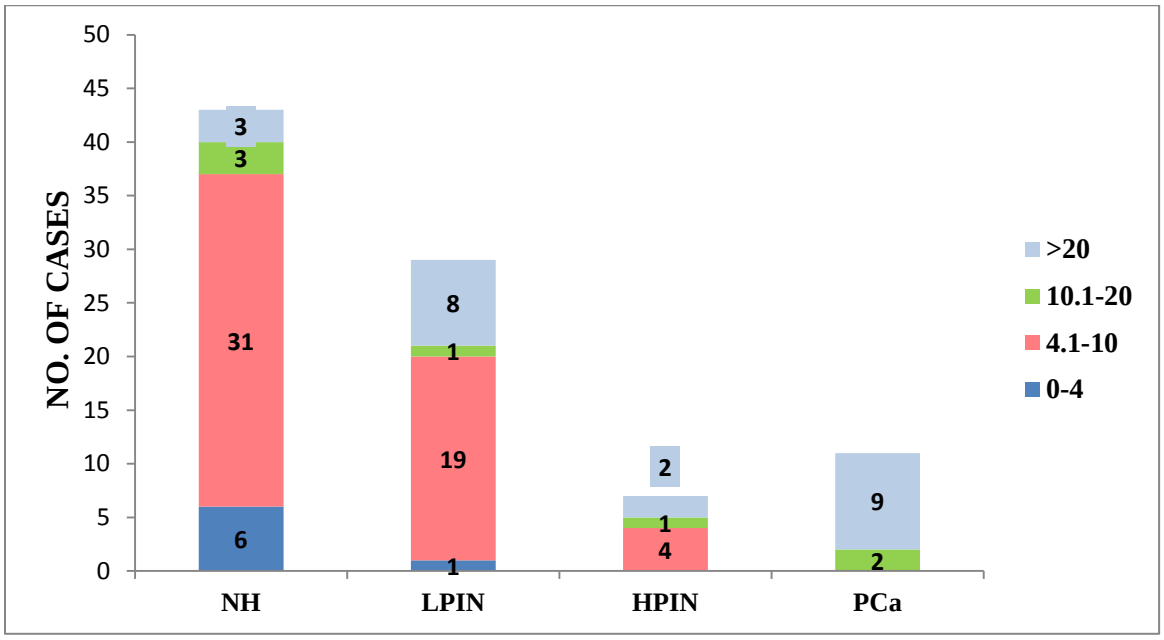
TABLE-11: DISTRIBUTION OF SERUM PSA

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
TOTAL	43	100	29	100	7	100	11	100

PSA (ng/ml)	NH		LPIN		HPIN		PCa	
	No.	%	No.	%	No.	%	No.	%
0-10	37	86	22	75.9	4	57.1	0	0
>10	6	14	7	24.1	3	42.9	11	100
TOTAL	43	100	29	100	7	100	11	100

Chi-square= 31.97 ; Degree of Freedom= 3 ; *p*-value < 0.001

CHART-8: DISTRIBUTION OF SERUM PSA



The Mean Sr PSA levels in PCa is 71.1± 34.4 ng/ml, much higher than the mean Sr PSA of NH (8.3± 8.6 ng/ml).

TABLE-12: Sr PSA (ng/ml)

	MEAN	STANDARD DEVIATION	MEDIAN	RANGE	TOTAL
NH	**8.3**	**8.6**	**6.2**	**1.23-52**	**43**
LPIN	**13.23**	**14**	**7.2**	**3.1-53.2**	**29**
HPIN	**16.8**	**17.5**	**9.9**	**5.1-53**	**7**
PCa	**71.1**	**34.4**	**100**	**13.7-100**	**11**

The association between Sr PSA levels and Inflammatory grade was not found to be significant.

TABLE-13: CORRELATION OF INFLAMMATORY GRADE WITH Sr PSA LEVELS IN BENIGN LESIONS

	PSA LEVELS (ng/ml)		
INFLAMMATION	**0-10**	**>10**	**TOTAL**
GRADE 0 & 1	**17**	**3**	**20**
GRADE 2 & 3	**46**	**13**	**59**
TOTAL	**63**	**16**	**79**

Chi-square= 0.46 ; Degree of Freedom= 1 ; *p*-value = 0.498

The association between Sr PSA levels and inflammatory aggressiveness was found to be highly significant.

TABLE-14: CORRELATION OF INFLAMMATORY AGGRESSIVNESS WITH Sr PSA LEVELS IN BENIGN LESIONS

	PSA LEVELS (ng/ml)		
INFLAMMATION	**0-10**	**>10**	**TOTAL**
GRADE 0 & 1	**48**	**6**	**54**
GRADE 2 & 3	**15**	**10**	**25**
TOTAL	**63**	**16**	**79**

Chi-square= 8.83 ; Degree of Freedom= 1 ; *p*-value = 0.003

The mean prostatic size is 50± 22.8 ml for HPIN, and 49.8 ± 27.2 ml for LPIN.

TABLE-15: SIZE OF PROSTATE BY TRANS-ABDOMINAL ULTRASOUND

	MEAN (ml)	STANDARD DEVIATION	MEDIAN (ml)	RANGE (ml)	TOTAL
NH	**46.5**	**25.7**	**56**	**24-130**	**43**
LPIN	**49.8**	**27.2**	**35**	**24-150**	**29**
HPIN	**50**	**22.8**	**48**	**24-84**	**7**
PCa	**34.9**	**7.3**	**34**	**26-50**	**11**

The association between inflammatory grade/ inflammatory aggressiveness and prostatic size was found to be highly significant.

TABLE-16: CORRELATION OF INFLAMMATORY GRADE WITH PROSTATE SIZE (ml)

INFLAMMATION	<46	>46	TOTAL
GRADE 0 & 1	**22**	**0**	**22**
GRADE 2 & 3	**39**	**29**	**68**
TOTAL			**90**

Chi-square= 13.8 ; Degree of Freedom= 1 ; *p*-value < 0.001

TABLE-17: CORRELATION OF INFLAMMATORY AGGRESSIVENESS WITH PROSTATE SIZE (ml)

INFLAMMATION AGGRESSIVENESS	<46	>46	TOTAL
GRADE 0 & 1	**53**	**8**	**61**
GRADE 2 & 3	**8**	**21**	**29**
TOTAL			**90**

Chi-square= 31.6 ; Degree of Freedom= 1 ; *p*-value <0.001

Ki-67 LABELING: 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. For statistical analysis the PI was divided into 2 categories. A significant association was found between the PI >25 and PCa with a chi-square of 38.77 and degree of freedom = 3.

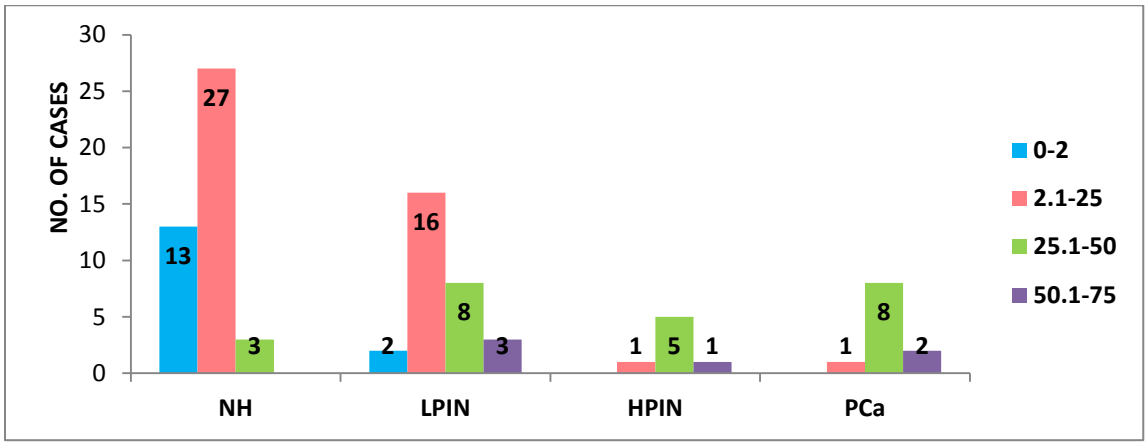
TABLE-18: DISTRIBUTION OF PROLIFERATIVE INDEX BY Ki-67 LABELING

IMMUNOSCORE (%)	NH		LPIN		HPIN		PCa	
	No	%	No	%	No.	%	No.	%
0-2	13	30.2	2	6.9	0	0	0	0
2.1-25	27	62.8	16	55.1	1	14.2	1	9.1
25.1-50	3	7	8	27.6	5	71.4	8	72.7
50.1-75	0	0	3	10.3	1	14.2	2	18.1
TOTAL	43	100	29	100	7	100	11	100

IMMUNOSCORE(%)	NH		LPIN		HPIN		PCa	
	No	%	No	%	No.	%	No.	%
0-25	40	93	18	62.1	1	14.3	1	9.1
>25	3	7	11	37.9	6	85.7	10	90.9
TOTAL	43	100	29	100	7	100	11	100

Chi-square= 38.77 ; Degree of Freedom= 3 ; *p*-value < 0.001

CHART-9: DISTRIBUTION OF PROLIFERATIVE INDEX BY Ki-67 LABELING



The mean PI of PCa is 42.1± 11.9 and NH is 7.6 ± 9.9 %. The association between Sr PSA levels and PI was found to be highly significant.

TABLE-19: PROLIFERATIVE INDEX

	MEAN	STANDARD DEVIATION	MEDIAN	RANGE	TOTAL
NH	**7.6**	**9.9**	**3.8**	**1.2-44.5**	**43**
LPIN	**22.7**	**17.8**	**20.8**	**2-60**	**29**
HPIN	**37.5**	**9.1**	**38.6**	**22.4-50.6**	**7**
PCa	**42.1**	**11.9**	**42.5**	**15-56.3**	**11**

TABLE-20: CORRELATION OF Sr PSA LEVELS WITH

PROLIFERAIVE INDEX (%)

PSA(ng/ml)	0-25	>25	TOTAL
0-10	49	14	63
>10	11	16	27
TOTAL	60	30	90

Chi-square= 11.66 ; Degree of Freedom= 1 ; *p*-value < 0.001

The mean PI increases as the Gleason's score increases. There was no significant association found between the Gleason score and the mean PI and mean Sr.PSA levels.

TABLE-21: COMPARISON OF GLEASON'S GRADE WITH MEAN PSA & MEAN PI

GLEASON SCORE	7	8	9	10
TOTAL CASES	3	1	5	2
MEAN PI	32.2	42.5	42.6	55.5
MEAN PSA	35.7	100	75	100

GLEASON SCORE	7 & 8	9 & 10	t- test	*p*- value
TOTAL CASES	4	7		
MEAN PI	34.8	46.3	-1.49	0.17
MEAN PSA	51.8	82.2	-1.68	0.13

Majority of PCa showed pink amorphous secretions (81.8%), followed by amphophilic cytoplasm (63.7%).

TABLE-22 : HISTOLOGICAL FEATURES IN PCa

	NUMBERS	PER CENTAGE
Collagenous micrnodules	1	9.1
Perineural invasion	6	54.5
Glomeruloid formation	1	9.1
Intraluminal blue mucin	2	18.2
Pink amorphous secretions	9	81.8
Mitotic & apoptotic figures	4	36.4
Amphophilic cytoplasm	7	63.7

MULTIPLE LOGISTIC REGRESSION

Multiple logistic regression suggest that Ki-67 acts as an independent parameter to indicate malignancy.

Variables in the Equation

		B	S.E.	Wald	df	Sig.	Exp(B)
Step 1[a]	I.AGGRE	-1.399	1.008	1.927	1	.165	.247
	PSArecoded	20.792	4557.743	.000	1	.996	1070829805.282
	KI67recoded	3.008	1.242	5.872	1	.015	20.257
	Constant	-22.527	4557.743	.000	1	.996	.000

a. Variable(s) entered on step 1: I.AGGRE, PSA recoded, KI67 recoded.

Parameter Estimates

Diagnosis new[a]		B	Std. Error	Wald	Df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
1	Intercept	-.125	.683	.034	1	**.854**			
	[I.AGGRE=0]	1.399	1.008	1.927	1	**.165**	4.050	.562	29.179
	[I.AGGRE=1]	0[b]	.	.	0	.	.	.	.
	[PSArecoded=0]	-22.614	.000	.	1	**0.996**	1.510E-010	1.510E-010	1.510E-010
	[PSArecoded=1]	0[b]	.	.	0	.	.	.	.
	[KI67recoded=0]	-3.008	1.242	5.872	1	**.015**	.049	.004	.563
	[KI67recoded=1]	0[b]	.	.	0	.	.	.	.

a. The reference category is: 0.

b. This parameter is set to zero because it is redundant.

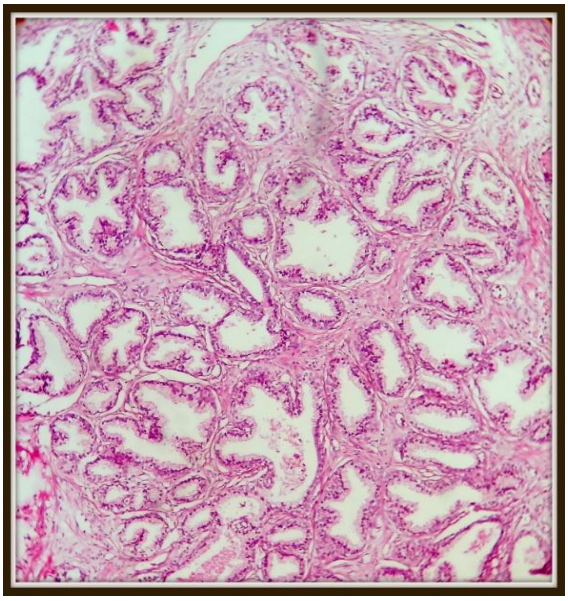


Figure-3: NH with more glandular hyperplasia (H&E, x100)

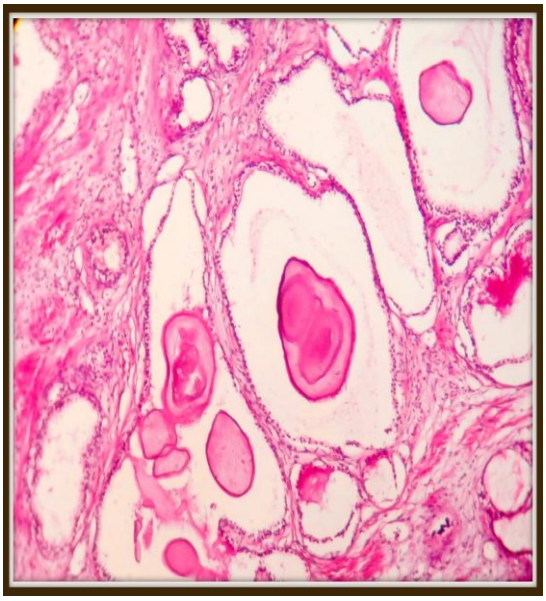


Figure-4: NH with corpora amylacea and calcification (H&E, x100)

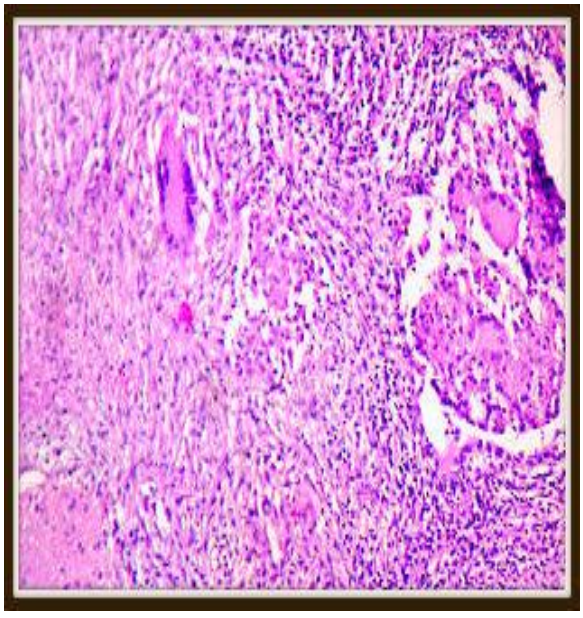


Figure-5:Epithelioid granuloma with multinucleate giant cell (H&E, x100)

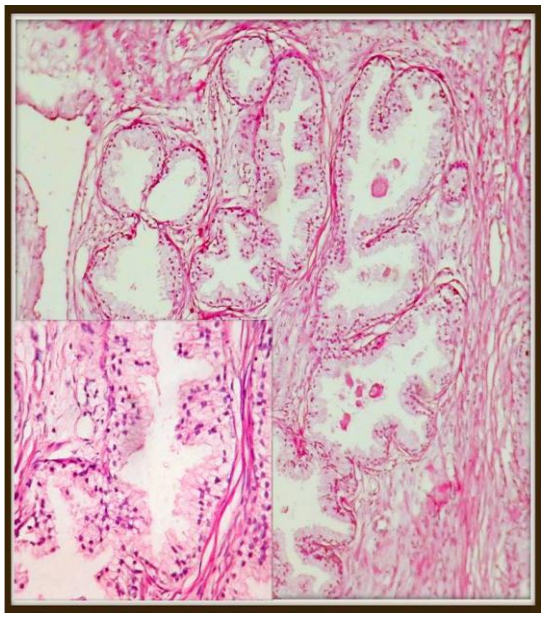


Figure-6: NH with clear cell hyperplasia (H&E,x100; Inset x400)

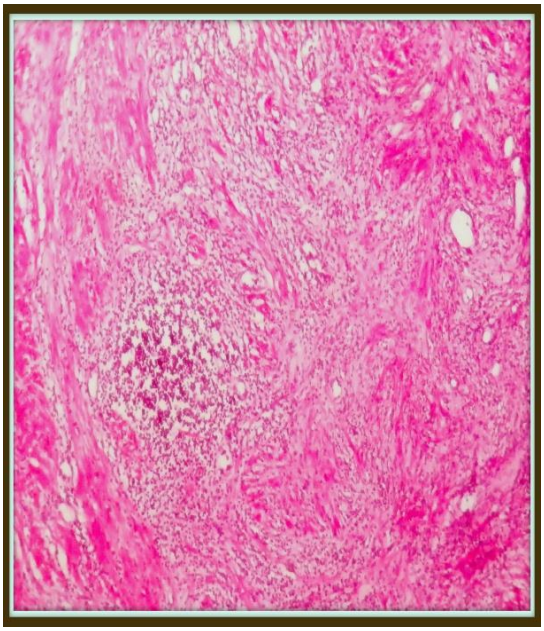


Figure-7: NH with Grade 2 inflammation (H&E, x100)

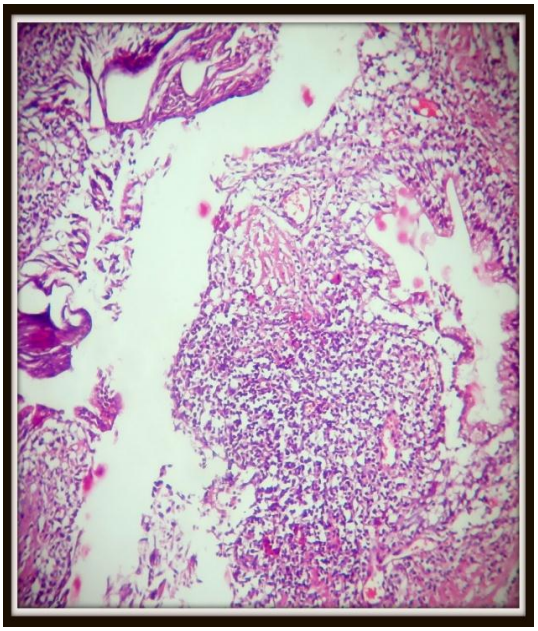


Figure-8: NH with Grade 3 inflammatory aggressiveness (H&E, x100)

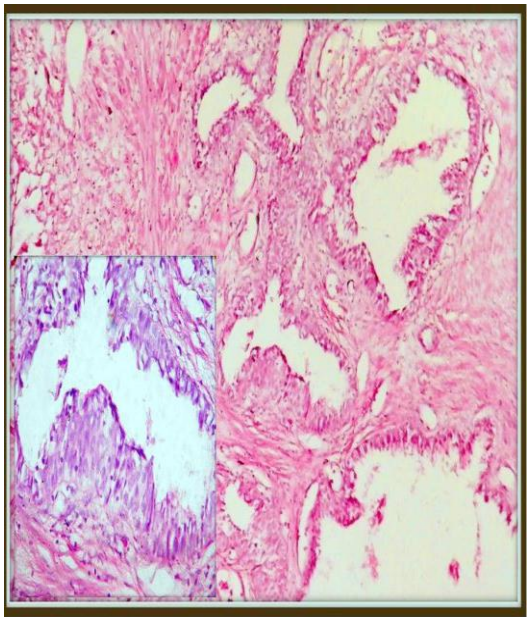


Figure-9: NH with LPIN (H&E, x100)

Inset showing stratification of nuclei (H&E, x400)

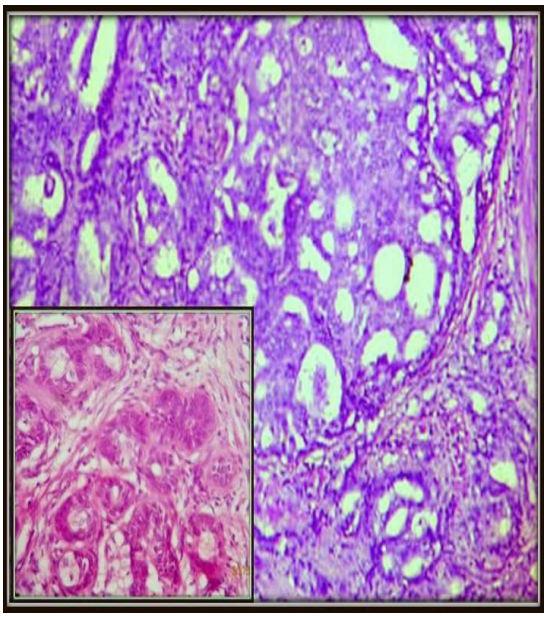


Figure-10: NH with HPIN (H&E, x100)

Inset showing coarse chromatin & prominent nucleoli (H&E, x400)

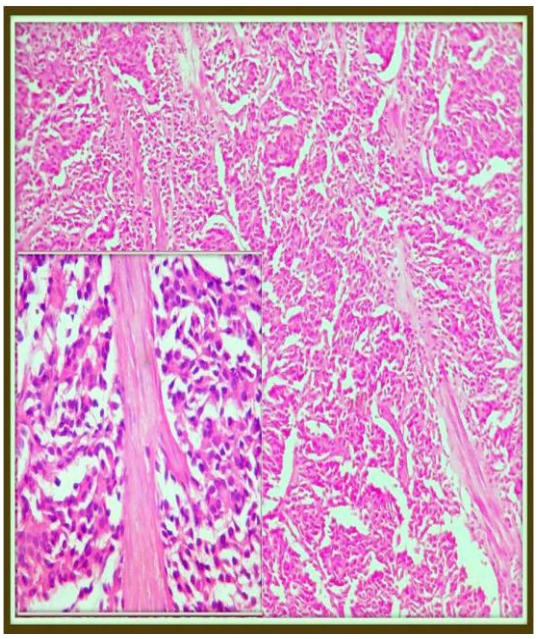


Figure-11: PCa with trabecular pattern & Gleason's pattern 5 (H&E, x100)

Inset shows squamous differentiation (H&E, x400)

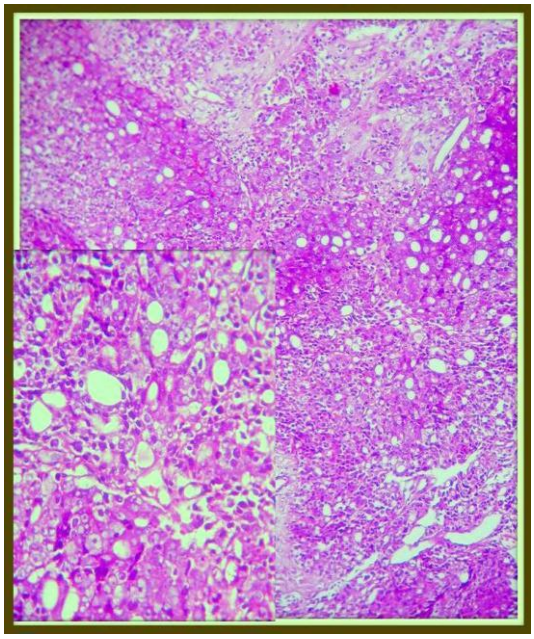


Figure-12: PCa in cribriform pattern & Gleason's pattern 4 (H&E, x100; Inset x 400)

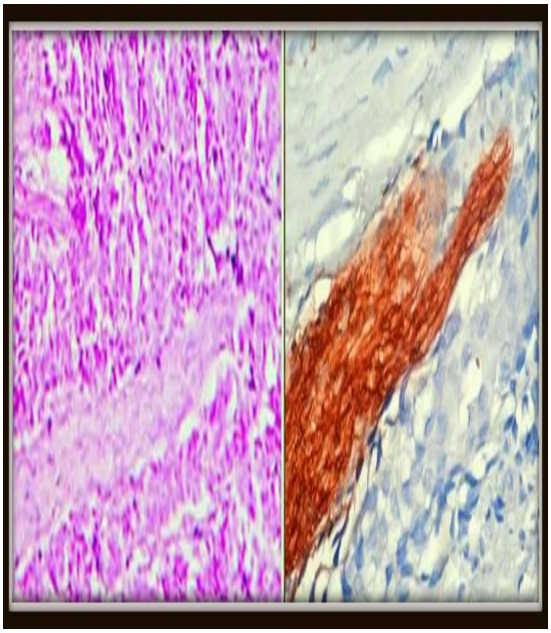


Figure-13: PCa with perineural invasion (H&E, x400)
Inset shows S-100 positivity of nerve bundle amidst tumor cells (x400)

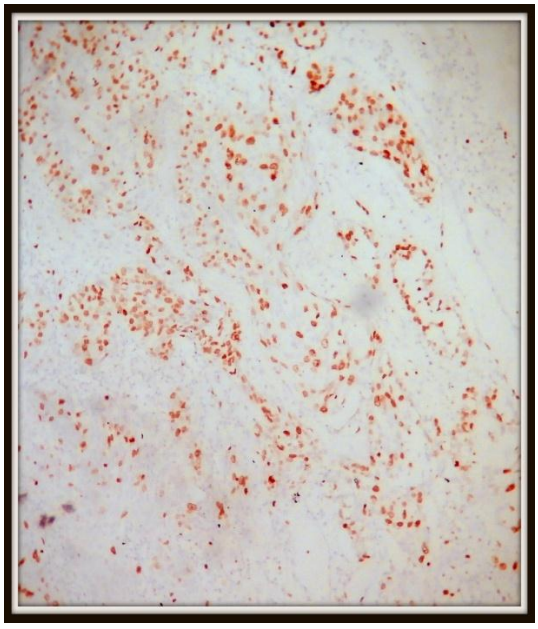


Figure-14: Ki-67 labelling in PCa with PI=42% (IHC, x100)

DISCUSSION

DISCUSSION

Across the globe, diseases of Prostate gland cause significant morbidity and mortality among adult males. It is basically a geriatric problem increasing in incidence with advancing age. 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-1) in the Indian subcontinent, except the study of Ghartimagar et al[86] ,whose findings relied on autopsy samples, hence the majority of cases were in their fourth decade.

TABLE -23: COMPARISON OF AGE DISTRIBUTION IN DIFFERENT STUDIES

AGE DISTRIBUTION		41-50		51-60		61-70		71-80		81-90		91-100		T
		No	%	No	%	No	%	No	%	No	%	No	%	
Present study	B	5	63.2	18	22.8	34	43	18	22.8	3	3.8	1	1.3	79
	M	0	0	1	9.1	7	63.6	2	18.2	1	9.1	0	0	11
Aslam et al (2013)	B	3	7.9	10	23.8	23	54.8	4	9.5	2	4.8	0	0	42
	M	1	16.7	5	83.3	0	0	0	0	0	0	0	0	6
Ghartimagar et al (2012)	B	23	52.3	13	29.5	6	13.6	2	4.5	0	0	0	0	44
	M	2	66.7	0	0	1	33.3	0	0	0	0	0	0	3
Talukder et al[87] (2008)	B	7	9.7	13	18.1	26	36.1	21	29.2	5	6.9	0	0	72
	M	1	5.3	6	31.6	8	42.1	4	21.1	0	0	0	0	19

B-Benign ; M-Malignant; T-Total

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%).[88] Clinically NH presents with lower urinary tract symptoms (LUTS) associated due bladder outlet obstruction (BOO), as a result of enlargement.

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. According to the American Cancer Society, United States is expected to have about 238,590 new cases of prostate cancer in 2013 and around 29,720 men would die of PCa.[89] However, detection rates among Asian population have been traditionally low. Interestingly, increase in the number of biopsies increases the detection rate by two times.[90]

In India the incidence of Prostate cancer is about 6.8/100000 (Anil Mandhani et al)[91], and a upward trend has been observed of late(B Yeole et al).[92]

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.[88] 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, where as fruits and vegetables reduce the risk of PCa.

TABLE-24: FREQUENCY OF BENIGN AND MALIGNANT CONDITIONS IN DIFFERENT STUDIES

Histopathological Diagnosis	Present study	Aslam et al (2013)	Ghartimagar et al (2012)	Sinha et al (2011)	Mohammed et al[93] (2005)	Talukder et al (2008)	Gupta et al (2005)
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%)
TOTAL	90	48	71	89	562	91	96

The most common lesion in prostate in all studies including our study has been NH comprising 47.7% of cases. It is defined as enlargement of the prostate gland from the progressive hyperplasia of stromal and glandular prostatic cells.[94] The percentage is higher in a few studies because we had 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[95] and Sinha et al.[96]

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-25: DISTRIBUTION OF NON-NEOPLASTIC CONDTIONS IN DIFFERENT STUDIES

Histopathological Diagnosis	Present study	Ghartimagar et al (2012)	Sinha et al (2011)	Mohammed et al (2005)	Gupta et al (2005)	Rekhi et al (2004)
LPIN	29 (32.2%)	12 (12%)	-	-	-	35 (17.5%)
HPIN	7 (7.7%)	1 (1%)	10 (8%)	69 (18.6%)	03 (2.1%)	40 (8%)
AAH	4 (4.4%)	4 (4%)	-	63 (16.9%)	-	40 (20%)
GRANULOMAS	3 (3.3%)	-	-	-	1 (0.7%)	3 (1.5%)
CHRONIC INFLAMMATION	67 (74.4%)	-	30 (25%)	88 (23.6%)	38 (26.8%)	157 (78.5%)
ATROPHY	32 (35.5%)	4 (4%)	-	-	-	-

Eosinophil granules contain high amounts of cytotoxic basic proteins, major basic protein (MBP), eosinophil cationic protein (ECP), eosinophil peroxidase (EPO), and eosinophil-derived neurotoxin (EDN). These cationic proteins have been described to exert cytotoxic properties for tumor cell lines with variable efficiency. Eosinophil granules contain multiple Th1, Th2, and immunoregulatory cytokines that are rapidly secreted in allergic

conditions, parasitic infestations and various malignancies. In our study, tissue eosinphils were present in 67.4% of NH, 65.5% of LPIN, 42.9% of HPIN and 90.9% of PCa.

Inflammation of prostate gland is called Prostatitis, it is characterized by urinary frequency, dysuria, body aches and sometimes fever. Prostatitis may be infective and non-infective.

Importantly, the MTOPS study demonstrated that men with NH and prostatic inflammation showed an increased percentage of disease progression. At 4-year follow-up, only NH patients with inflammation developed acute urinary retention.[2]

We graded inflammation in our cases as done by sciarra et al[85] and further clubbed grade2 and 3 as significantly higher inflammation. We report significant inflammation in 74.4% of our cases. It is consistent with the finding of Rekhi et[97] al who reported in 78.55% of cases. However, other studies showed much lesser cases of chronic inflammation.

Histologic aggressiveness grading seems to have more clinical relevance and also has a correlation with Sr PSA levels. Irani *et al.* analysed 66 patients with exclusively benign prostatic tissue on prostate biopsies and found a significant correlation between the aggressiveness grading of the inflammatory reaction and Sr PSA.[98] Even in our study we found the association between inflammatory aggressiveness and elevated PSA levels significant. PSA levels are said to rise with glandular disruption by inflammatory cells.

Inflammation is a complex phenomenon consisting of humoral (cytokines) and cellular (leukocytes) components. Inflammation can influence the tissue microenvironment through the production of free radicals, COX activity, and NO synthesis, all linked to the

deleterious oxidative effect of inflammation on prostate tissue. These factors can alter protein structure and function, induce gene changes, cause posttranslational modifications, including those involved in DNA repair and apoptotic processes, and provoke cellular proliferation. All these aspects generate an important link between inflammatory processes and the induction of prostate growth or of preneoplastic and neoplastic lesions.[85] However, some authors showed that men with chronic inflammation exhibited HPIN (2.7% vs. 20.3%, $p < 0.01$) and PCa (13.6% vs. 43.5%, $p < 0.01$) less frequently than their counterparts without chronic inflammation.[99]

Interestingly, Sinha et al[96] found that the use of an antibiotic led to PSA fall in 55% of their patients . The use of antibiotics has been shown to reduce PSA values in Chinese men and has the potential to reduce unnecessary biopsies in some men with elevated PSA.[100]

Another approach has been to examine prostatic secretions following a prostatic massage and treating those with increased leukocyte count. Thirty percent of Japanese men with more than 10 WBC in the prostatic massage secretion showed reduction in PSA after a course antibiotics.[101] The empirical use of antibiotics in men with an elevated PSA is not without risks. Besides the delay in diagnosis in those men who are actually suffering from cancer, there is the possibility of inducing drug resistance.

Different methods have been proposed to increase the specificity of PSA when it is between 4-10 ng/ml including age specific PSA, PSA density (PSAD) and percent free

PSA (% fPSA). Percentage free PSA and PSAD both provide comparable results, which are better than age specific PSA.[102]

Sr PSA at presentation was significantly higher in the group with NH plus prostatitis than in the group with NH alone, and approached significance in the group with PCa plus prostatitis compared with the group with PCa alone.[103]

Nadler *et al.* found that acute and chronic inflammation was significantly more prevalent in patients with an elevated Sr PSA level (>4.0 ng/ml) (63% v. 27% and 99% v. 77%, respectively).[104] Recently a prospective study of 51 patients without evidence of PCa demonstrated extension of the inflammatory process directly related to elevations of Sr PSA levels.[105]

Data from the Medical Therapy of Prostate Symptoms (MTOPS) trial suggested that about 40% of baseline biopsy specimens had chronic inflammatory infiltrates—in particular, in men with higher prostate-specific antigen (PSA) values and larger prostate volumes.[2]

The REDUCE trial[106,107] confirmed these data. Prostatic inflammation was also associated with higher prostatic volume (46.5ml vs 43.4ml; $p < 0.0001$) and higher International Prostate Symptom Score(IPSS) results(8.8vs8.2; $p < 0.0001$). Even in our study we found higher grades of inflammation were significantly associated with enlarged prostate size, as revealed by ultrasound. All the cases having low inflammation (Grade 0 & 1) had a prostate size less than the mean prostate volume (46ml), where as 42.6% of cases with high inflammation (Grade 2 & 3) had a prostate size >46ml.

This is because T cell activity in inflammatory infiltrates may result in stimulation of stromal and epithelial cell proliferation that is sustained by autoimmune mechanism. Tissue damage and the subsequent chronic process of repetitive wound healing induced by inflammation end up in the development of NH nodules and it is also considered a potential risk factor for malignancies as in many organs, such as the liver, colon, bladder, lung, and pancreas.[108]

So patients with chronic prostatic inflammation are not only at risk for NH development but also its progression and—if associated with PIA and having a genetic predisposition—a higher risk for PCa. Hence, prostatic inflammation has been considered a possible target for NH and PCa prevention, and treatment with different anti-inflammatory agents have been tested in vitro and in vivo for the management of both conditions.[109,110]

Traditionally prostatic biopsy has been recommended for men with a prostate-specific antigen (PSA) level above 4 ng/ml after an assessment of co-morbidity, life expectancy, and a detailed discussion regarding the implications of a biopsy and its result.[111] The prostate cancer prevention trial data show that no level of PSA is "normal", and there is a continuum of risk for prostate cancer based on the level of PSA. This data have also suggested that the threshold for prostatic biopsy may need to be revised downward since about 25% of American men with a PSA of less than 4 ng/ml have clinically significant malignancy.[112] Biopsy-detected prostate cancer, including high-grade cancers, is not rare among men with PSA levels of 4.0 ng per milliliter or less — levels generally thought to

be in the normal range. 15 percent of men with a "normal" PSA level had prostate cancer.[113] However in our study none of the PCa had a PSA below 4ng/ml.

The American Cancer Society estimates the risk of prostate cancer 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[96] and Dublin et al[114] . Dublin found cancer in 10% of men with PSA of 4.1–20 ng/ml. A total of 60.5% of his patients had histological prostatitis and there was no difference in the biopsy outcome between men of Malay, Chinese, or Indian origin.

In a study from Mumbai, Chavan et al[115] 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[116] reported an accuracy rate of 68% with Sr PSA and many patients with PSA values which were between 4 -9ng/dl had benign biopsies. In the present study, the accuracy rate was 95.6%.

Richie et al[117] 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[118] 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/d;l 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 attributed to a difference in the sample size.[119]

Bains et al[120] found a significant association between the PSA levels and the glandular proliferation. Chronic prostatitis and glandular proliferation are the two most important factors which contribute to the Sr PSA elevation in hyperplastic prostates. In our study, among the 27 patients who had a 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.

PIN and PSA Levels

Another area of concern has been whether PIN itself is associated with an elevation in serum PSA levels. Initially in men undergoing simple prostatectomy, the finding of PIN was associated with a high PSA level. Alexander and colleagues subsequently reported that PIN does not appear to increase PSA levels.[121]

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). Statistically, Sr PSA showed an association with the diagnosis.

Gerstenbluth et al[122] demonstrated that a Sr PSA level of 20 ng/ml or greater, independent of DRE 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[123] 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. The need for detection rate and the accuracy of cutoff value is important in counseling the patients for the chances of positive finding prior to the biopsy. 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 frequency of HPIN in needle biopsy series ranges from 5 to 16%. HPIN is relatively uncommon in TURP, with studies reporting a rate of 2.3% and 2.8%, respectively.

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.[121]

CLINICAL SIGNIFICANCE OF LPIN ON BIOPSY

College of American pathologist (CAP) advises not to mention LPIN on biopsy. It is mainly because there is a lack of reproducibility in its diagnosis, even by uropathologists, and it is not associated with a higher risk of cancer on re-biopsy than the

risk after a benign diagnosis on initial biopsy. 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. For example, there are no criteria as to how prominent or how frequent the nucleoli must be to diagnose HPIN. Different thresholds for the diagnosis of HPIN include: (i) any visible nucleoli; (ii) nucleoli visible in at least 10% of the cells in the gland; (iii) complete involvement of a gland with cells having nucleoli; and (iv) nucleoli visible at 20 × magnification. Technical factors relating to the processing of needle biopsy specimens can also contribute to the reported variability in the incidence of HPIN on biopsy. Fixatives that enhance nuclear detail and nucleolar prominence can increase the diagnosis of HPIN, whereas thick sections and increased uptake of dyes can obscure fi ne nuclear detail. 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.[124] 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 signifi cantly 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.[125]

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%).

Recently, some studies have suggested that molecular findings associated with HPIN might be able to predict which men are more likely to have cancer on re-biopsy. In one study using radical prostatectomy specimens, HPIN lesions adjacent to carcinoma had more AMACR overexpression (56%) than HPIN lesions away from carcinoma (14%). In a study using needle biopsy cores, patients with atleast one AMACR-positive HPIN gland were 5.2 times more likely to have a subsequent diagnosis of PCa on repeat biopsy than those without any AMACR positive HPIN.[126]

The prevalence of PIN in malignant prostate samples has been reported to vary from 60–100%. HPIN reportedly is detected in 33–100% of malignant prostates compared with benign prostates (range, 4–18%).[127] Borges et al[128] reported 85.24% HPIN in a majority of PCa.

Specimens. 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.[129]

In our study, HPIN was seen in 9 cases. Only 2 cases were associated with PCa and 7 of them were associated with NH.[130]

Studies have reported AAH in at least 20% of TURP specimens, but its occurrence in the general population is unknown.[130]

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[86], yet much lesser than the number reported by Rekhi et al[97] and Mohammed et al[93] In none of our cases AAH was associated with PCa. The PI was relatively higher in these cases than exclusive NH. The significance of identification of AAH lies in the fact that marked small glandular proliferation present in this condition may be confused with carcinoma. These microglandular proliferation may even show few large glands with PCa and the basement membrane is intact in AAH whereas, PCa and basement membrane will be absent in carcinoma. Gaudin et al[131] 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[86] 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. It consists of a thickness of two or more basal cells at the periphery of the prostatic acini. The cells were cuboidal to low columnar with round to oval nuclei. It was seen as solid or cystically dilated gland. A minimum thickness of two basal cells is required for the diagnosis although the criteria are arbitrary.[132] BCH sometimes appears as small nests of cells surrounded by a few concentric layers of compressed stroma, often associated with chronic inflammation. 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. It is believed that corpora amylacea (CA), formed from retained and stagnating secretions within the prostatic acini, increases in number with increasing age. CA in the glands with nodular hyperplasia may act as the nucleus for stone formation as a result of improper drainage, infection of the acini, and calculi deposition.[45] These bodies were large, faceted and centrally homogenous, surrounded by 7-10 concentrically arranged distinct regular rings.

TABLE-26: COMPARISON OF GLEASON SYSTEM OF GRADING IN PROSTATE CANCER

GLEASON SCORE	Present study	Sinha et al (2011)	Mohammed et al (2005)	Gupta et al (2005)	George et al (2004)
2-4	0	0	99(86.9%)	05(14.7%)	11(8.88%)
5-6	0	05(17.24%)	4(3.4%)	08(23.5%)	31(25%)
7	3(27.3%)	18(62.06%)	1(0.9%)		
8	1(9%)	06	2(1.7%)	21	82
9	5(45.45%)	(20.68%)	3(2.6%)	(61.7%)	(66.12%)
10	2(18.18%)		5(4.5%)		
TOTAL	11	29	114	34	124

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%).

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 (atypical adenomatous hyperplasia), low grade carcinoma, PIN and high grade carcinoma has been established, considering PIN as a pre-neoplastic lesion (Helpap,1995).[134]

Thus, within the normal prostate epithelium, the majority of the cells immunoreactive for Ki-67 are of the phenotype of basal cells, but in the HPIN lesions, only 6-10% of the immunolabeled cells are located in this layer, with a concomitant increase in the immunologically labeled dysplasic luminal cells (Myers, 1997). For this reason it has been suggested that, in PIN lesions, the luminal cells also acquire a proliferative potential. In non-invasive proliferative lesions of the prostate, the global analysis of Ki-67 does not seem to be very important.

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.[133]

Theodoropoulos et al[135] showed a significant relationship between Ki-67 index and Gleason's grading of tumors with low- to high-grade differentiation. Nilson et al[136] 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 benign hyperplasia 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).[137] 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.

We had a case of PCa showing squamous differentiation. Morphologically, squamous differentiation in prostate cancer can be encountered in pure form or associated with adenocarcinoma, urothelial carcinoma or sarcoma. Given its multiple possible origins, a decision as to whether the squamous component develops through divergent differentiation from adenocarcinoma following treatment or it represents squamous differentiation of a transitional cell carcinoma, or is a pure second prostatic malignancy can be very challenging. Our literature review shows that the etiology of squamous differentiation in PCa is not well defined. Understanding the biology of this tumor might help to develop more efficient therapies for this aggressive malignancy with a poor prognosis.[138]

SUMMARY

A cross-sectional study to evaluate the various histological lesions in prostatic specimens was undertaken during the period from January 2011 to June 2013. The following are the salient observations noted in this study.

1) Out of 90 cases studied, commonest pathology encountered was benign lesion constituting 88.7% and malignant lesions were 12.3%.

2) The commonest clinical presentation in both benign and malignant lesions was difficulty in micturition, followed by urgency.

3) NH, HPIN and PCa were common in age group of 61-70 years, where as LPIN was more common between 71-80 years.

4) Majority of the patients had high inflammation (Grade 2 & 3) comprising of 74.4% of NH, 75% of LPIN, 71.4% of HPIN and 72.7 % of PCa.

5) 62.8% of NH, 79.3% of LPIN, 57.1% of HPIN and 63.6% of PCa show a lower inflammatory aggressiveness (Grade 0 & 1).

6) Histological eosinophilia was present in 90% of PCa, 67.4% of NH, 65.5% of LPIN and 42.9% of HPIN.

7) Majority of the benign cases (74.4%) show a predominantly glandular component. 11.2 % of the cases had equal amount of glandular and fibromuscular component.
8) 71.1 % of cases show a papillary hyperplasia followed by BCH in 14.4%.

9) Out of the 90 cases, squamous metaplasia was seen in 38 cases (31.3%), atrophy in 33 cases (36.7%), Calification 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%).

10) Out of 33 cases of atrophy, Cystic atrophy comprised of 81.8% of all atrophies, followed by simple and partial atrophy (9.1%) each.

11) 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.

12) The association between Sr PSA levels (>20ng/ml) and PCa was found to be highly significant.

13) The Mean Sr PSA levels in PCa is 71.1± 34.4 ng/ml, much higher than the mean Sr PSA of NH (8.3± 8.6 ng/ml).

14) The association between Sr PSA levels and inflammatory aggressiveness was found to be significant.

15) The Mean prostatic size is 50± 22.8 ml for HPIN, and 49.8 ± 27.2 ml for LPIN

16) The association between inflammatory grade/ Inflammatory aggressiveness and prostatic size was found to be highly significant.

17) 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.

18) A significant association was found between the PI >25 and PCa with a chi-square of 38.77 and degree of freedom = 3.

19) The association between Sr PSA levels and PI was found to be highly significant**.**

20) The mean PI of PCa is 42.1± 11.9 and NH is 7.6 ± 9.9 %.

21) Multiple logistic regression suggest that Ki-67 acts as an independent parameter to indicate malignancy.

22) 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%)

CONCLUSION

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%). The elderly age group is most commonly afflicted with prostatic diseases. A high grade of inflammation was seen in three-fourths of the cases and it bears as significant association with increase in prostatic size. Inflammatory aggressiveness is significantly associated with increase in Sr PSA levels and also prostatic size. 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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ANNEXURES

PROFORMA CASE NO._____

Name: _____ Age: Biopsy No. :_____ Hospital No.:__

C.Presentations: Difficulty in passing urine/ Urinary retention/ Burning micturation Urgency

Clinical Examination : Grade of prostatomegaly on P/R : _____

USG: Size:___ Hydrouretronephrosis: _____ PSA levels: _____

INFLAMMATION- Grade: Aggressiveness: Granulomas: Eosinophils:

ATROPHY- Diffuse: Focal: Partial/Complete(simple, cystic,hyperplastic)/Combined

Necrosis: Infarction: Sq.metaplasia: Reparative changes: Calcification:

BPH- More fibromuscular: More glandular: Both equal:

HYPERPLASIA- Cribriform: Papillary: Basal cell: Clear cell:

AAH: LPIN: HPIN: flat/ tufting/micropapillary/cribriform
Variant:Signet/Mucin/Foamy/Invert/Sm/C

Adenocarcinoma: Collagenous micrnodule

Perinueral invasion Glomeruloid formation

Intraluminal blue mucin Pink amorphous secretions

Mitotic & apoptotic figures Crystalloids

Amphophilic cytolplasm

Gleason Grade: Gleason Score:

Primary	secondary	Tertiary	Total

Ki-67	Glandular (500cells)	Stromal (500)	P.Index(%)

Ki-67 Intensity:

Mesenchymal Tumor: Any other type specify:

KEYS TO THE MASTERCHART

S.No- Serial Number

Clinical presentations: 1-Difficulty in micturation, 2- urinary retention

3- Burning micturition, 4- Urgency

I.G- Inflammatory grade

I.A- Inflammatory aggressiveness

SQ- Squamous metaplasia

F- Predominantly fibromuscular

G- Predominantly glandular

E- Both equal

Atrophy (A) : C-cystic, S-simple, P- partial

G- Granulomas present

HPIN type: T- Tufted, F- Flat, M-Micro papillary, C- Cribriform

Misc.- Miscellaneous

PCa F- Features in PCa

Collagenous micrnodules	C
Perineural invasion	PI
Glomeruloid formation	G
Intraluminal blue mucin	I
Pink amorphous secretions	P
Mitotic & apoptotic figures	M
Amphophilic cytoplasm	A

NA- Not applicable

S.NO	NAME	IP/OP	AGE	DIAGNOSIS	PSA	1	2	3	4	USG SIZE	I.GRADE	I.AGGRE	EOSINO	G	A	SQ	F/G/E	HYPERPLASIA	LPIN	HPIN	G.SCORE	Ki67	MISC.	Pca F
1	GOVINDAPPA	762438	65	NH	5.16	1		3		41	2	2	1				G	CP2	NA		NA	1.2		
2	MUNISWAMY	741730	70	NHH	26	1	2		4	77	2	2	2	G		1	E	CP2	NA	T	NA	35.1		
3	MUNISWAMY	758276	72	NHL	33.4		2	3	4	92.6	3	2	3	G			E	CP1	LPIN		NA	3		
4	PUTTAPPA	769780	70	NH	25	1	2			40.7	2	1	1			1	F	B	NA		NA	7.2		
5	VEERABHEDRA	767436	70	CA	100	1	2			27	1	1	1				G	NA	NA	C	8	42.5		PI+A
6	VENKATARAPP	692621	80	CA	100	1	2			26	1	1	1				G	NA	LPIN		10	56.3		PI+P+A
7	VENKATARAYA	692621	70	CA	100	1			4	39	2	2	1				G	NA	NA		9	47.4	NECROSIS	PI+G
8	VENKATAREDD	770901	69	NH	9.43			3		29	1	1	1		C		G	P2	NA		NA	2.4	NECROSIS	
9	CHOWDAPPA	773272	70	NHL	52.08		2			130	2	2	2			1	G	P2	LPIN		NA	23.4	MX	
10	MUNIVENKATA	722827	79	NH	8.64	1			4	42	2	2	2			1	G	C	NA		NA	1.6	MX	
11	MUNISWAMY	781049	60	NH	8.71	1	2	3		28	1	1	0			1	E	P1	NA		NA	1.5	CALCIFI	
12	NAWAB SAB	740887	65	NH	6.64				4	45	2	1	1				F	B	NA		NA	2.2	CALCIFI	
13	RAMAIAH	678607	85	NHL	7.2	1			4	52	2	1	1		C	1	F	NA	LPIN		NA	4.4		
14	NANJUNDAPPA	773215	71	NHL	6.67			3		39	2	1	2		C	1	G	P2	LPIN		NA	4.3	CALCIFI	
15	CHIKKANAKAT	785903	55	NH	6.41		2	3		38	2	2	1				G	P2	NA		NA	1.5		
16	NARAYANAPPA	785918	65	NH	6.1			3		42	2	1	0				G	P1	NA		NA	3	C+SN	
17	RAMACHANDRA	783380	65	NH	5.45		2		4	42	2	2	2		C		G	P1	NA		NA	1.2	C	
18	NASARAJ	791106	68	NH	17.03	1				30	1	1	0				E	CL	NA		NA	2.3		
19	MUNIYAPPA	604061	65	NH	4.45	1			4	95	2	3	2		P		G	NA	NA		NA	3.7	AAH	
20	MANKAPPA	794001	65	NH	5.05	1			4	40	2	1	0			1	F	P1	NA		NA	2.5	C	
21	SEETHA RAMAI	793190	70	NHL	9.77	1	2		4	42	2	1	1			1	G	P2	LPIN		NA	41	MX+SN	
22	RAMAREDDY	798784	94	NH	7.11	1	2			56	3	3	2		C	1	G	NA	NA		NA	1.9		
23	NADERPANNA	799248	70	NH	1.76	1		3		43.8	2	1	0		P		F	P1	NA		NA	4.5	C	
24	VENKATESHAPI	799627	76	NHL	8.2	1		3	4	65	2	1	0			1	G	P2	LPIN		NA	2		
25	SRINIVASAPPA	805912	55	NH	6.2			3		38	2	1	1			1	E	P2	NA		NA	1.4		
26	DEVARAYAPPA	806290	80	CA	13.78	1	2			34	2	1	2				G	NA	LPIN		7	33.5		PI+P+A
27	BALA SUNDARA	801679	79	NH	5.45	1	2		4	55	2	2	2		C	1	G	P2	NA		NA	1.3		
28	HANUMPPA	OP-812858	75	NHL	6.51	1			4	28	1	1	0			1	G	P1B	LPIN		NA	56.7		
29	NARASIMHAPPA	OP-814978	70	CA	32.42	1			4	42	2	1	1			1	G	NA	NA	M	9	49.4		C+P+A
30	MALLAPPA	813823	70	NH	7.2	1	2			52	2	2	2				G	P2	NA		NA	10.1	C	
31	KRISHNAPPA	814573	60	NHL	6.8		2	3		31	2	1	0				G	B	LPIN		NA	22		
32	NARAYANA GO	813155	80	NH	4.3	1			4	30	2	1	3				G	P2	NA		NA	16	SN	
33	KANNAIAH	818968	57	NH	4.42			3	4	45	2	1	0		C		F	NA	NA		NA	6.3		
34	MUNIVENKATA	818475	60	NH	1.23	1			4	60	3	2	1	G		1	F	P1CL	NA		NA	2		
35	DODDA MUNIY	820299	59	NH	4.73	1		3		26	1	0	0			1	F	CC	NA		NA	10.9		
36	PAPAMMA	818036	65	NHH	8.06		2	3	4	84	3	2	1		C	1	E	P2	NA	C	NA	32		
37	RAMACHANDRA	OP-	73	NHL	4.21	1	2			28	1	1	0				E	P1	LPIN		NA	9.4		
38	CHIKKANANJAP	815434	70	CA	41.22	1			4	32	2	2	2		C		G	P1	NA		7	48	SN	P+I+M
39	MUNIYAPPA	82406	75	NH	5.59	1	2	3		28	1	1	1				G	P2	NA		NA	5.6		
40	NANJAPPA	829759	85	NHL	6.2	1			4	44	2	1	1				G	P2B	LPIN		NA	4.4		
41	KONAPPA	829763	57	NHL	9.1	1		3	4	24	1	1	0			1	G	P2B	LPIN		NA	46.8		
42	KRISHNAPPA	819692	74	NH	6.21	1	2			35	2	1	0				G	P2C	NA		NA	11.4		
43	SYED GHOUSE	834980	70	CA	52		2		4	26	1	1	1				G	NA	LPIN		7	15	C	P+M
44	MUNIYAPPA	833119	70	NH	14.3	1	2		4	44	2	1	1		C		G	P1	NA		NA	1.9		
45	MUNISHAMAPP	837757	62	NHL	3.5		2		4	28	1	1	0		C		E	P1	LPIN		NA	2		
46	KRISHNAPPA	835007	70	NHL	7.1	1		3		42	2	1	2			1	G	P2	LPIN		NA	8.6		
47	KRISHNAPPA	840995	65	NHL	8	1			4	46	2	1	1		C	1	G	P1	LPIN		NA	60		

48	NARAYAN RAO	847498	85	NHH	5.1	1	2		4	48	2	1	0		C		E	P1	NA	FT	NA	50.6		
49	SRIRAM GOWDA	768415	60	CA	43	1	2			36	2	2	1				G	NA	NA		9	30.9		PA+M
50	NARAYANAPPA	843541	50	NH	6.4	1	2	3		54	3	2	1				G	NA	NA		NA	8.8	MX	
51	MUSTAFA SAB	848996	70	NH	6.2	1		3		35	2	1	0				G	P2B	NA		NA	2.3	AAH	
52	KRISHNA MURT	849741	78	NHH	10.2	1		3		24	1	1	0				G	P2C	NA	T	NA	44.9		
53	NARAYANAPPA	853510	70	NH	8.2	1			4	34	2	1	0		C		G	P2	NA		NA	1.9		
54	JOSEPH	853138	55	NH	3.24			3		25	2	1	1			1	E	B	NA		NA	7.4		
55	BALAPPA	852614	40	NH	4	1		3		30	2	1	2		C	1	G	P2	NA		NA	8.4		
56	BASAPA GOWDA	858243	65	NH	7.32	1			4	48	2	2	1		C		G	P1CL	NA		NA	3.8		
57	DEVAN	863105	60	NHH	9.9	1			4	29	1	2	0			1	E	P1B	NA	T	NA	22.4		
58	SRINIVAS	OP	45	NHL	11.21		2	3		56	2	2	1			1	G	P1B	LPIN		NA	32.2		
59	HARI HANUMAI	855149	70	NH	7.2	1			4	28	1	1	1		S	1	G	P1CL	NA		NA	5.4		
60	NANJE GOWDA	862047	65	NHL	5.4			3		26	1	1	1			1	G	P1B	LPIN		NA	17		
61	SARDAR	869186	55	NHL	35	1		3	4	60	3	2	2			1	G	P1	LPIN		NA	10.4		
62	NARAYANAPPA	869958	45	NH	3.2	1			4	24	1	1	1				G	P1	NA		NA	10.4	C+MX	
63	NANJUNDAPPA	870761	52	NHL	6.41	1			4	34	2	1	2				G	P2	LPIN		NA	30	SEC	
64	RAHMUTULLAH	869929	62	NHL	4.4			3	4	44	2	1	0				G	P2	LPIN		NA	57.6	C	
65	MUNIVENKATA	861678	80	NHL	5.34			3		42	2	1	0		P		E	P1	LPIN		NA	14.2		
66	MUNIYAPPA	871797	74	NHL	4.1	1			4	29	1	1	0		C		G	P2C	LPIN		NA	33		
67	NARAYANA GO	874212	72	NHH	5.32	1			4	40	2	1	1				G	P2C	NA	T	NA	38.6		
68	GOPINATH	877493	60	NHL	23.47	1	2		4	78	3	2	2		S		G	P2C	LPIN		NA	10.4		
69	BYRAPPA	878803	60	NHL	9.21	1			4	27	1	1	1		C	1	G	B	LPIN		NA	9.9	SN+TDYSPLASIA	
70	MUNIYAPPA	868353	75	NHL	6.231	1		3		48	2	1	2		C	1	G	P2	LPIN		NA	21.2	INFCT	
71	SHIVANANDIAH	878630	58	NH	5.21		2		4	30	2	1	1			1	F	NA	NA		NA	3.4	SN	
72	VENKATA CHAI	883484	62	NH	8.34	1	2			120	3	2	2			1	G	P1CL	NA		NA	7.2		
73	NAGAPPA	878711	50	NHL	7.21	1			4	42	2	1	1		C		G	P2B	LPIN		NA	8.1		
74	MUNIYAPPA	886463	60	NHL	3.1	1			4	55	3	1	1		C		G	P2C	LPIN		NA	37.2		
75	VENKATERHAP	885949	62	NH	15.23		2	3		86	2	2	2		C	1	G	P2C	NA		NA	18.2	SN	
76	MUNIVENKATT	886073	70	NH	4.2	1			4	26	1	1	1		C		G	NA	NA		NA	38.3		
77	GOPALLAPPA	897977	65	NH	5.1	1	2			86	3	2	3				F	NA	NA		NA	37	AAH	
78	HANUMAPPA	900721	65	NH	3.4	1	2	3	4	48	2	1	0				G	P3C	NA		NA	10.2		
79	SIDDAPPA	896316	70	NH	6.2	1			4	29	1	1	0			1	G	NA	NA		NA	6.2	AAH+SN	
80	KRISHNA SINGH	899765	70	NH	26.39		2			150	2	2	2		C	1	G	P1CL	NA		NA	44.5		
81	VASANTH KUM	883076	72	NH	52		2	3		52	3	2	2		C		G	P1	NA		NA	1.7		
82	THIPPAIAH	906918	75	NHL	53.21		2	3		130	3	2	2			1	G	P1	LPIN		NA	34.9	INFCTMX	
83	NANJAPPA	905026	62	CA	100	1		3		50	3	3	1				G	NA	LPIN		9	41.7		PI+I+P+M
84	SUBBA REDDY	904956	70	NH	4.31	1			4	42	2	1	0		C		G	P1B	NA		NA	4.4	MX	
85	CHINAPAIAH	888956	70	NHL	32.69	1	2			37	2	1	2		C	1	E	P2	LPIN		NA	20.8		
86	MUNIYAPPA	907221	75	NH	4.47	1	2			27	1	1	0		S			NA	NA		NA	1.6		
87	MUNIGIDDAPPA	911613	55	NHL	8.2		2	3		45	2	1	0			1	G	P1CL	LPIN		NA	33.7		
88	AMEER JAN	965700	57	NHH	53	1	2		4	48	2	1	0				G	P2	NA	M	NA	39.1		
89	CHIKKA GRADA	925046	82	CA	100	1		3	4	34	2	1	1				G	P1	LPIN		9	43.7		P+A
90	VENKATAPPA	865326	70	CA	100	1			4	38	2	1	1				G	P2	LPIN		10	54.8		PI+P+A