ROLE OF PROSTATE SPECIFIC ANTIGEN IN DIFFERENTIATING VARIOUS PROSTATIC PATHOLOGY

BY:

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CERTIFICATE

This is to certify that Dr. Prabhakar Kumar has worked under my direct supervision and guidance on the thesis entitled *ROLE OF PROSTATE SPECIFIC ANTIGEN IN DIFFERENTIATING VARIOUS PROSTATIC PATHOLOGY.* The work done in connection with this thesis is genuine and was done by the candidate himself.

Guide

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DEDICATED TO MY TEACHERS AND MY LATE MOTHER MRS. NAIN DEVI

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ABSTRACT

The main objective of this study was to see relationship between histopathological diagnosis and total serum PSA values, correlation between weight of the prostate and serum PSA levels and also the sensitivity and specificity of serum PSA values in differentiating benign and malignant lesions of the prostate.

Fifty prostatectomy specimens were studied during a study period from 1st January 2003 to 30th December 2003 at Department of Pathology, TU, Teaching Hospital, Institute of Medicine. Patients with history of enlarged prostate were studied. Blood samples were collected pre-operatively at the time of admission and detail clinical history was obtained along with USG findings.

Histopathological sections were stained by Haematoxylin and Eosin for microscopic features. Total serum PSA level estimation was done using PSA serozyme kit, manufactured by adaltis Italia S.P.A, via Magnanelli, 2, Italy.

The commonest disease encountered was benign prostatic hyperplasia (40%), Adenocarcinoma (18%), benign prostatic hyperplasia with chronic prostatitis (26%), benign prostatic hyperplasia with stromal hyperplasia (2%) and prostatic intraepithelial neoplasia (14%)

All 7 cases of prostatic intraepithelial neoplasia diagnosed as PIN-grade 1 and among malignant cases, 4 cases found to be well differentiated, 3 moderately differentiated, 2- poorly differentiated adenocarcinomas.

Majority of the malignant tumors were found between age group 70-79 years, whereas most of the benign lesions also in the same age group.

The results of this study highlighted that 51.2% cases of benign lesions had values less than or equal to 4 ng/ml, 48.8% had values between 4.1-10 ng/ml, sensitivity of 100% and specificity 51.2%.

77.8% of prostatic carcinoma showed elevate serum PSA values, (> 10ng/ml) with p value=.000004, and serum PSA values (>50 ng/ml) in 44.4% of cases with significant p. value=.001.

The total serum PSA values in all cases of Prostatic Intraepithelial Neoplasia (PIN) were found to be in between 0.4-10 ng/ml. Similarly, the weight of the prostate didn't correlate with elevated serum PSA values, P value = 0.761 also Karl Pearson Correlation (r)= -0.044.

The test has a high sensitivity and specificity, is rapid, and inexpensive, and is minimally invasive. Therefore, serial annual PSA measurements may provide an alternative means of screening men over 50 years of age.

ABBREVIATIONS

PSA	=	Prostate Specific Antigen
BPH	=	Benign Prostatic Hyperplasia
PIN	=	Prostatic Intraepithelial Neoplasia
AAH	=	Atypical Adenomatous Hyperplasia
USG	=	Ultrasonography
W.D.	=	Well- Differentiated
M.D.	=	Moderately Differentiated
P.D.	=	Poorly Differentiated
ng/ml	=	Nanogram per milliliter
TURP	=	Trans-urethral Resection of Prostate

1. INTRODUCTION

The pathologic processes, which affect the prostate gland with sufficient frequency to merit discussion are: inflammation, benign prostatic hyperplasia Prostatic Intraepithelial Neoplasia (PIN) and malignancy. [1]

Benign prostatic hyperplasia is extremely common disorder in men over age 50. 20% of the men suffer with this lesion, which increases to 70% by age 60 and 90% by age 80.[2]

Carcinoma of the prostate is the most common form of cancer in males and third leading cause of death cancer. Prevalence of latent prostatic cancer is even higher, 30%. Most cases of prostatic carcinoma are diagnosed after age of 50 years, but they can be seen in younger adults and even in children. [2]

The frequency of high grade prostatic intraepithelial neoplasia in recent biopsy series is 4 to 16 percent. Some patients present with elevated prostatic specific antigen levels, but this is likely to be due to undetected invasive carcinoma. Elevated serum PSA level upto 20 ng/ml has been associated with PIN.[2]

Although the etiology of benign prostatic hyperplasia and prostatic carcinoma is unknown, hormonal factors and several epidemiological risk factors have been studied.[3]

Many of these pathologic process, which affect the prostate gland are associated with elevated serum PSA levels. PSA is biochemically a glycoprotein, is the most valuable tool available for the early diagnosis and staging o the prostate cancer and one of the most widely used laboratory tests in oncology. Serum PSA can detect twice as many prostate cancers

as digital rectal examination can and approximately 70% of these cancers are potentially curable.[4]

In our country, many elderly men are unaware that something can be done for their troublesome urinary symptoms. It was therefore proposed to study the values of serum PSA levels in different prostate pathology, correlation between weight of the prostate and serum PSA level and sensitivity and specificity of serum PSA level in early detection of prostate cancer.[1]

2. LITERATURE REVIEW

2.1 The prostate gland

The male prostate gland is located below the bladder. The seminal vesicles are located posterior to the prostate. The urethra exists from the bladder and traverses the prostate before existing to the penile urethra. [1]

2.2 Anatomy and physiology

The prostate is a pear-shaped glandular organ that weighs 20 to 30 gm.[2] Traditionally, it has been divided into five lobes. These five lobes include a posterior, middle, anterior and two lateral lobes. Histologically, the prostate is composed of glands and stroma. The glands are seen in cross section to be rounded to irregularly branching. The glands are lined by two cell layers: an outer low cuboidal layer and inner layer of tall columnar mucin-secreting epithelium. These cells project inward as papillary projections.[3] The secretary cells, which are located in the luminal side of the gland, contribute a wide variety of products to the seminal fluid. They produce Prostatic Acid Phosphatase (PAP) and Prostatic Specific Antigen (PSA). Secretary cells also co-express low molecular wt. keratin and vimentin. The fibromuscular stroma between the glands accounts for about half of the volume of the prostate.[4,5]

As a male ages, there are more likely to be small concretions within the glandular lumina, called corpora amylacea, that represent laminated concretions of prostatic secretions. The glands are normally separated by stroma.[6,7] The prostate is surrounded by a thin layer of connective tissue that merges with surrounding soft tissues, including nerves. There is no distinct capsule. Prostatic stromal cells have been found to contain androgen receptors.[8]

2.3 Pathologic processes [1]

Broadly, the pathologic process that affect the prostate with sufficient frequency to merit discussion can be divided into:

1) **Benign lesions**
   - Inflammation
   - Hyperplasia
   - Others

2) **Precancerous lesions**
   - Prostatic Intraepithelial Neoplasia (PIN)
   - Atypical Adenomateus Hyperplasia

3) **Malignancy**

2.4 Inflammations [1]

Prostatitis: may be divided into three categories:

a. Acute bacterial prostatitis:
b. Chronic bacterial prostatitis
c. Chronic abacterial prostatitis

2.4.1 Acute bacterial prostatitis: is not common.

Causative agents: include bacterial organisms similar to those causing urinary tract infections.

- Strains of E.Coli
- Other gram-negative rods.
- Enterococci
- Staphylococci and
- Neissesia gonorrhaea

- Surgical manipulation on the urethra a prostate gland.
- Examples are:
  - Catheterisation.
  - Cystoscopy
  - Urethral dilation and
  - Resection procedure

Pathogenesis The organisms become implanted in the prostate usually by intraprostatic reflux of urine from the posterior urethra or from the urinary bladder. Occasionally, they seed the prostate by the lymphohematogenous routs from distant foci of infection.

Clinical features

- Fever
- Chills and
- Dysuria

Per Rectal Examination *(P/R)* Prostate is exquisitely tender and boggy.

Microscopically The glands are filled with neutrophills and the intervening stroma may also contain a few neutrophils.

Diagnosis can be established by urine culture and clinical features.

4.2. Chronic bacterial prostatitis: [7]

- Difficult to diagnose and treat.
- In some cases, bacterial organisms can be cultured from urine that indicate the etiology. A common historical characteristic to recurrent urinary tract infections- cystitis and urethritis.

Pathogenesis Most antibiotics penetrate the prostate poorly, bacteria find safe haven in the parenchyma and constantly seed the urinary tract.

Clinical features

- Dysuria
- Low-back pain
- Low grade pelvic pain
- Suprapubic discomfort

Microscopically Lymphocytes, Plasma cells and macrophages as well as neutrophils appear in the stroma.

Diagnosis depends on the documentation of leucocytosis in the expressed prostatic secretions along with positive bacterial cultures in the prostatic secretions.

2.4.3. Chronic abacterial prostatitis [1] most common form of prostatitis seen today.

Clinically, inidistinguishable form chronic bacterial prostatitis. There is no history, however of recurrent urinary tract infections. Expressed prostatic secretions contain more than 10 leukocytes per high power field, but bacterial cultures are uniformly negative. The affected patients are usually sexually active men. Several sexually transmitted pathogens have been implicated.

- C. trachomatis.
- Ureaplasma urealytium and;
- Mycoplasma hominis.

Microscopically lymphocytes, plasma cells and macrophages appear in the stroma.

2.5 Abscess [3]

Causative agents : Neisseria gonorrheae
: Escheria coli

Clinical features : Acute urinary retention
: Perineal or suprapubic pain

On Digital Examination Prostatic fluctuation i.e. the most characteristic sign.

Transrectal ultrasonography is the most reliable diagnostic methods.

2.6 Radiation effect [2]

This is the most common form of "reactive atypia" in the prostrate.

Cytologic features

Enlargerd and hyperehromatic nucleli with prominent nucleoli present in approximately three quarters of radiated prostate. The "Spotty" nature of the atypia, being seen in some acini and not in others. In benign glands cytologic atypia involves both secretory and basal cells, resulting in an atypia that has a more heterogeneous appearance than usual in carcinoma.

Other radiation induced changes in the prostate include a decrease in the ratio of neoplastic glands to stroma, atrophy, squamous metaplasia, and basal cell hyperplasia, stromal fibrosis with atypical, fibroblasts, occasional foreign body giant cells initial proliferation of arteries, and foam cells in vessel walls.

2.7 Eosionophilic prostatitis (allergic prostatitis, allergic granuloma of prostate): [3]

Characterized by small stellate necrobiotic nodules surrounded by palisading epithelioid histiocytes, eosinophils resembling rheumatoid nodules. Vasculitis may be found. Patients often have a history of allergy and asthma and usually exhibit peripheral eosinophilia. Elevation of serum PSA levels may occur.

2.8 Urethral polyps [3]

Composed of tall columnar cells of prostatic origin are a common source of hematuria in young adults. They may have a villous configuration ("Villous Polyps") and tend to be found in the verumontarum but also along most of the posterior and lateral surfaces of the prostatic urethra.

They stain intensely for both PAP and PSA.

2.9 Classification of Granulomatous Prostatitis [2]

1. **Infections**

   Bacterial

   Tuberculosis

   Brucellosis

   Syphilis

   Fungal

   Coccidioidomycosis

   Cryptococcosis

   Blastomycosis

   Histoplasmosis

   Para coccidioidomycosis

Parasitic

Schistosomiasis

Echinococcosis

Enterobiasis

Viral

Herpes virus infection

II **Iatrogenic**

Postsurgical

Postradiation

BCG induced

Teflon- associated

III **Malakoplakia**

IV **Systemic granulomatous disease**

- Allergic
- Sarcoidosis
- Rheumatoid arthritis
- Autoimune
- Wegener's granulomatosis
- Polyartertis nodosa
- Benign lymphocytic angitis and granulomatosis
- Churg strauss disease

V. **Idiopathic ("Non-specific")**

Typical nonspecific granulomatous prostatitis

Xanthoma-xanthogranulomatous prostatitis.

Others:

2.10 Tuberculosis and BCG- induced granulomas[3]

The prostate is the organ most commonly involved in tuberculosis of the male genital system. In most cases, the infection is the result of hematogenous spread from the lungs (or less often, from the skeletal system). May also result from direct invasion from the urethra. On palpation, fluctuant, tender zones may be felt.

Grossly

Usually, bilateral confluent caseous zones occur with liquefaction and caseation. Later, the prostate becomes an enlarged organ with multiple cavities. It may perforate membranous urethra and extend into the urinary bladder sinus tract may form into the rectum, perineum and peritoneal cavity. Healing with calcification can be detected by radiographic examination. In advanced stage, the prostate becomes shrunken fibrotic and hard, to the point that it may stimulate carcinoma on palpation.

Microscopically

Well-developed lesions show confluent foci of caseation with incomplete fibrous encapsulation. There is little tendency for the formation of typical tubercles.

Patients treated with intravesical Bacillus Calmete Guerin (BCG) for bladder carcinoma may develop granulomas in the prostate similar to those seen more often in the bladder. These granulomas may be of non-caseating or caseating type. Stains for acid-fast organisms are usually negative, although occasionally a few organisms are visualized.

2.11 Malakoplakia [3]

- Can involve the prostate with bladder disease.
- Patients with malakoplakia of the prostate gland usually have an enlarged gland.
- In early phase of malakoplakia, there are numerous hostiocytes with esinoplilic cytoplasm (Ven Hansemann Histocytes). The admixed inflammatory infiltrate, atleast focally lack of small acinar diffrentiation, and identification of the typical Michaelis-Guttmann bodies are all helpful. In classic and late stages of the process there is admixture of inflammatory cells (lymphocytes, plasmacells neutrophils and histiocytes, whereas in the latter the fibrous imparts a picture dissimilar to that of prostatic carcinoma.

- The immunohistochemical demonstration of histocytic markers (CD 68) resolve this differential diagnosis but are rarely required.

2.12 Postoperative spindle cell nodule and post needle biopsy changes [2]

The designation "postoperative spindle cell nodule" was given in 1984 to a proliferative spindle cell lesion that developed in the lower urinary tract of five men and the lower genital tract of four women. All of the lesions developed within 3 months after a surgical procedure at the same site. Three of the lesions in men were found in transurethral resections of the prostate following a similar procedure.

Microscopic examination reveals intersecting fascicles of spindle cells which often show striking mitotic activity (upto 25 mitotic figures per 10 high- power fields), resulting in a marked resemblance to a sarcoma. The cells, however, do not exhibit high-grade cytologic atypia. Additional microscopic features include prominent blood vessels, which are often small; scattered acute and chronic inflammatory cells; small foci of hemorrhage; mild to moderate edema; focal myxoid change in the stroma. In some cases, a granulamatous process with fibrinoid change.

2.13 Inflammatory pseudotumor (pseudosarcomatous fibromyxoid tumour) [5]

Only a few prostatic examples have been encountered to-date, all in adults, There may be significant enlargement of the prostate gland, mimicking a neoplasm. On microscopic examination, there is a proliferation of spindle cells in a loose edematous to myxoid stroma that is prominently vascular and typically contains many acute and chronic inflammatory cells.

The nuclei of the spindle-shaped cells may be moderately hyperchromatic with a mild degree of pleomorphism, and there is often abundant eosinophilic cytoplasm, these features could potentially lead to confusion with rhabdomyoblasts. Mitoses are usually seen, but atypical mitotic figures are not. Immunohistochemical and ultrastructural examination has shown features of myofibroblasts.

2.14 Calculi [3]

Prostatic calculi are seen in about 7% of prostate with modular hyperplasia.

Pathogenesis

The corpora amylacea seen in glands with nodular hyperplasia may act as the nucleus for stone formation as a result of improper drainage infection of the acini, and calcium deposition. Blood clots, epithelial detritus and bacteria are also present in the stone nucleus. The main inorganic elements are phosphated salts (calcium, magnesium, aminomagnesium, potassium), calcium carbonate, and calcium oxalate.

Because of their extreme hardness as carcinoma on palpation. They are radiopague and can be easily detected by radiographic examination. If extremely large and numerous they may require a prostatectomy.

2.15 Infarct [7]

Infarct of the prostate occurs predominantly in large prostates, that exhibit modular hyperplasia.

Etiolosy:

- Unknow.
- Prostatitic infection
- Trauma: Indwelling catheter
- Cystitis
- Prostatitis

Pathogenesis: As a result of thrombosis of the intraprostatic portion of the urethral arteries.

Grossly

Vary in size from a few millimeters upto 50 cm. They are speckled, greyish yellow and often contain streaks of blood. The peripheral margins are usually sharp and hemorrhagic and may impinge on the urethra.

Microscopically

The infarcts are of ischemic type with sharply outlined areas of coagulative necrosis involving glands and stroma. Prominent squamous metaplasia may develop in the ducts at the periphery of the infarct.

Clinical features

Most infarcts are clinically silent. Occasionally, they cause acute retention because of the accompanying edema. They may cause serum elevation of PAP and PSA.

2.16 Endometriosis [5]

Beckman and Colleagues described a unique case in which endometriosis involved the prostate of a 78 year old man who had received estrogen for almost 6 years for treatment of adenocarcinoma of the prostate. The patient developed gross hematuria and investigation disclosed a small raised area proximate to the internal urethral orifice that was clinically suspicious for a neoplasm. A transurethral resection disclosed involvement of prostatic tissue by endometriosis with the typical glandular and stromal components.

2.17 Verumontanum [5]

Because of the closely packed small acini, the process can be confused with prostatic adenocarcinoma on needle biopsy. Findings helpful in indicating the non-neoplastic nature of this process include awareness of the histologic features of the glands of the verumontanum, including the distinctive orange- brown luminal secretions, the presence of basal cells, the lack of prominent nucleoli and the frequent lipofuscin pigment.

2.18 Paraganglia [9]

Paraganglia may be present in prostate specimens and may result in a misdiagnosis of cancer. Paraganglia appear as small clusters or nests of cells with clear to eosinophilic or amphophilic cytoplasm and may display a " zellballen" arrangement.

They usually occur in the periprostatic soft tissue but may rarely be present in the lateral prostatic stroma. Nuclear atypia may provoke concern for carcinoma, but the atypia has the dense chromatin quality and facility typical of degenerative atypia. Positive immunoreaction for chromgramin and negativity for PSA and PAP help in the differential with carcinoma

2.19 Classification of Prostatic Hyprplasia [2]

I. **Benign Nodular Hyperplasia**

- Usual patterns
- Glandular
- Stromal
- Mixed

Special Patterns

- Epithetial Predominant
- Small Glandular
- Cribriform
- Cribriform
- Basal cells
- Stromal
- Leiomyomatous
- Mixed glandular-stromal
- Fibroadenoma-like
- Phyllodes-like

II **Atrophy- associated hyperplasia**

- Basal cell hyperplasia
- Postatrophic hyperplasia

III **Atypical Adenomatous hyperplasia-**

- Adenosis

2.20 Benign nodular hyperplasia (also termed benign prostatic hyperplasia or BPH):

Definition

Benign nodular hyperplasia represents nodular expansion of prostatic glandular elements, stromal elements or both. [2]

2.20.1 Incidence

Nodular hyperplasia can be seen in approximately 20% of men 40 years of age, 70% by age 60 and 90% by age 70. However, in only a minority of cases (about 10%) will this hyperplasia be symptomatic and, severe enough to require surgical or medical therapy. In men older than 65 yrs. of age, TURP is second only to cataract extraction. [1]

2.20.2 Etiology and Pathogenesis of nodular hyperplasia[2,10,11,13]

- Remain poorly understood.
- A number of factors, including marital status, socio-economic status, and libido, diseases such as diabetes mellitus, hypertension and cirrhosis have been investigated and are not thought to be etiologically related to nodular hyperplasia.
- Age is clearly ad important factors as evidenced by its
  strong correlation with the prevalence of nodular hyperplasia.
- Moderate alcohol consumption and avoidence of smoking may benefit BPH.

The mechanism for hyperplasia may be related to accumulation of dihydrotestosterone in the prostate, which then binds to nuclear hormone receptors, which then trigger growth. The effect of drugs which act to inhibit the enzymes 5 alpha reductase, which converts testosterone to dyhydrotestoster-one (DHT) within cells.

This blocks the growth promoting androgenic effect and diminishes prostatic enlargement. Such drugs include finasteride and episteride.

With increasing age there are elevations in estrogenic coumpounds, principally 17-B estradiol and estrone, which are produced by peripheral conversion of testosterone and androstenedione respectively which also serve in the pathogens of nodular hyperplasia.

Nodular hyperplasia preferentially involves the proximal periurethral tissues (so called estrogen sensitive zone). In the anatomic model of MC Neal, the tissue surrounding the proximal urethral segment include the submucosal compartment, the specialised mesenchyme of the preprostatic sphincter and the transition zone.

The earliest lesion of nodular hyperplasia in the transition zone consists of epithelial budding. [12,13]

Clinical Features [2]

About 50 percent of patients with grossly enlarged glands develop prostatism. The symptoms of prostatism may be categorized as either obstructive or Irritative.

Obstructive symptoms include

- hesitancy
- weak stream and;
- terminal dribbling.

Irritative symptoms include

- urgency
- frequency
- dysuria and
- nocturia
- infection

In severe cases the bladder incompletely drains leading to stagnant residual urine and cystitis; long standing bladder neck obstruction results in bladder dilatation, hypertrophy and trabeculation. This may be complicated by hydroureter and hydronephrosis and eventually chronic pyelonephritis and renal insufficiency. Patients may present with acute urinary retention resulting from a complete blockage of flow at the level of the proximal prostatic urethra.

Patients with benign prostatic hyperplasia may have elevations in their serum Prostatic Specific Antigen (PSA) level in the absence of prostatic adenocarconoma. Since the prevalence of benign hyperplasia increases with advancing age, age specific values for the general population is given in the table:-

On digital rectal examination [3]

- The prostatic gland is typically large and may have a nodular contour.

- The enlargement is often symmetric and the texture is rubbery.
- Tenderness may bye present, especially if there is superimposed prostatitis.

Gross findings [3]

Most prostate with nodular hyperplasia can weigh from 50 to 100 gm. Not uncommonly, aggregate weights of upto 200gm are encountered. Multinodular masses of variable sized that are occasionally massive are seen. Nodular hyperplasia of the prostate originates almost exclusively in the inner aspect of the prostate gland, in the transitional and periurethral zones. Th first nodules composed almost entirely of epithelial cells arise from the transitional zone; later predominantly stromal nodules arise in the periurethral zone.

Sectioning shows nodules that may be bulging are often numerous and range in size from millimeters to several centimeters. They are usually tan-white and firm but may be spongy and honeycomb like due to interspersed cysts or occasionally predominantly cystic. The nodules do not have true capsules, the compressed surrounding prostatic tissue, creates a plane of cleavage about then used by the surgeon in the condition of prostatic masses in so called suprapubic prostatectomies.[1]

Pure stromal nodules may have a tan-gray to white whorled appearance similar to uterine leiemyomas. Secondary infarction may be present and is characteristically either yellow or red depending on the amount of blood [5]

Microscopic Findings [11]

Microscopically, the modularity may be due to glandular proliferation a dilatation or to fibrous or muscular proliferation of the stroma. Although all_three elements are involved in almost every case. The stromal (fibroblastic) component predominates in most cases. Glandular proliferation takes the form of aggregations of small to large to cystically dilated glands lined by two layers, an inner columnar and an enter cuboidal or flattered epithelium, based on an intact basement membrane. The epithelium is characteristically thrown up into numerous papillary buds and infoldings, which are more prominent than in the normal prostate. Two other histologic changes are frequently found:

1) Foci of squamous metaplasia and;

2) Small areas of infarction. The former tend to occur in the margins of the foci of infarction as nests of metaplastic, but orderly, squamous cells. Common patterns of modular hyperplasia are epithelial predominant, stromal and mixed, nodular hyperplasia is not a precursor to carcinoma.

2.20.3 FRANKS' classification of hyperplastic nodules [2]

1. The stromal (fibrous or fibrovascular) nodule.
2. The fibromuscular nodule.
3. The muscular nodule ("leiomyoma")
4. The fibroadenomatous nodule
5. The fibroadenomatous nodule.

2.20.4 Special Histologic Patterns

1. Small glandular hyperplasia [2]

This is a variant of the epitherlial- dominant pattern of nodular hyperplasia in which there is a circumscribed proliferation of relatively small glands in a fibromuscular stroma. The secretary cells are often less columnar than in typical modular hyperplasia. The basal cells may be increased. The small glandular variant of nodular hyperplasia in distinguished from atypical adenomatous hyperplasia by its more uniform appearance, more commonly associated stromal hyperplasia and absence of parent ducts.

2. Cribriform hyperplasia[3]

This is an uncommon variant of nodular hyperplasia in which part of the epithelial component consists of medium to large glands with a cribriform architecture. The cells comprising the cribriform glands may have abundant clear cytoplasm. The cells living the glands have uniform nuclei with fine chromatin and inconspicuous nucleoli. The stroma around the cribriform glands is usually similar in appearance to that of mixed hyperplastic nodules.

3. Leiemyomatous Nodules [5]

Occasionally, nodular hyperplasia is characterised by stromal nodules with prominent smooth muscle differentiation. Leiomyomatous hyperplasia is often cellular with mild nuclear variability and, rarely, occasional necrosis; atypical mitoses are not seen. Infarction may be present and mimic tumour necrosis. Diagnosis greater than 1 cm. composed purely of smooth muscle elements, and lacking and admixed fibroblastic proliferation or prominent thin walled vessels.

4. Fibroadenoma-like hyperplasia [14]

Hyperplastic patterns in which the glands and cellular fibrovascular stroma are organized in a fashion similar to fibroadenoma of the breast. Rare being noted in only 1% of cases of nodular hyperplasia.

5. Phyllodes- type hyperplasia [2]

Sometimes myxoid, stromal proliferation, usually associated with cleft-like spaces with intralumial polypoid projections, imparts a pattern similar to a phyllodes tumour of the breast. Phyllodes-like hyperplasia is very rare and typically associated with usually nodular.

2.21 Basal cell hyperplasia [5]

Basal cell hyperplasia is typically found in the transition zone and is therefore usually identified in transurethral resection prostatectomy specimens, but it may be encountered, infrequently in needle biopsies.

Microscopic finding

The normal prostatic ducts and acini have a well-defined basal cell layer, which may undergo proliferation. The baseline nests and cords are often solid (complete basal cell hyperplasia), but tubules occasionally liked by secretary cells may be seen (incomplete basal cell hyperplasia). The basal cells are multilayered and relatively uniform, with a high nuclear to cytoplasmic ratio. The nuclear chromated is evenly distributed. Small amounts of pale eosinophilic cytoplasm are apparent rarely, the cytoplasm is more conspicuous and clear. When tubules are present, they are lived by cuboidal or low columnar cells with basically located, round, uniform nuclei and apical clear to light eosinophilic cytoplasm. Sometimes, psammoma body-like structure and calcofrcation may be noted. Focal keratinining or non-keratinning squamous metaplasia may also be present. The stroma of basal cells hyperplasia usually resembles the fibroblastic a fibromuscular stroma of ordinary nodular hyperplasia but may be more cellular and occasionally myxoid.

The stroma of basal cell hyperplasia usually resembles the fibroblastic a fibromuscular stroma of ordinary nodular hyperplasia but may be more cellular and occasionally myxoid.

The nuclei of the hyperplastic basal cells are typically small, round to oval and uniform and lack prominent nucleoli or pleomorphism. When nuclear enlargement nodular prominence, hyperchromasia ad mitoses are identified the term 'Atypical basal cell hyperplasia" to be used. Prominent nucleoli are occasional seen in the basal cells in the absence of basal cell hyperplasia.

2.22 WHO histological classification of tumours of the prostate [15]

Epithelial tumours

Glandular neoplasms

Adenocarcinoma (acinar)

- Atrophic
- Pseudohyperplastic
- Foamy
- Colloid
- Signet ring
- Oncocytic
- Lymphoepithelioma-like

Carcinoma with spindle cell differenatiation

(Carcinosarcoma, sarcomatoid carcinoma)

Prostatic Intraepithelial Neoplasia (PIN)

Prostatic Intraepithelial Neoplasia,grade III (PIN III)

Ductal adenocarcinoma

- Cribriform
- Papillary
- Solid

Urothelial tumours
Urothelial carcinoma

Squamous tumours
Adenosquamous carcinoma
Squamous cell carcinoma

Basal cell tumours
Basal cell adenoma
Basal cell carcinoma

Neuroendocrine tumours
Endocrine differentiation within adenocarcinoma
Carcinoid tumour
Small cell carcinoma
Paraganglioma
Neuroblastoma

Prostatic stromal tumours
Stromal tumour of uncertain malignant potential
Stromal sarcoma

Mesenchymal tumours
Leiomyosarcoma
Chondrosarcoma
Rhabdomyosarcoma
Angiosarcoma
Malignant fibrous histiocytoma
Malignant peripheral nerve sheath tumour
Haemangioma
Chondroma
Leiomyoma
Granular cell tumour
Haemangiopericytoma
Solitary fibrous tumour

Hematolymphoid tumours
Lymphoma
Leukaemia

Miscellaneous tumours
Cystadenoma
Nephroblastoma (Wilms tumour)
Rhabdoid tumour
Germ cell tumours

- Yolk sac tumour
- Seminoma
- Embryonal carcinoma & teratoma
- Choriocarcinoma

Clear cell adenocarcinoma
Melanoma

Metastatic tumours

Tumours of the seminal vesicles

Epithelial tumours
Adenocarcinoma
Cystadenoma

Mixed epithelial and stromal tumours
- Malignant
- Benign

Mesenchymal tumours
Leiomyosarcoma
Angiosarcoma
Liposarcoma
Malignant fibrous histiocytoma
Solitary fibrous tumour
Haemangiopericytoma
Leiomyoma

Miscellaneous tumours
Choriocarcinoma
Male adnexal tumour of probable Wolffian origin

Metastatic tumours

2.23 Prostatic Intraepithelial Neoplasia (PIN)[2]

Definition

Prostatic Intraepithelial Neoplasia (PIN), which is dysplasia of the epithelium lining prostate glands, is a probable precursor of prostatic carcinoma.[2]

General features

PIN is found predominantly in the peripheral zone of the prostatic rarely in the central zone and extremely rare in the transition zone. PIN is multifocal, and prostates with carcionoma has a greater number of few of PIN than prostatic without cancer. The appearance of PIN may precede carcinoma by 10 a more year.[16]

In 1986 MC Neal & Bosturik, whole studying 100 serially blocked prostate adenocarcinomas and 100 benign prostates obtained at autopsy, gave a further account of the significance of PIN as a precursor of invasive carcinoma; in this study 82 prostates with carcinoma and 43 benign prostates contained foci of PIN. They reported that high grade lesions (grade 3) were more common in prostates with carcinoma (33%) than in those without carcinoma (4%) and concluded that in the majority of prostate cancers, PIN may be the antecedent lesion. [17,18]

Clinical features

There are no specific associated clinical features. PIN doesn't routinely increase the serum Prostate Specific Antigen (PSA), however, some patients present with elevated Prostate Specific Antigen (PSA) levels, but this is likely often due to undected invasive carcinoma. PIN does not cause a gross abnormality. Low grade PIN may be found even in men in middle age. [18]

The appearance of PIN warrants increased surveillance of the prostate for development of an invasive carcinoma because the presence of PIN that is high grade suggests an increased risk for subsequent appearance of adenocarcinoma. PIN itself is not an indication for aggressive treatment. [19,20]

Microscopic findings

PIN usually involves an acinus or a small cluster of acini, but it can be more extensive on occasion. The acini are usually medium-sized to large, with rounded borders. The partial involvement of an acinus is helpful feature to distinguish PIN from adenocarcinoma. PIN is characterized histologically by progressive basal cell layer disruption, loss of markers of secretary differentiation, nuclear and nucleolar abnormalities increasing proliferative potential, increasing microvessel density, variation in DNA content and allelic loss. Unlike adenocarcinoma with which it may coexist, glands with PIN retain and intact a fragmented basal cell layer [21,22,23,24]

2.23.1 Grading of Prostatic Intraepithelial Neoplasia (PIN) [5]

1) Low-grade PIN (grade-1): is characterised by:
   i) A slight increase in cellularity
   ii) Some variation in nuclear size.
   iii) Focal hyperchromasia.
   iv) Appearance of small nucleoli.

2) High-grade PIN (grades 2 and 3): is characterized by:
   i) A definitive increase in cellularity
   ii) Nuclear pseudostratification and
   iii) Hyperchromasia.
   - The hallmark of high-grade PIN is the presence of large nucleoli (few in PIN grade 2 numerous in PIN grade 3) which is larger than 1 μm.
   - Mitotic figures are uncommon in PIN, but can be seen.
   - High grade PIN exhibits a variety of architectural patterns: tufting, micropapillary, cribriform or flat.

2.24 Atypical Adenomatous Hyperplasia [25,26]

Atypical Adenomatous Hyperplasia (AAH) is a term that has been utilized to describe changes histologically seen in prostatic glands in the apex, periurethral region, and/or transition zone of the prostate. AAH is a localized proliferation of small acini within the prostate. Such proloferations may be confused with carcinoma, but the glands with AAH still have a fragmented basal layer. AAH can be difficult to distinguish from hyperplasia. There is no clear association between the presence of AAH and the development of prostatic adenocarcinoma.

2.25 Prostatic Adenocarcinoma

2.25.1 General features [2]

Adenocarcinoma of the prostate is common. It is the most common non-skin malignancy in elderly men. It is rare before the age of 50, but autopsy studies have found prostatic adenocarcinoma in over half of men more than 80 year of old. Many of these carcinomas are small and clinically insignificant. However, some are not, and prostatic adenocarcinoma is second only to lung carcinoma as a cause for tumour related deaths among males.

2.25.2 Etiology and Pathogenesis [27,28,29,30,31]

- Poorly understood
- High risk patients include- older age
- Black race
- Family history

Those with an affected first-degree relative have double the risk.

- Viruses: herpes simplex virus type II
  - Cytomegalo virus
  - RNA viruses
- Cadmium exposure
- Occupational factors- workers exposed to chemicals in the rubber, textile, chemical drug, fertilizer
- High fat diet.
- Vit. A deficiency and increased Vit. A intake
- Vit. D deficiency
- Underwent vasectomy
- Increased and reduced sexual activity.

- Hormonal activity increase concentration of testosterone, dihydrotestostenne and androsteredione
- Chemical carcinogens, radiation therapy ad hormone administration.
- PIN-high grade
- Atypical adenumatous hyperplasia -(not exactly known)

2.25.3 Clinical features

- Patients are most often asymptomatic
- Extensive tumors may cause patients to present with pelvic pain, rectal obstruction or bleeding.
- Bladder obstruction are also common.
- Presenting symptoms of metastatic disease include bone pain and tenderness.
- Rare presentation includes paraneoplastic syndrome.

Microscoping finding [32,33,34,35]

Prostatic adenocarcinomas are composed of small glands that are back-to-back, with little a no intervening stroma. Cytologic features of adenocarcinoma include enlarged sound hyperchromatic nuclei that have a single prominent nucleolus. Mitotic figures suggest carcinoma. Less differentiated carcinomas have fused glands called cribriform glands, as well as solid nexts or sheets of tumour cells, and many tumours have to more of these patterns Prostatic adenocarcinomas almost always arise in the posteria enter zone of the prostate and are often multifocal.

Prostatic adenocarcinomas are usually graded according to the Gleason grading system based on the pattern of growth. There are 5 grades (from 1 to 5) based upon the

architectural patterns. Adenocarcinomas of the prostate are given two grade based on the most common and second most common architectural patterns. These two grades are added to get a final grade of 2 to 10. The stage is determined by the size and location of the cancer, whether it has invaded the prostatic capsule a seminal vesicle and whether it has metastasized.[36,37]

The grade and the stage correlate well with each other and with the prognosis. The prognosis of prostatic adenocarcinoma varies widely with tumour stage and grade. Cancers with a Gleason score of <6 are generally low grade and not aggressive. Advanced prostatic adenocarcinomas typically cause urinary obstruction, metastasise to regional (pelvic) lymphnodes and to the bones, causing blastic metastases in most cases. Metastases to the lungs and liver are seen in a minority of cases. [38,39]

2.25.4 Histologic Criteria For Gleason Grading[1, 39]

1. Single, separate, uniform glands closely packed, with definite edge.
2. Single, separate uniform glands loosely packed with irregular edge.

3.A Single, separate, uniform glands, scattered.

3.B Single separate, very small glands, scattered.

3.C Papillary Cribriform masses, smoothly circumscribed.

4.A Fused glands, raggedly infiltrating.

4.B Same with large pale cells (" hypernephroid")

5.A Almost solid, rounded masses, necrosis ("comedocarcinoma")

5.B Anaplastic, raggedly infiltrating.

Adenocarcionomas of the prostate are graded by the pathologist according to their degree of differentiation and overall aggressiveness. They are given a Gleason score which is a number from 2.10. Numerous grading systems have existed for evaluation ad diagnosis of prostate cancer. By far, the Gleason grading system is clearly the most widely accepted. The Gleason system of prostate cancer grading is based on the glandular and cellular pattern of the tumour as evaluated at relatively low magnification.

The Gleason grading system combines the two most common (Primary and Secondary) architectural patterns of cancer within the sampled specimen. Each of the two most common patterns in assigned a grade from one to five, with one the most differentiated and least aggressive and five the least differentiated or most aggressive pattern. The value of the Gleason grading system is its ability to predict survival rates. Importantly, Gleason grading may provide prognostic information that is to some degree independent of the extent of local tumour. Gleason sum score is reported as the two scores added together. For example, if the most common pattern of grading was a 3 pattern and the second most common pattern was a 4, the Gleason grade would be reported as Gleason 3+4=7. [2]

2.26

TNM classification of carcinomas of the prostate (15 WHO)

T-Primary tumour

TX Primary tumour cannot be assessed

T0 No evidence of primary tumour

T1 Clinically inapparent tumour not palpable or visible by imaging

T1a Tumour incidental histological finding in 5% or less of tissue resected.

T1b Tumour incidental histologtical finding in more than 5% of tissue resected.

T1c Tumour identified by needle biopsy (e.g. because of elevated PSA)

T2 Tumour confined within prostate[1]

T2a Tumour involves one half of one lobe or less.

T2b Tumour involves more than half of one lobe, but not both lobes.

T2c Tumour involves both lobes

T3 Tumour extends beyond the prostate[2]

T3a Extracapsular extension (unilateral or bilateral)

T3b Tumour invades seminal vesicle(s)

T4 Tumour is fixed or invades adjacent structures other than seminal vesicles: bladder neck, external sphincter, rectum, levator muscles, or pelvic wall [4]

Notes:

1. Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is fclassified as T1c.
2. Invasion into the prostatic apex yet not beyond the prostate is not classified as T3, but as T2.
3. There is no PT1 category because there is insufficient tissue to assess the highest PT category.

4. Microscopic bladder neck involvement at radical prostatectomy should be classified as T3a.

N- Regional lymphnodes

NX	Regional lymphnodes cannot be assessed
N0	No regional lymphnode metastasis
N1	Regional lymphnode metastasis

Note: Metastasis no larger than 0.2 cm can be designated PN1 mi.

M- Distant metastasis

MX	Distant metastasis cannot be assessed
M0	No distant metastasis
M1	Distant metastasis
M1a	Non-regional lymphnode(s)
M1b	Bone(s)
M1c	Other site(s)

G 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)

Stage grouping

Stage I	T1a	N0	M0	G1
Stage II	T1a	No	M0	G2,3-4
	T1b,c	No	M0	Any G
	T1,T2	N0	M0	Any G
Stage III	T3	No	M0	Any G
Stage IV	T4	N0	M0	Any G
	Any T	N1	M0	Any G
	Any T	Any N	M1	Any G

2.27 Malignant soft tissue tumours[5]

Sarcomas of the prostate are rare, comprising fewer than 0.1% of all primary prostatic neoplasms. Most of the sarcomas of the prostate are:

1. Leiomyosarcomas: occurs in older age group.
2. Rhabdomyosarcomas-occurs in children and young adults.
3. Fibrosarcomas.
4. Malignant fibrous histocytomas.
5. Chondrosarcoma
6. Malignant nerve sheath tumor
7. Neuroblastoma.

} Rarely reported.

Sarcomas are not associated with elevated serum PSA level.

2.28 Malignant lymphoma [5]

Malignant lymphoma of the prostate, either as a primary tumor or as a tumour secondary to systemic involvement, is rare. However, 100 well-documented cases have been reported. The predominant types are large cell, mixed cell and small cleared cell lymphomas.

2.29 Metastatic tumors of the prostate [5]

The most common tumor secondarily involving the prostate is bronchogenic carcinoma, followed by melanoma. Other frequent sites include the gastrointestinal tract and kidney. A metastatic testicular germ cell tumour has also been reported.

2.30 Prostate Specific Antigen (PSA)

Prostate-specific antigen is the most important, accurate and clinically useful biochemical marker in the prostate. The PSA gene is located on chromosome 19.[15 WHO] PSA is a glycoprotein, member of kallikrein gene family, manufactured by the secretary epithelial cells and drains into the ductal system, where it catalyzes the liquefaction of the seminal coagulum after ejaculation.[4] Normally it is found in low concentration in sera. Most PSA in serum is complexed with antiprotease which are alpha-1 antichymotrypsin and alpha-2 microglobulin. Clearance of complexed PSA is thought to be through liver. Serum half-life of PSA after removal of prostate is 2-3 days. Thus several weeks may be necessary for PSA to become undetected. Serum levels are normally less than 4 ng/ml (monoclonal) but vary according to patient age and race; any process that disrupts the normal architecture of the prostate allows diffusion of prostate specific antigen into the stroma and microvasculature.

Elevated serum prostate-specific antigen levels are seen with:

- Prostatitis
    - Infarcts
    - Hyperplasia
    - After biopsy (transiently)
    - Prostatic adenocarcinoma

Digital rectal examination also changes PSA value but this change is not significant. ([40])

Cancer produces less prostate specific antigen per cell than benign epithelium, but the greater number of malignant cells and the stromal disruption associated with cancer account for the increased serum prostate-specific antigen level. Serum prostate specific antigen level correlates positively with clinical stage, tumour volume, histologic grade and the presence of capsular perforation and seminal vesicle invasion.

- ***PSA level > 10 ng/ml is indicative of prostatic carcinoma***

- ***PSA level of 30+ng/ml highly suggestive of carcinoma***

- ***Serum PSA, when increased above 50 ng/ml is 98.5% accurate in predicting the presence of prostate cancer on tissue biopsy*** [41,42]

- By itself, PIN doesn't give rise to elevated serum PSA levels, but in one study serum PSA level upto 20 ng/ml have been found [43]

- For well to moderately differentiated tumours, further investigations to assess the presence of metastases may be omitted with no great risk for understand if serum PSA <20 ng/ml. [44]

- ***Lowering PSA cut-off (i.e. from 4.0ng/ml to 2.5 ng/ml)) may reduce unnecessary biopsies in some men*** [45]

- Serum PSA is the most accurate of the three diagnostic tests evaluated (comparison of serum prostate specific antigen digital rectal examination and transrectal ulstrasonography). The addition of DRE or TRUS improves the detection rate of prostate cancer over PSA alone. [46]

- Undetected prostate cancer appears to be a major cause of the increasing serum PSA seen with advancing age [47]

- Rectal examination as initial screening test for prostate cancer at low PSA values (<3.0 ng/ml) may be replaced by screening using serum PSA only.[48]

- Patients with serum PSA levels greater than 20 ng/ml were at high risk for positive margins (relative risk 5.42, P<0,001). PSA level was the strongest predictor of pathologic stage, irrespective of tumour palpability. [49,50]

- PSA-based screening for prostate cancer in asymptomatic younger males-pilot study in blood donors -study shows that PSA measurement in blood donors is a useful method for recruiting screening volunteers, and therefore represents and additional possibility for early detection of prostate cancer in asymptomatic younger males. [51]

- The combination of systemic biopsy and serum PSA may be useful in predicting extraprostatic cancer patients with >/= 8ng/ml serum PSA and more than half the biopsy cores positive could avoid a prostatectomy because there is a high probability that they have extraprostatic disease [52]

- PSA level <4 ng/ml had better disease free survival rates than those with a PSA level between 4.1-10 ng/ml eliminating an arbitrary cut off of 4 ng/ml, may lead to improved disease free survival [53]

- Combination of DRE and PSA value >4.0 ng/ml appears to be superior to DRE alone with a positive predictive value of 50% versus 1.9% i early detection of prostate cancer. [54]

- Elevated serum prostate specific antigen (PSA) related to asymptomatic prostatic inflammation [55]

- No diagnostic marker was able to rule out or detect early PCa in patients with a PSA level of 4.1-9.9 ng/ml. Using the PSA-based parameters together can be helpful in management of these patients. Patient's age and race should be considered in clinical decision- making. ([56]

- PSA level less than 2.0 ng/ml, elimination of annual PSA testing for these men would result in large health care cost savings. [57]

- Clinical stage T1C was introduced to describe cancers discovered on prostate biopsy as a result of an abnormal serum PSA level without a palpable. Prostatic abnormality on digital rectal examination. The majority of men with stage T1C tumours have significant disease warranting treatment. [58]

- The most clinically useful model for predicting histologically identifiable residual cancer was either a serum PSA value greater than 2 a PSA value less than or equal to 2 and abnormal TRUS findings [59]

- For patients with newly diagnosed prostate cancer who have biopsy Gleason scores <=6 and preoperative PSA concentrations < = 10ng/ml, a staging pelvic lymphadenectomy appears to be unnecessary[60]

- A patient with prostate cancer and a serum Prostate Specific Antigen (PSA) level over 200 ng/ml, submitted to Radical Retropubic Prostatectomy (RRP) and after 2 months presenting with two painful nodules in the penis. [61]

- Serial annual PSA measurements may provide an alternative means of screening men over 50 years of age [62]

- The use of age specific PSA reference ranges doesn't totally account for the effect of prostate volume on serum PSA. Therefore PSAD can still be used to reduce safely the number of biopsies performed in patients with negative DRE and TRUS results and a serum PSA level 10.0ng/ml a less & above the age specific upper limit of normal. [63]

- Although early detection of prostate cancer has traditional both PSA measurement and DRE, PSA testing alone could be more easily implemented and may encourage some men to seek consultation who might not otherwise have done so.[64]

- Pretreatment serum PSA is the single most important predictor of disease outcome after radiation or local prostate cancer. Tumour grade has a lesser though significant prognostic role. Postirradiation nadir PSA value during the first year is a sensitive indicator of response to treatment. Only nadir-values <1 ng/ml are associated with a favourable outlook. [65]

- Serial PSA determinations should reflect the growth of the cancer as well as the gradual evolution of more malignant cells with the passage of time.[66]

- The major source of pretreatment serum PSA in patients with clinically localized disease is the primary tumor itself, the new major message conveyed by serum PSA related to the primary tumor and likely outcome. Gleason grade and T- stage remain major determinants of metastatic relapse. [67]

- In asymptomatic patients with newly diagnosed untreated prostate cancer and serum PSA levels of less than 10 ng/ml, a staging radio nuclide bone scan may not be necessary. [68]

- With long-term follow-up, the pretreatment PSA level continuous to be a powerful predictor of clinical and biochemical outcome in patients irradiated for apparently localised prostate cancer. [69]

- Men who have baseline PSA levels that are normal but reflect risk of prostate cancer may be the most appropriate candidate for future pretrials. While PSA is a relative specific marker of prostatic adenocarcinoma, it has been described in some esxtraprostatic tumours including mature teratoma periurethral gland adenocarcinoma in females, villous adenoma and adenocarcinoma of the bladder, extra mammary paget's disease of the penis and pleomarplic adenoma and carcinoma of the salivary gland in males. [70]

2.31 *Age Specific Reference Range for Serum Prostate Specific Antigen (PSA).*[2,63]

Age(Year)	*PSA Range (ng/ml)***	*Age (Year)*	*PSA Range (ng/ml)***
40	2.0	60	3.8
41	2.1	61	4.0
42	2.2	62	4.1
43	2.3	63	4.2
44	2.3	64	4.4
45	2.4	65	4.5
46	2.5	66	4.6
47	2.6	67	4.7
48	2.7	69	4.9
49	2.7	69	5.1
50	2.8	70	5.3
51	2.9	71	5.4
52	3.0	72	5.6
53	3.1	73	5.8
54	3.2	74	6.0
55	3.3	75	6.2
56	3.4	76	6.4
57	3.5	77	6.6
58	3.6	78	6.8
59	3.7	79	7.0

*** From 0.0 to the specified value.*

3. LACUNAE OF KNOWLEDGE

Most of the previous studies on the prostate pathology that were preformed in Nepal were either limited to only benign prostatic hyperplasia or symptoms related correlation. However, this study covers almost all prostatic pathology and aimed to see the sensitivity and specificity of serum PSA level to differentiate prostatic neoplasm.

Role of serum prostate specific antigen in differentiating different prostate pathology, including inflammation, benign prostatic hyperplasia, Prostatic Intraepithelial Neoplasia (PIN) and prostate carcinoma had not been studied.

4. AIMS AND OBJECTIVES

General

1. To study serum PSA values in different prostatic pathology, and findout relationship between histopathological diagnosis and total serum PSA values.

Specific

1. To correlate between weight of the prostate and serum PSA level in prostatic pathology.
2. To study the sensitivity and specificity of serum PSA level in prostate cancer.
3. To study the relationship between serum PSA level and Prostatic Intraepithelial Neoplasia (PIN).

5. MATERIALS AND METHODS

Fifty patients with prostate pathology who underwent TURP or prostatectomy were studied during a period of 1st January 2003 to 30th December 2003 at TUTH. Detailed clinical history, serum PSA level, USG measurement of the weight of the prostate was taken according to proforma and their relationship with hisotopathological diagnosis were studied.

Inclusion Criteria

Fifty patients with history of enlarged prostate who underwent TURP or Prostatectomy.

Exclusion Criteria

1. If serum PSA level is not done.
2. If serum PSA was performed after: -
   a. Catheterisation or if previous catheterization was done 4 weeks before.
   b. Cystoscopy
   c. Biopsy

5.1. USG methodology for assessment of weight of prostate gland[38]

The assessment of size, outline, shape and echogenicity of prostate gland is done using a convex probe of 3.5 MH (megahertz) from the suprapubic region in lower anterior abdominal wall. Patient should hae sufficient urinary bladder distension for better visibility and kept in supine position.

The length of the normal prostate is 2.5-3.0cm, the transverse diameter at the base is 4.0-4.5 cm and the thickness is 2.0-2.5 cm. The size of prostate (in grams) upto 2.0cm, the transverse diameter at the base is 4.0-4.5 cm and the thickness is 2.0-2.5 cm. The size of prostate (in grams) upto 30 grams is taken as with in normal limits.

The dimensions of prostate are measured in three planes. Since the apex of prostate points downwards, two measurements are taken in sagittal/vertical plane. All the three measurements are multiplied by a factor of 0.523 to arrive at the weight in grams of the prostate gland, e.g.

l x b x h x 0.523=weight of prostate in grams.

5.2 Prostate specimens

The specimens of prostate were formalin fixed. Detailed macroscopic examination of the specimen was done after complete fixation. The sections were taken from the different parts of the Radical Prostatectomy specimen. Additional sections were taken in case there was an abnormal/ suspicious looking area. All Trans-urethral-resection of prostate specimens were embedded. Then, the tissue were placed into tissue teks and processed in the histokinette in the following sequence.

1. Firstly, the sections were put into 10% formalin for 3 hours.
2. The sections were then put into increasing concentration of alcohol 70%,80%, 90% and 100% for 1½ hours in each.
3. The sections were put into *xylene I, xylene II, xylene III* and *xylene IV* for 1½ hours in each and finally into paraffin wax for 3 hours. The total duration for fixation was 18 hours.

   After processing, the sections were embedded in paraffin and blocks were made.

4 µ/m sections were cut from the blocks and put into albuminised slides. The sections were then stained with Haematoxylin and Eosin stain for microscopic examination. The procedure for staining is given below:

5.3 Haematoxylin and Eosin staining

1. Dewaxation of the sections was done in xylene for 10 minutes.
2. The slides were then put into decreasing concentration of alcohol 100% (5 minutes), 90% (3 minutes), 80% (2 minutes), ad finally to water (6 dips).
3. They were then stained with Harris Haematoxylin for 15 minutes.
4. Washing was done in tap water by dipping 6 times.
5. The slides were dipped in acid alcohol twice.
6. Further washing was done in tap water for another 6 dips.
7. The slides were then immersed in lithium carbonate 1% for 2 minutes.
8. Washing was repeated in tap water by dipping 6 times.
9. The slides were stained with eosin for 10 minutes.
10. They were then dipped into increasing concentration of alcohol 70%, 80% and 90% six times each.
11. They were put into *xylene I and II* for 5 minutes each.
12. Finally, mounting of the slides were done with DPX.

The slides were then examined under the microscope.

5.4 Estimation of Serum Prostate Specific Antigen Level

1. Specimen collection and storage

5 ml of venous blood was collected in a glass tube without additives. Allowed to clot at room temperature (18-25^{0}c). Then centrifuged and serum fraction separated and stored.

2. Principle of the procedure

In the serozyme PSA assay, a mouse monoclonal anti-PSA antibody is used in an enzyme immunometric assay system, which incorporates magnetic solid phase separation. All incubation times and reagent volumes are determined by an assay specific software protocol.

Fixed amounts of fluorescein-labelled anti-PSA antibody conjugated to alkaline phosphatase are added to the sample, control or standard. The reactants are incubated at 37^{0}c for 12 minutes. During the incubation PSA in the sample, control or standard binds to both anti-PSA antibodies forming a "sandwich".

At the end of the incubation period antifluorescein coupled to a magnetic solid phase is added in excess. This rapidly and specifically binds to PSA- antibody complex and is sedimented in a magnetic field.

After aspirating the liquid phase and washing the solid phase, a solution of the enzyme substrate phenolphthalein monophosphate is added to the cartridge and incubated at 370c for 12 minutes. After incubation the enzyme reaction if

stopped by the addition of a reaction stop reagent and the intensity of the colour developed is measured photometrically. The intensity of the colour developed is directly proportional within the working range of the assay to the concentration of PSA in the sample. The concentration of PSA in a patient sample or control is then determined by interpolation from the standard curve.

3. Reagents

The PSA serozyme kit contains sufficient reagents for 100 tubes, a approximately 42 patient samples assayed in duplicate. On receipt, store the kit at 2.8^0c and use until the expiration date on the label.

3.1 *Serozyme Anti-PSA Reagent, 1 vial*

The vial contains fluorescein- labeled monoclonal antiserum to PSA with sheep, horse and ster serum in Tris buffer with sodium aside 0.09% W/V and Proctin 300 (0.05% V/V). 10 ml.

3.2 *Serozyme PSA Derivative, 1 vial*

The vial contains bovine alkaline phosphatase labeled anti-PSA antibody with sheep, horse and steer. Serum in Tris buffer with sodium aside 0.09% W/V and Procin 300 (0.05% V/V) 10 ml.

3.3 *SRI/SZ PSA standards, 6 vials*

Each vial contains 0-0.5-2.0.5.0-11.0 and 35 ng/ml of PSA in Tris buffer with bovine proteins. Sodium aside (0.05%) W/V) and Procin 300 (0.0.5% V/V, 1.0 ml per vial for each standard. The exact concentrations of each standard are printed on the "Certificate of Analysis" enclosed in the kit.

3.4 *Serozyme separation reagents 0.6% 5, 1 vial*

The vial contains sheep antiserum to fluorescein, covalently bound to magnetizable particles, 0.6% W/V, in Tris buffer containing bovine serum albumin, 0.5% W/V and sodium aside, 0.2% W/V, 20 ml.

3.5 *Serozyme wash concentrate (33 ml), 1 vial*

The vial contains a surfactant and a preservative in Tris buffer, 33 ml.

3.6 *Serozyme separation reagent 0.6% 5, 1 vial*

The vial contains sheep antiserum to fluorescein, covalently bound to magnetizable particles, 0.6% W/V, IN Tris buffer containing bovine serum albumin, 0.5% W/V and sodium aside 0.2% W/V, 20 ml.

3.7 *Serozyme substrate, 2 vials*

Each Vial contains phenolphthalein monophosphate (PMP) and an enzyme cofactor in a buffer solution, 15.0ml.

3.8 *Serozyme stop solutions, 1 vial*

Each vial contain a cheating agent and sodium hydroxide <1% w/w in buffer, PH >10. 100 ml.

4. Materials and Equipment required

- Distilled or dieonizer water.
- Disposable round- bottomed clear (12x55 or 12x75 mm) polystyrene test tubes.
- Precision 0.10, 0.15,0.2 and 1.0 ml pipettors with disposable tips.
- 0.2 and 1.0 ml repeating dispensers
- 250 ml graduated cylinder for wash Buffer preparation
- $37.^{0}c \pm 1^{0}c$ water both
- Multi-vortex or mixer
- Magnetic separator and rack
- Serozyme I or II photometer or equivalent.

5. Preparation for Essay

For each essay, prepared the following groups of tubes and placed in the rack:

- 2 tubes for zero standard.
- 2 tubes for each standard concentration.
- 2 tubes for each serum, plasma and control.

Reagents were allowed to warm to room temperatured (18-25^{0}c) and mixed gently before using. Water both set up at 37^{0}c ± 1^{0}c.

6. Pipetting and incubation steps

6.1 Pipetted 0.100 ml standards, samples ad control into appropriately labeled tubes in duplicate.

6.2 Dispensed 0.100 ml serozyme Anti-PSA Reagent into each tube.

6.3 Dispensed 0.100 ml serozyme PSA derivative into each tube.

6.4 Using a multivortex all tubes gently mixed.

6.5 Incubated the tubes for 12 minutes at 37^{0}c.

6.6 Dispensed 0.200 ml of thoroughly mixed separation Reagent into each tube.

6.7 Gently vortex mixed and incubated for 6 minutes at 37^{0}c.

6.8 Slided the rack of tubes into the magnetic separator and allowed the particles to sediment magnetically for 2 minutes. Decant the supernatant from all tubes in the rack by inverting the separator in one large, slow circular movement. Placed the inverted separator a absorbent paper and hit the base of the separator firmly several times to dislodge any droplets of liquid adhering to the sides of the tubes.

6.9 Separator was set upright and 1.0 ml of wash Buffer to each tube.

6.10 Vortex vigorously slided the rack of tubes into the magnetic separator checked to see that all tubes are in area in contact with the surface of the separator. Waited for 2 minutes to allow particles to sediment magnetically. Decant the supernatant from all tubes in the rack by inverting the separator.

6.11 The separator set up upright and 1.0 Ml of wash buffer to each tube.

6.12 Vortex vigorously. Slided the rack of tubes into the magnetic separator. Checked to see that all tubes are in contact with th surface of the separator. Waited for 2 minutes to allow particles to sediment magnetically. Decant the supernatant from all tubes in the rack by inverting the separator.

6.13 Removed rack from the separator and pipette 0.300 of substrate solution into each tubes.

6.14 Vortex and incubated 12 minutes at 37^0c

6.15 Pipetted 1.0 ml of stop solution

6.16 Slided the rack into the magnetic separator and allowed the particles to sediment for 10 minutes.

6.17 Measured the absorbencies for standards, controls and samples at 550 and 492 mm.

5.5 Gleason's System [2, 39]:

Gleason's system is the gold standard for clinical reporting and often used to predict regional lymphnode metastasis.

- Two predominant patterns are graded from 1 to 5.\
- The sum of these patterns constitute a score which ranges from 2 to 10. Details of these five patterns are given below.

Pattern-1 Closely packed, single, separate, round, uniform glands with well-defined margin.

Pattern-2 Similar to pattern 1, but the glands are less uniform and less well-defined margin.

Pattern-3 The size of the glands is variable both small and large glands and a papillary or cribiform pattern appear.
Margins are poorly defined.

Pattern-4 Small fused glands with infiltrating cords; the glands may have papillary cribiform or solid patterns and the cytoplasm of the tumor cells may be clear

Pattern-5 few discernible glands; a comedo pattern is usually present, tumor cells infiltrate the stroma as single cells or as ill-defined cords.

Note: ***The presence of necrosis in any pattern automatically upgrades it to pattern 5.***

Grading

1. Low-grade - ***score upto 5.***
2. Intermediate - grade- ***score 6-8***
3. High- grade - ***score 9-10***

Difterentiation		Score
1.	Well - differentiated	2-4
2.	Moderately differentiated	5-6
3.	Moderately differentiated/Poorly differentiated	7
4.	Poorly differentiated	8-10

This grading system has been used in classifying the malignant tumors in this study

5.6 Prostatic Intraepithelial Neoplasia (PIN): [5]

Epithelial proliferation of PIN manifested by:

1. Increased cellularity.
2. Pseudostratification.
3. Intraluminal papillary formations
4. Bridging of the lumen and;
5. Cribriform formation.

Grading of PIN

1. Low –grade PIN (grade-1) is characterized by:

- Slight increase in cellularity.
- Some variation in nuclear size.
- Focal hyperchromasia and;
- Appearance of small nucleoli.

3. High – grade PIN (grade 2 and 3) is characterized by:

- Drefinitive increase in cellularity.
- Nuclear pseudostratification and;
- Hyperchromasia
- Presence of large nucleoli (few in PIN grade 2, numerous in PIN grade-3 which are larger than 1 μm).
- Exhibits a variety of arechitectural patterns: tufting, micropapillary cribriform or flat.

Note: Mitotic figures are uncommon is PIN, but can be seen. The basal cell layer is retained in low and high - grade PIN.

This grading system has also been applied in this study.

6. RESULTS

Fifty cases of prstatectomy specimens were studied between January 2003 to December 2003. Out of these, 20(40%) were found to have benign prostatic hyperplasia, 13(26%) benign prostatic hyperplasia with chronic prostatitis, 1(2%) benign prostatic hyperplasia with stromal hyperplasia, 7(14%) prostatic intraepithelial neoplasia (PIN) and 9 (18%) malignancy.

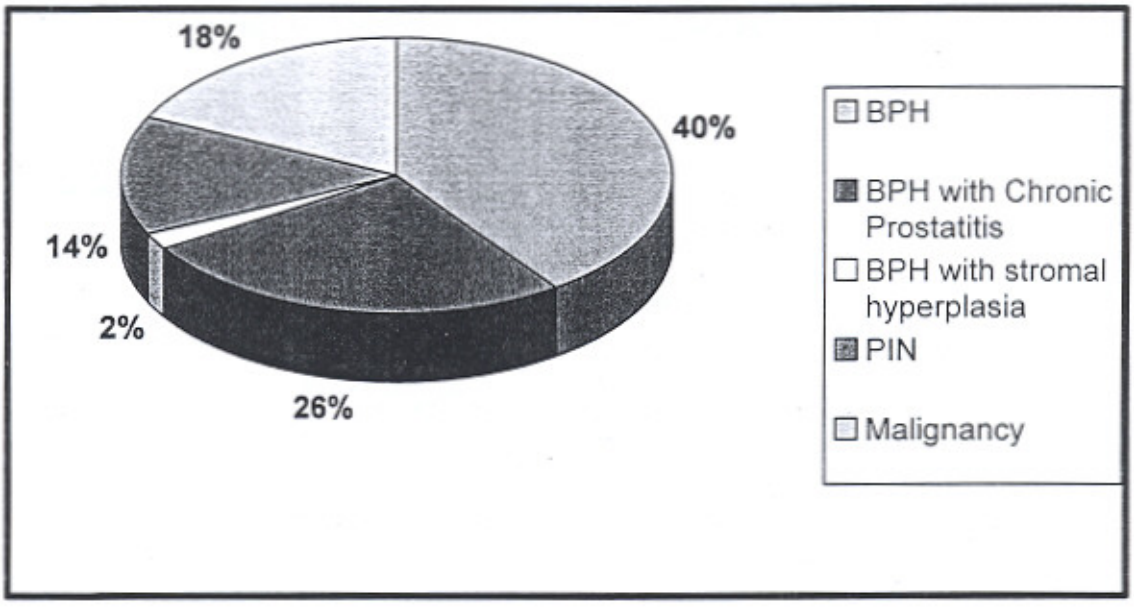
Of the total Prostatic Intraepithelial Neoplasia (PIN) cases all were diagnosed as PIN - grade 1 and among malignant cases 4 cases were found to be well-differentiated, 3 moderately differentiated, 2 poorly-differentiated adenocarsinomas.

51.2% cases of benign diseases had values equal to or less than 4 ng/ml, 48.8% had values between 4.1-10 ng/ml. All cases of prostatitis showed elevated values, whereas all cases of prostatic intraepithelial neoplasia had values between 0.4-10 ng/ml.

77.8% of prostatic carcinoma showed elevated serum PSA values, >10 ng/ml, with p value = .000004, sensitivity of 78% and specificity 100%. Whereas serum PSA values >50 ng/ml found in 44.4% of cases with p value= .001 sensitivity 45% and specificity 100%.

Weight of the prostate did not correlate with elevated serum PSA values (P Value= 0.761 and Karl Pearson Correlation Coefficient (r)= -0.044). Similarly no significant correlation was found between serum PSA values and Prostatic Intraepithelial Neoplasia (PIN).

Fig.-1 Pie Chart – Frequency of prostatic diseases



Benign prostatic hyperplasia was the most common disease encountered, (40%)

Table no.-1 Relation between age and types of lesion

Types of lesion	Age (years)				Total
	50-59	60-69	70-79	>80	
Malignant	1(11.1%)	3(33.3%)	4 (44.4%)	1(11.1%)	9(100.0%)
Benign	7(17.1%)	14(34.1%)	16(39%)	4 (9.8%)	41(100.0%)
Total	**8 (16.5%)**	**17 (34%)**	**20(40%)**	**5(10%)**	**50 (100.0%)**

Of the malignant tumors 44% occurred in the age group of 70-79 years. Similarly, 39% of the benign tumors occurred in the same age range.

Table no. -2 Serum PSA level in Benign and Malignant Prostatic lesions.

Table no. -2(A) Suggestive of Malignancy (> 4ng/ml)

PSA level (ng/ml)	Types of mass		Total
	Malignant	Benign	
> 4	9 (100.0%)	20(48.8%)	29 (58%)
<=4	0.00	21(51.2%)	21 (42%)
Total	**9(100.0%)**	**41 (100.0%)**	**50 (100.0%)**

P= 0.006

51.2% cases of benign diseases had serum PSA level < 4 ng/ml.

Table no. -2(B) Indicative of Malignancy (>10ng/ml)

PSA Level (ng/ml)	Types of Mass		Total
	Malignant	Benign	
>10	7(77.8%)	0.00	7(14%)
<=10	2(22.2%)	41(100%)	43(86%)
Total	**9 (100%)**	**41 (100%)**	**50 (100%)**

P= .000004

Serum PSA level <= 10 ng/ml was found in all benign prostatic lesions.

- Of the malignant tumors, 77.8% showed PSA values> 10 ng/ml which is indicative for malignancy.

Table no. -2(C) Diagnostic of malignancy (> 50 ng/ml)

PSA level (ng/ml)	Types of Mass	Total
	Malignant	
>50	4(44.4%)	
<=50	5 (55.6%)	9 (100.0%)

P= .001

The cut-off PSA value of >50 ng/ml was demonstrated in 44.4% of the malignant cases.

Table no:- 3 Calculation of sensitivity and specificity of serum PSA values in Prostatic cancer

For this study, I have considered following working operational definitions to calculate sensitivity and specificity. I have taken three serum PSA values as a cut-off value, >4 ng/ml, > 10 ng/ml awnd > 50 ng/ml for comparision which are suggestive, indicative and diagnostic of malignancy respectively. These are expressed in percentage (%) with 95% confidence interval (CI).

Sensitivity = $\frac{True Positive (TP)}{True Positive (TP) + False Negative (FN)}$

Specificity = $\frac{True Negative (TN)}{False Positive (FP) + True Negative (TN)}$

Positive Predictive Value (PPV) = $\frac{True Positive (TP)}{True Positive (TP) + False Positive (FP)}$

Negative Predictive Value (NPV) = $\frac{True Negative (TN)}{False Negative (FN) + True Negative (TN)}$

True Positive (TP) = Histologically malignant with serum PSA level >4,>10 and >50 ng/ml respectively.

True Negative (TN) = Histologically not malignant, with serum PSA level <4,<10 and < 50 ng/ml respectively.

False Positive (FP) = Histologically not malignant but serum PSA level >4,>10 and >50 ng/ml respectively.

False Negative (FN) = Histologically malignant but serum PSA level <4,<10 and <50 ng/ml respectively.

Serum PSA level (ng/ml)	Sensitivity	Specificity	Positive predictive value
> 4	100%	52%	31%
>10	78%	100%	100%
>50	45%	100%	100%

Results demonstrated that serum PSA level >10 ng/ml has sensitivity of 78% and specificity 100% with 100% positive predictive value, whereas sensitivity rate dropped to 45% with serum PSA level >50 ng/ml.

Table no. -4 Correlation between weight of the prostate and type of lesion: (Malignant anrd Benign)

USG (wt. in gms.)	Types of lesion		Total
	Malignant	Benign	
> 30	8 (88.9%)	41(100%)	49(98%)
< =30	1(11.1%)	0.0	1(2%)
Total	**9(100%)**	**41(100%)**	**50 (100%)**

P=0.761

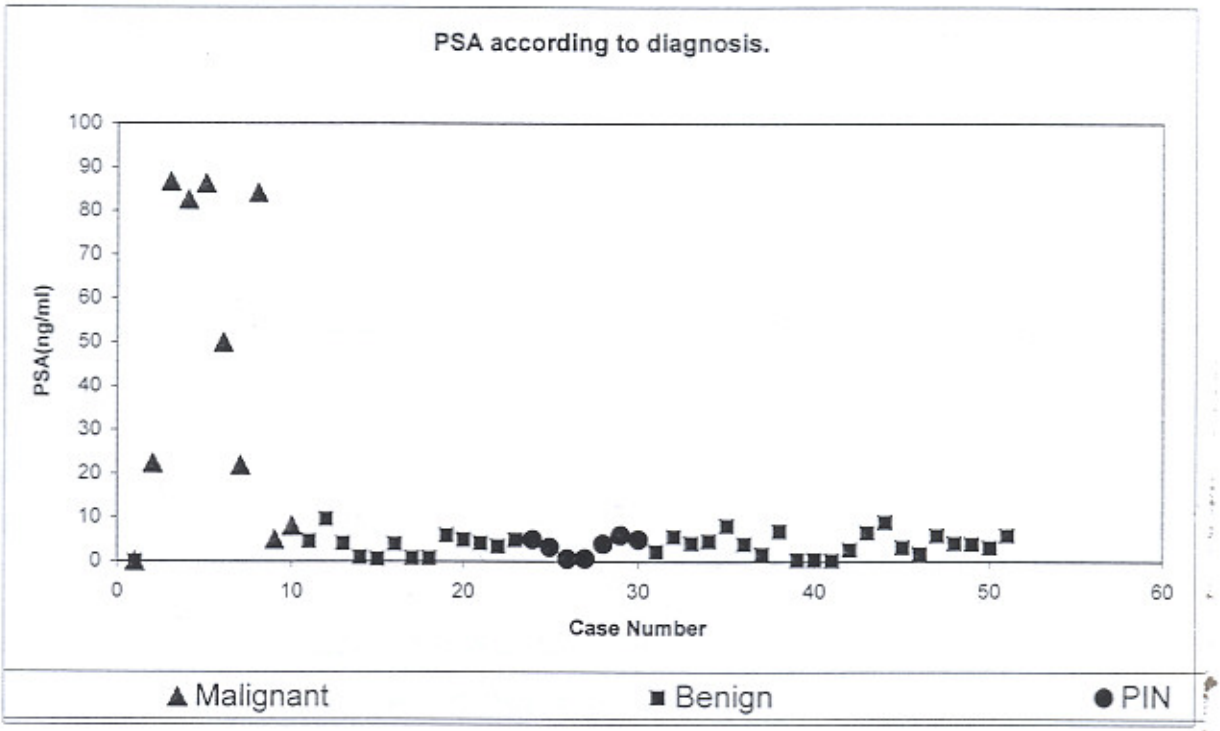
Weight of the prostate> 30 gms were found in 88% of the malignant tumor and in 100 % of the benign lesions.

Also

Karl Pearson Correlation Coefficient (r) = - 0.044 and;

Low degree of negative correlation between USG and PSA p=0.761

Table no. -5 Scattered Diagram: Serum PSA Level according to diagnosis



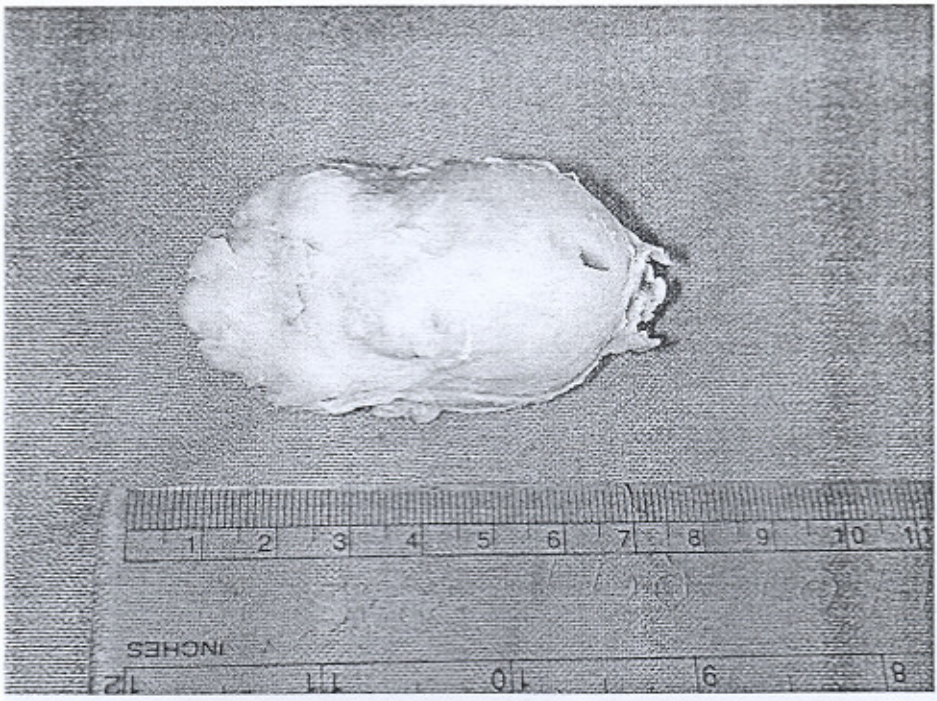
Highest serum PSA value (86.7 ng/ml) was recorded in malignancy whereas all benign prostatic lesions including PIN had serum PSA values less than 10 ng/ml.

Table no. –6 **Correlation between serum PSA Level and Prostatic Intraepithelial Neoplasia (PIN)**

Microscopic diagnosis	PSA Lev el				Total
	0-4	4.1-10	10.1-35	>50	
BPH	11	9			20
BPH with Chr. Prostatitis	6	7			13
PIN grade 1	**4**	**3**			**7**
BPH with stromal hyperplasia		1			1
Well diff. Adenocarcinoma		1	1	2	4
Mod. Diff. Adenocarcinoma		1		2	3
P.D. Adenocarcinoma		1	1		2
Total	**22**	**21**	**1**	**6**	**50**

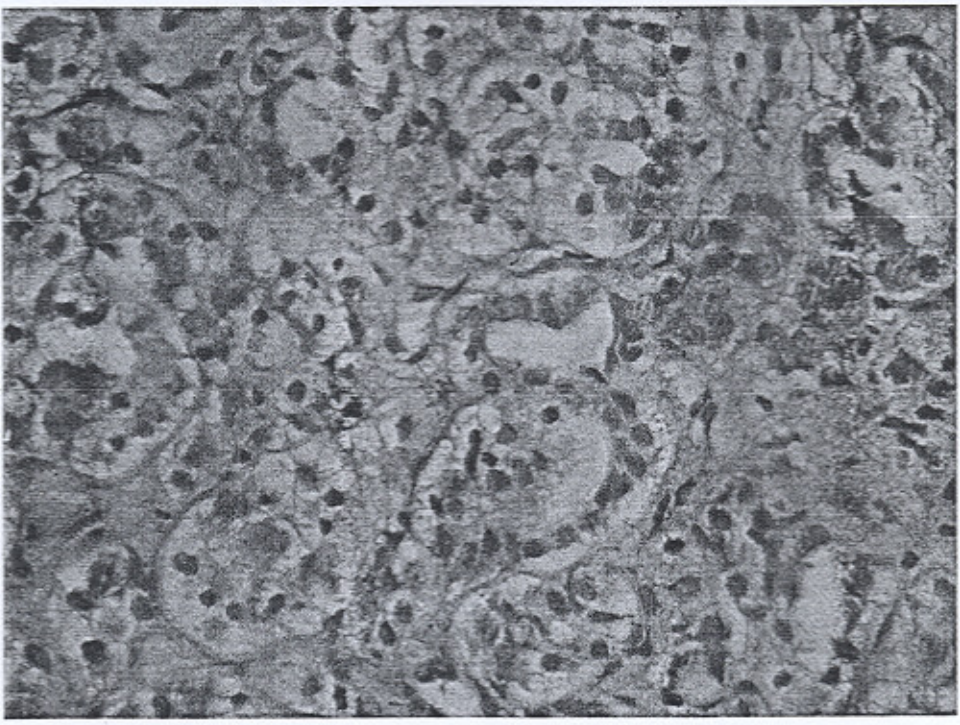
4 cases of the PIN grade - 1 had serum PSA value <= 4 ng/ml while 3 cases demonstrated > 4 ng/ml. No significant correlation was found between serum PSA level and PIN.

1. PHOTOGRAPH - 1



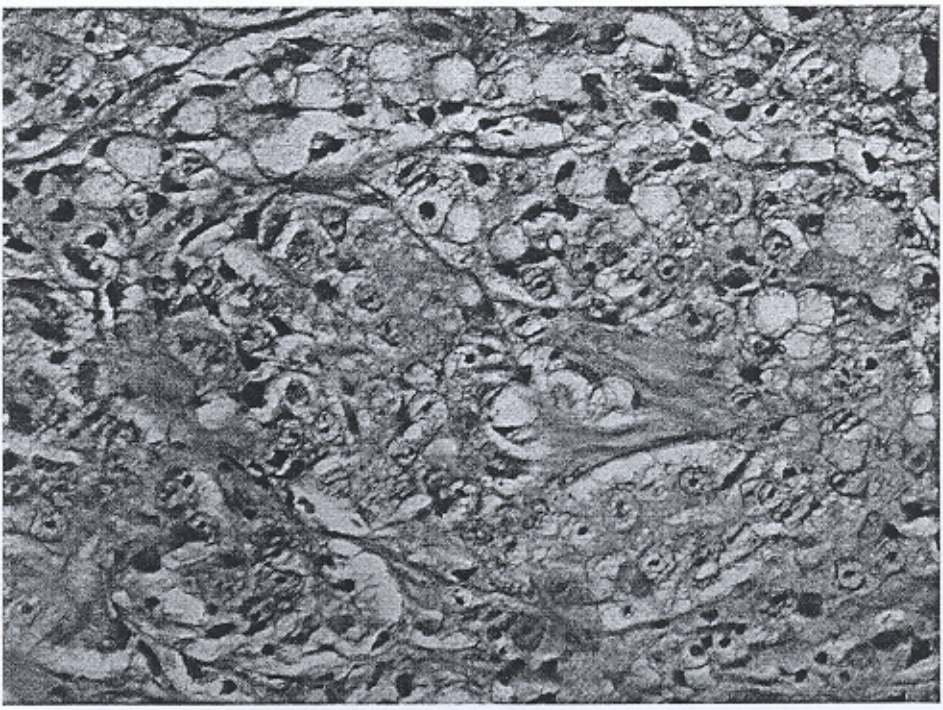
Adenocarcinoma Prostate - External Surface

2. PHOTOGRAPH - 2



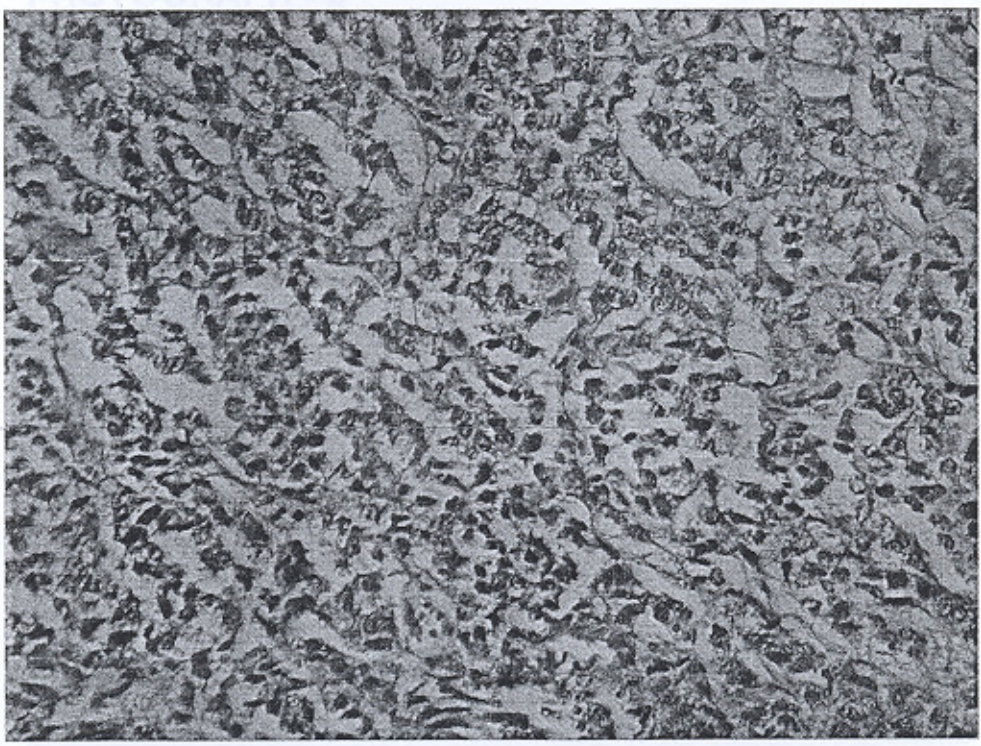
Adenocarcinoma Prostate (Well differentiated): H & E x 400 HPE

3. PHOTOGRAPH - 3



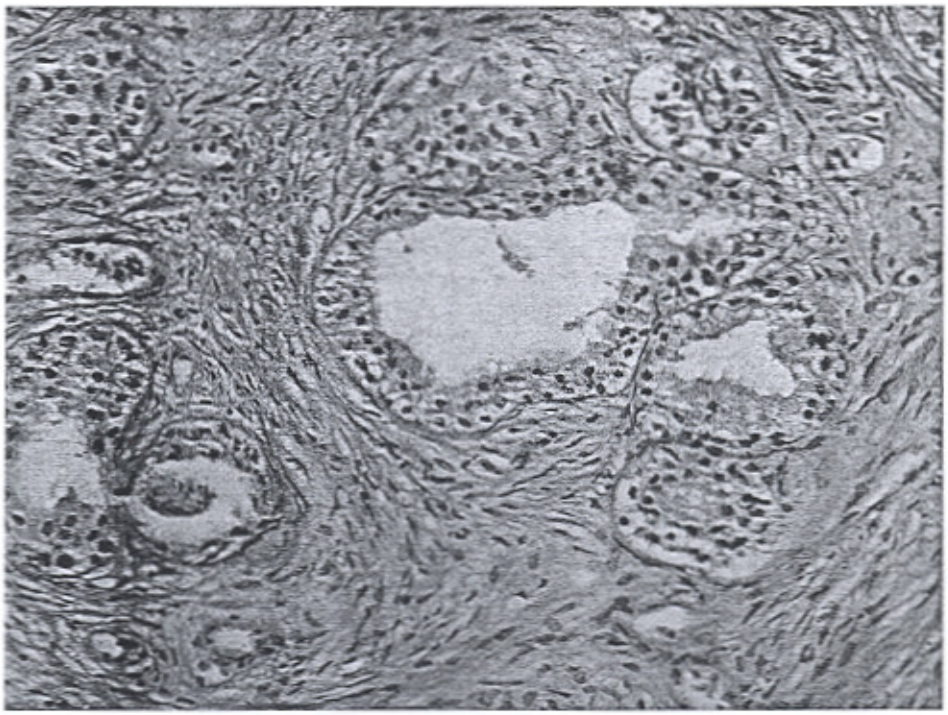
Adenocarcinoma Prostate (Moderately differentiated) : H & E x 400 HPE

4. PHOTOGRAPH - 4



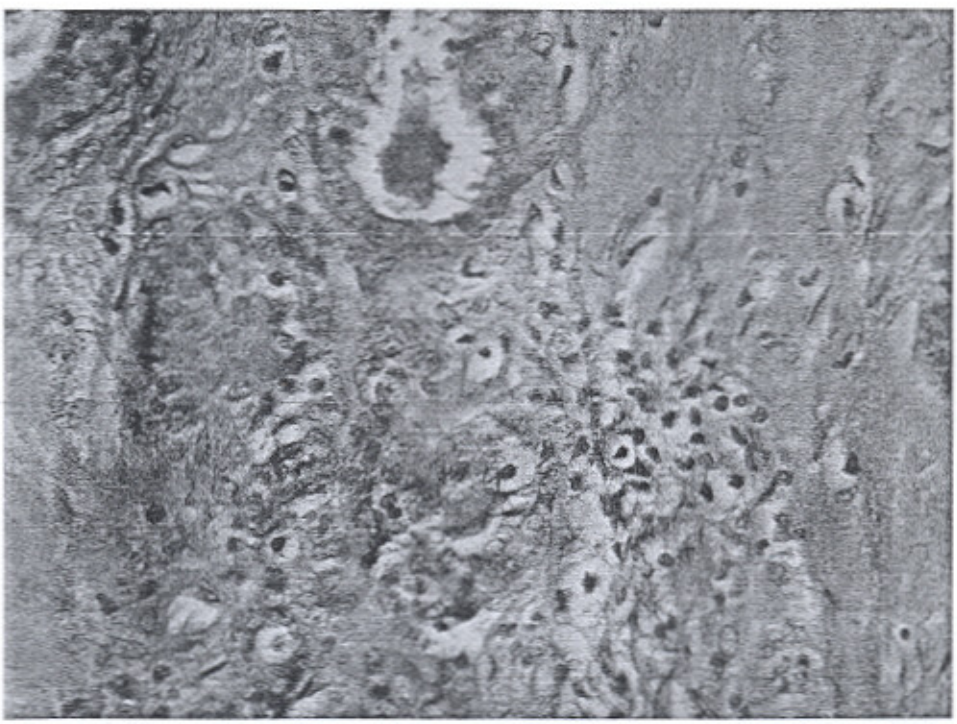
Adenocarcinoma Prostate (Poorly differentiated) : H & E x 200 HPE

5. PHOTOGRAPH - 5



Benign Prostatic Hyperplasia : H & E x 400 HPE

6. PHOTOGRAPH - 6



Prostatic Intraepithelial Neoplasia (PIN I) x 400

8. DISCUSSION

Benign prostatic hyperplasia is extremely common disorder in men over age 50. The prevalence of this disease is believed to be highly significant in most communities. The incidence of Prostatic Intraepithelial Neoplasia (PIN) is increasing in tissue biopsies and also which is a precursor lesion to malignancy. *(2)*

Prostate Cancer 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 c ases was 513000 in the year 2000. This represents 9.7% of cancers in men (15.3% in developed countries and 4.3% in developing countries). It is the third leading cause of death cancer. In recent years, incidence rates reflect not only differences in risk of the disease, but also the extent of diagnosis of latent cancers both by screening of aymptomatic individuals, and by detection of latent cancer in tissue removed during prostatectomy operations, or at autopsy. *(15, WHO)*

In our country, many elderly men are unaware that something can be done for their troublesome urinary symptoms and undetected prostate cancer appears to be a major cause of the increasing Serum PSA seen with advancing age. *(46)*

During the study period of one year, fifty patients with history of enlarged prostate were studied. Serum PSA level were estimated preoperatively at the time of admission. Clinical history was obtained and relationship between histopathological diagnosis and total serum PSA level along with weight of the prostate were studied.

Correlation with frequency of prostatic lesions

Out of fifty cases, the commonest disease encountered was BPH (40%), (26%) benign prostatic hyperplasia with chronic prostatitis, PIN (14%),

(2%) benign prostatic hyperplasia with stromal hyperplasia and (18%) malignancy. Other prostatic pathology such as granulomatous prostatitis, infarct, adenomatous hyperplasia were not found. The reason could be becaue the bulk of the prostatic lesion is comprised of inflammation, benign prostatic hyperplasia and tumours as seen in other studies. [3] In the similar study done by Xess A et. al [43] at the department of microbiology, Indira Gandhi Institute of Medical Sciences, Sheikhpura, Patna, out of 98 cases, 52% were adenocarcinomas and 42.8% cases were benign prostatic hyperplasia. A study done by Tay KP et. al [44] in Singapore found that the prevalence of BPH was higher, similar to the finding of this result.

Correlation with age

In this study, the commonest age group for malignancy was found to be 70-79 years and for benign prostatic lesions. A study done by Shakya G, Malla S, Shakya K.N. [20] on a histopathological study of the prostate in Nepal found adenocarcinomas occurred in 60-80 yrs. Opalinsk E. et. al [23], found as a result of screening procedure among 1,004 men in the lublin district; BPH and prostatic cancer occurred most often in men saged 51-70 years. In a similar study by sandblom G. et. al [24], studying on the Prostatic Carcinoma trends in three countries in Sweden, found mean age at diagnosis was 74.2 years with a peakage 74.8 years, findings consistent with this study.

Correlation with serum PSA values in benign and malignant lesions

Results of this study highlighted that all cases of benign prostatic hyperplasia and inflammation had serum PSA values less than 10 ng/ml. Similarly, 77.8% of prostatic carcinoma had elevated serum PSA level more than 10ng/ml, P value= 0.00004, sensitivity of 78% and specfificfity

100% with 100% positive predictive value. While only 44.4% of prostatic carcinom had elevated serum PSA value >50 ng/ml with P value = 0.001, dropping sensitivity of 45 % and specificity 100%.

In a study done by Arista - Nasr J et al [41] in Mexico found that the median PSA values was 11.2 ng/ml, and there was a considerable overlap of PSA levels in benign and malignant cases, because of the type or reagent kits used or PSA assays in that study. (Cedex from France and Diagnostic Products Corp from US).

A study performed by Gerstenbluth RE et. al [42] in Western Reserve University School of Medicine, Ohio, USA, demonstrated that serum PSA > 50 ng/ml was 98.5% accurate in predicting the presence of prostatic carcinoma in tissue biopsy which supports the findings.

Cookson MS et. al [49] investigated that PSA levels > 20 ng/ml were high risk for positive margins.

Shakya A, Singh S., Malla S, Bajaj S. K. [50] at Siddhartha Apollo hospital found high PSA in younger age group between 40-50 years, correlating with histopathological correlation of cancer and recommends to screen the patient for prostatic carcinoma starting from 40 years.

Shekarriz B et al [53] in his study at the department of Urology, Michigan USA suggested that PSA level <4ng/ml had better disease survival rates than those with a PSA level between 4.1-10ng/ml.

The study done by Babarian RJ et. al [59] concluded that serum PSA value > 10 ng/ml had a positive biopsy compared with those with a PSA value less than or equal to 10. Such findings are similar with this study.

Correlation between serum PSA level with Prostatic Intraepithelial Neoplasia (PIN)

All PIN-grade-1 in this study had serum PSA level less than 10 ng/ml in contrast to the study done by Xess A et al [43] in Indira Gandhi Institute of Medical Sciences, Sheikpura, Patna that 40% had serum PSA values upto 20 ng/ml, majority belonged to PIN grade-3. The reason could be due to the fact that case of Prostatic Intraepithelial Neoplasia diagnosed microscopically in this study were all PIN - grade- 1.

Correlation with serum PSA level and weight of the Prostate measured by USG.

Findings of this study, did not show any significant correlation between elevated serum PSA level and weight of the prostate, as P value= 0.761. And, also Karl Pearson Correlation Coefficient (r) = -0.044 with a low - degree of negative correlation. The various studies done by different authors have different opinion. In a study, done by Omacini S. et. al (72), PSA were higher where Prostate was heavier in BPH, however, author could not find a consistent factor which could correlate weight increase to marker levels, also, ultrasound cannot determine whether lumps are cancerous or non-cancerous (benign).

Stamey TA et. al [73] in his study found, preoperative Serum PSA has a clinically useless relationship with cancer volume and grade in radical prostatectomy specimens, and a limited relationship with PSA levels of 2 to 9 ng/ml. In contradict to this study, Vesely S. et. al [74] correlated positively with serum PSA ($r=0.54, P<0.0001$) and prostate volume.

Wu B. et. al [75], concluded that PSA elevates not only in the cases of prostatic cancer but also in the cases of BPH and that PSA correlates with the whole prostatic weight.

In a similar study done by Yu HJ et. al [76], at the department of Urology, College of Medicine, National Taiwan University, Taipei, ROC, observed that serum PSA levels increased with age and prostate volume, and correlated better with the latter.

To conclude most of the various studies performed before highlighted that serum PSA level >50 ng/ml is highly accurate (98.5%) in diagnosing prostate cancer, whereas, results of this study focused that, serum PSA level >10 ng/ml has higher sensitivity (78%) and specfificity (100%) rate as compare to serum PSA level >50 ng/ml. However, the PSA test can produce false positive and false negative results, because of this biopsy has to be performed to confirm or rule out prostate cancer when the PSA is higher.

9. SUMMARY AND CONCLUSION

A total of fifty cases of prostatectomy specimens were studied during the study period from January 2003 to December 2003. Out of which (40%) were found to have beign prostatic hyperplasia, (26%) benign prostatic hyperplasia with chronic prostatitis, (2%) benign prostatic hyperplasia with stromal hyperplasia, (14%) Prostatic Intraepithelial Neoplasia (PIN) and (18%) malignancy.

All 7 cases of prostatic intraepithelial neoplasia were diagnosed as PIN-grade 1 and among malignant cases, 4 cases were found to be well-differentiated, 3 moderately differentiated, 2 poorly differentiated adenocarcinomas.

(51.2%) cases of benign lesions had values equal to and less than 4 ng/ml, (48.8%) had values between 4.1-10 ng/ml, sensitivity of (100%) and specificity (51.2%). All cases of prostatic intraepithelial neoplasia had values between 0.4-10 ng/ml.

(77.8%) of prostatic carcinoma showed elevated serum PSA values, (>10 ng/ml) with p value = .000004, sensitivity of (78%) and specificity (100%) with 100% positive predictive value. Whereas, serum PSA values >50 ng/ml found in (44.4%) of cases with p value = .001, and sensitivity (45%) and specificity (100%).

Weight of the prostate did not correlate with elevated serum PSA values. Similarly no significant relation was found between serum PSA level and Prostatic Intraepithelial Neoplasia (PIN).\

(44.4%) of the malignant tumours were found between age group 70-79 years and most of the benign lesions also in the same age group.

Prostate -specific antigen is biochemically a glycoprotein, is the most important, accurate and clinically useful biochemical marker in the prostate. It is the most valuable tool available for the diagnosis and staging of prostate cancer and one of the most widely used laboratory tests in oncology.

The test has a high sensitivity and specificity, is rapid and inexpensive, and is minimally invasive.

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PROFORMA

ROLE OF PROSTATE SPECIFIC ANTIGEN IN DIFFERENTIATING VARIOUS PROSTATIC PATHOLOGY

Case No.: **Date:**

I.P. No. **Age**

Name:

Address:

Ethnicity:

Hindu ☐

Muslim ☐

Buddhist ☐

Christian ☐

Clinical History:

Symptoms of Prstatism	**Yes**	**No**
• Increase frequency of urination	☐	☐
• Burning micturation	☐	☐
• Dribbling of urine	☐	☐
• Decrease flow of urine	☐	☐
• Retention of urine	☐	☐
• Hematuria	☐	☐
• Urgency of prolong voiding	☐	
• Nocturia	☐	☐
• Feeling of incomplete voiding	☐	☐

Personal History:

	Yes	No
• Smoking	☐	☐
• Alcohol	☐	☐
• Dietary habit (fat intake)	☐	☐

Past history:

	Yes	No
• STD	☐	☐
• UTI	☐	☐
• Gonorrhea	☐	☐

Surgical Procedure:

In GU tract

	Yes	No
• V asectomy	☐	☐
• Any others	☐	☐

P/R Findings:

	Yes	No
• Enlargement	**median**	**lateral**
• Sulcus obllitered		

- Consistency — Benign/ Firm/Hard
- Weight in gms:

Investigations:

1. Serum PSA level (ng/ml)
2. USG – weight of prostate in gms
3. Urine R/M/E
4. TURP on Prostatectomy specimens –H/E stain

Clinical Diagnosis (√)

1. BPH
2. BPH with Chronic prostatitis
3. PIN
4. Carcinoma
5. Others

Bipsy results (√)

1. BPH
2. BPH with chronic prostatitis
3. PIN grade
   - I.
   - II.
   - III.
4. Adenocarcinoma
   - W.D.
   - M.D.
   - P.D
5. Others: