"THE ROLE OF PROSTATE SPECIFIC ANTIGEN LEVELS AND PROSTATE SPECIFIC ANTIGEN DENSITY IN PATIENTS WITH LOWER URINARY TRACT SYMPTOMS AGED OVER FORTY FIVE YEARS – A ONE YEAR HOSPITAL BASED PILOT STUDY"

By

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Dissertation submitted to the
KLE University, Belgaum, Karnataka

In Partial Fulfillment
Of the requirements for the degree of

MASTER OF SURGERY (M.S.)
IN
GENERAL SURGERY

Under the Guidance of

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ACKNOWLEDGEMENT

I take this opportunity to express my respect and heartfelt gratitude to all my teachers.

First and foremost I would like to express my sincere gratitude and appreciation for my guide **Dr. A. C. PANGI** MS, Associate Professor, Department of Surgery, for his constant guidance, valuable suggestions, unparalleled encouragement and co-operation provided to me throughout the course of this study. It has been a great pleasure and privilege to work under him. Without his professional insight and guidance I would have not completed this study.

I would also like to thank my co-guide **Dr. S. I. Neeli** MS MCh for the guidance and insight in conceptualizing this study. It would not have been possible to go through with this dissertation without his support and guidance.

I avail this opportunity to thank **Dr. A. S. Godhi** MS, FICS Professor and Head, Department of Surgery, for his keen interest, unparalleled encouragement and co-operation.

I express my sincere gratitude to **Dr. V. D. Patil** MD, DCH Principal J. N. Medical College, Belgaum, **Dr. M. V. Jali** MD, Director and Chief Executive, KLES Dr. Prabhakar Kore Hospital and Medical Research Centre, Belgaum for allowing me to utilise facilities in the above institution for this dissertation.

I express my sincere gratitude to **Dr. S. M. Uppin** MS, FICS, **Dr. Veerendra M. Uppin** MS, **Dr. P. S. Pattanashetti** MS, **Dr. V. B. Dhaded** MS, FICS, **Dr. M. S. Sangolli** MS, **Dr. S. S. Shimikore** MS, **Dr. I. V. Uppin** MS, (Late) **Dr. B. V. Gogeri** MS, FRCS, **Dr. A. S. Gogate** MS and **Dr. S. C. Metgud** MS, Professors who have encouraged me during the course of study. I thank them for their inspiration and moral support.

I owe my sincere gratitude to **Dr. R. R Rao MS, Dr. S. T. Vedbhushan MS, Dr. Santhosh Patil MS, Dr. B. M. Kajagar MS, Dr. Sanjay Karpoor MS** Associate Professors of Surgery.

I express my special gratitude to **Dr. R. S. Koujalagi MS, Dr. S. N. Halabhavi MS Dr. V. M. Pattanshetti MS, Dr. J. S. Uttur MS, Dr. Sharat MS, Dr. Uday MS** Assistant Professors of Surgery for their valuable support and guidance in carrying out this study.

I sincerely thank all my post graduate colleagues for their help in the study. I am also thankful to my batch mates **Dr. Prashanth. T, Dr. Gautham. M, Dr. Rakesh Pandey, Dr. Pramod S., Dr. Manoranjan, Dr. Soumitra Saha, Dr. Sushanth, Dr. Tilak. S** for their kind help rendered throughout the course of my study.

I whole heartedly thank **Mr. Dhareshwar** for his immense help in conducting the statistical analysis.

From the bottom of my heart I convey my heartfelt gratitude to **All Patients** without whose co-operation this study would have been incomplete.

I also thank the authors of numerous publications whose knowledge have been freely utilized in the preparation.

With deep sense of gratitude and affection, I am very thankful to my parents **Dr. Anilkumar V. Saraf** and **Dr. Sanjivani A. Saraf** who have always been pillars of strength for me.

Last but not the least; I would be failing in my duty if I don't thank our ward nursing staff without whose co-operation this study would not have been completed.

Finally, I thank **Almighty** for all the blessings.

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LIST OF ABBREVIATIONS USED

AJCC	-	American Joint Committee for Cancer Staging and End Results Reporting
AUA	-	American Urological Association
BPH	-	Benign prostatic hyperplasia
CT	-	Computed tomography
DHT	-	Dihydrotestosterone
DRE	-	Digital rectal examination
EBRT	-	External Beam Radiotherapy
HGPIN	-	High-grade Prostatic intraepithelial neoplasia
IPSS	-	International Prostate symptom score
LHRH	-	Luteinizing hormone releasing hormone
MRI	-	Magnetic Resonance Imaging
MRS	-	Magnetic resonance spectroscopy
PCa	-	Prostate cancer
PIN	-	Prostatic intraepithelial neoplasia
PSA	-	Prostate specific antigen
PSAD	-	Prostate specific antigen density
PSMA	-	Prostate specific membrane antigen
ROC	-	Receiver operating characteristic
SPECT	-	Single photon emission computed tomography
TRUS	-	Trans Rectal Ultrasound

ABSTRACT

Background and objectives

Widespread screening tests for prostate cancer (PCa) based on serum Prostate specific antigen (PSA) are undertaken in the western world where a majority of cases are detected at stage T1c. The concept of prostate specific antigen density (PSAD) is based on the fact that non-malignant prostatic tissue leaks some PSA into the blood. The objectives of this study was to determine the sensitivity and specificity of PSA and PSA density to detect PCa in patients aged over 45 years presenting with lower urinary tract symptoms.

Methods

This study was conducted at a tertiary research centre for a period of one year from October 2007 to September 2008. It was designed as a pilot study, which had 50 males over 45 years of age. Patients who had undergone any genitourinary intervention, those who had a previously detected lower urinary tract malignancy or infection were excluded from the study. A questionnaire was supplied which ascertained the International prostate symptom score (IPSS), followed by a clinical examination which included a digital rectal examination (DRE). Serum PSA levels were determined following which Transrectal ultrasound (TRUS) was performed to ascertain the volume (for PSAD calculation) of the gland and to obtain a biopsy.

Results

The majority of the patients (72%) had a PSA in the traditional grey area between 4 and 10 ng/ml. For a PSAD below the threshold of 0.3 ng/ml/cc no cases of PCa were encountered in our study. Most patients presented to the clinic

when their symptoms were moderately severe (48%). The sensitivity (88.9% vs. 100%), specificity (14.6% vs. 95%), positive predictive value (18.6% vs. 81.2%), negative predictive value (85.2% vs. 100%) for PSAD (at 0.3ng/ml/cc) was superior to PSA.

Conclusion

The use of PSAD increases the accuracy and improves the sensitivity and specificity for detection of cancer. In this study the PSA density of 0.3 ng/ml/cc was found to be highly specific and sensitive for detection of prostate cancer.

Key Words

Prostate carcinoma; PSA; PSA density; Transrectal Ultrasound.

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INTRODUCTION

Prostate cancer (PCa) has become the single most common malignant visceral neoplasm in men in the Western world since 1984, and its incidence has been rising rapidly in most countries including low risk countries like India.[1] Ever increasing mortality rates are being observed. According to the World health organization the total number of worldwide deaths due to PCa has shown an increase from 239,000 deaths in 1998 to 262,000 in 2002.[2] It is estimated that PCa was responsible for 11,700 deaths in India in 2005.[3]

Till 25 years ago, digital rectal examination (DRE) was the primary mode of evaluation of PCa. This method of clinical examination is however subjective, and therefore difficult to standardise. Moreover over 70% of the patients detected to have malignancy by this examination are already at an advanced stage wherein curative treatment is not possible.

Majority of the newly detected cases of carcinoma of prostate in North America are staged T1c.[4] This is attributed to the presence of a comprehensive screening programme with the Prostate specific antigen (PSA) as its screening tool. But the detection of cancer at a stage (T3 and beyond) where a curative procedure is not possible is a major stumbling block in India.

The concept of PSA density (PSAD) is based on the assumption that, as non-neoplastic prostate tissue especially, Benign prostatic hyperplasia (BPH) does leak some PSA into the circulation, for PSA to be useful in diagnosing prostate cancer, values should be corrected for total gland volume.[5]

No study targeting the Indian population exists which aims to stratify the incidence of prostatic carcinoma based on PSA or PSAD measurements.

The aim of this study was to ascertain whether the estimation of PSA and PSAD values lead to an increase in the detection rates of PCa in patients aged over forty five presenting with lower urinary tract symptoms in a tertiary care setting.

OBJECTIVES

The objectives of the present study were;

1. To determine the occurrence of PCa in patients aged over 45 years presenting with lower urinary tract symptoms.
2. To calculate PSA and PSAD values in the subjects.
3. To correlate the above values with prostatic malignancy

REVIEW OF LITERATURE

HISTORICAL BACKGROUND

Herophilus of Chalcedon made first use of the term 'prostate', because of the organ's location "standing before" the urinary bladder. PCa was first described by anatomist Niccolo Massa in 1536 but was not identified until 1853. At the time, PCa was considered a rare disease, due to the shorter life expectancies of the population and poor detection methods. Civillard in 1639 performed the first perineal resection of the prostate. Jean Zulema Amussat removed a part of the prostate through a suprapubic cystotomy in 1832.[6]

Max Neitze in Berlin invented the cystoscope in 1877, which helped visualize the prostate endoscopically. The last decade of the 19th century saw many surgeons performing radical prostatectomies, via the perineal approach. The middle of the 20th century saw the popularisation of simple retropubic prostatectomies, and the use of novel methods of administration of radiation to the prostate in cases of PCa. By the late 1950's attempts had been made to resect the prostate trans-urethrally. Higgins in 1966 won the Nobel Prize for his studies on anti-androgen therapy. Whitmore in 1970 described the use of retropubic iodine 125 brachytherapy. Patrick C. Walsh in 1982 advocated identification and preservation of neurovascular bundle to avoid impotence after radical prostatectomy.[7] Schuessler et al demonstrated laparoscopic pelvic lymphaedenectomy in 1991.

Novel new methods have been attempted for management of focal PCa like transperineal cryoablation which was first described by Onik and Cohen in 1993.[8]

ANATOMY OF THE PROSTATE

Embryology

The prostate gland is formed around the end of the third month (first trimester) from the epithelium of the future prostatic urethra. The epithelium proliferates and penetrates the surrounding mesenchyme, which is the future fibromuscular prostatic tissue.

Surgical Anatomy

Topographic Anatomy and Relations

The classical description of the adult prostate is that it has the size, shape, and consistency of a large chestnut. The form of the prostate is that of a compressed inverted cone: pyramidal, having a base and an apex. It is located between the vesical neck of the bladder and the apex of the urogenital diaphragm.

The normal weight of the prostate in a young adult is from 17 to 19 g. The numbers four, three and two are useful as a mnemonic for remembering the transverse, vertical, and sagittal dimensions in centimeters, respectively, of the gland.

The prostate is enveloped by extraperitoneal connective tissues that cover the thin anatomic capsule (true capsule) of the organ, and it in turn envelops the proximal male urethra.

Fixation and Suspension

The following structures are responsible for the fixation of the prostate in its bed:

- The puboprostatic ligaments
- Urogenital diaphragm
- Bladder
- Prostatic sheath
- Fascia of Denonvilliers
- Prostatic Urethra

The prostatic urethra begins at the urethral meatus at the apex of the trigone of the bladder. This opening is crescent-shaped, invaginated posteriorly by a protuberance caused by the underlying glandular tissue (median lobe of the prostate), thus forming the uvula vesicae. This is continuous with a posterior midline urethral ridge, or crest, in the urethra. The urethral ridge has a distinctly expanded portion called the verumontanum, or seminal colliculus.

The urethral crest is a ridge located on the floor of the posterior urethra between the bladder and the membranous urethra. It is wider at the vesical neck (the uvula) than on its pathway to the membranous urethra. The verumontanum (colliculus seminalis) is a small elevated hillock at the middle area of the urethral

crest. The prostatic utricle or uterus masculinus is a crypt located in the middle portion of the verumontanum, approximately 6 mm deep.

The orifices of the ejaculatory ducts are located on the right and left sides of the verumontanum.

The prostatic sinus is a depression located on the right or left side of the urethral crest, home of the openings of the prostatic ductules and the urethral glands.

Prostatic Surfaces

There are four prostatic surfaces: one posterior, one anterior, and two inferolateral.

The posterior surface is flat transversely and convex vertically. It is separated from the rectal ampulla by the bilaminar fascia of Denonvilliers. This surface is characterised by a midline groove that is wider toward the base of the gland, and serves to partially separate the gland posteriorly into left and right lobes.

The posterior surface may be palpated by DRE. The vesicoprostatic junction is located at the upper border of the posterior surface.

The narrow and convex anterior surface is located between the apex and the base. Multiple large veins separate this surface from the symphysis pubis. The distance between the pubic symphysis and the anterior surface is approximately 2 cm.

The avascular puboprostatic ligaments are fibrous cords, wide or narrow. They connect the upper limits of the anterior surface of the prostate to the pubic bone, at the right and left sides of the cartilaginous area.

The right and left inferolateral surfaces are embraced by the anterior part of the levator ani muscles. They are fixed to the levator by the arcus tendineus of the fascia pelvis ("white line"), sagittal connective tissue bands between the ischial spine, and the pubic bone. Here there is a very rich venous network and fibrous tissue which contributes part of the lateral prostatic sheath.

The levator prostatae muscle is the most anterior and most medial part of the levator ani muscle. These muscle fibers pass about the prostate gland and insert into the perineal body beneath the prostate gland, related to the anterior parts of the levator ani muscle.

Fascia of Denonvilliers

In early fetal peritoneal development, the peritoneum extends downward as a pouch reaching the muscular pelvic floor and perineal body. Later the pouch disappears as the growing organs lift the peritoneal covering, resulting in fusion of the more anterior and posterior parts of the peritoneal covering, producing a bilaminar transverse septum. This septum is continuous with the peritoneum above and the perineal body below, and is continuous between the ischial spines. Layers unite with each other, forming a potential space. The union of these two layers produces the fascia of Denonvilliers.

Structure

Lowsley[9] reported that the prostate gland can be divided into six lobes: anterior, posterior, median, subcervical, right lateral, and left lateral. His description is no longer accepted, however, because it was based on studies of fetal and newborn prostates, and is not an accurate description of the adult gland.

Avoiding use of the term "lobes" because of the confusion it engenders, McNeal[10] described four regions or zones in the prostate: peripheral, central, transition, and anterior fibromuscular stroma (Figure 1).

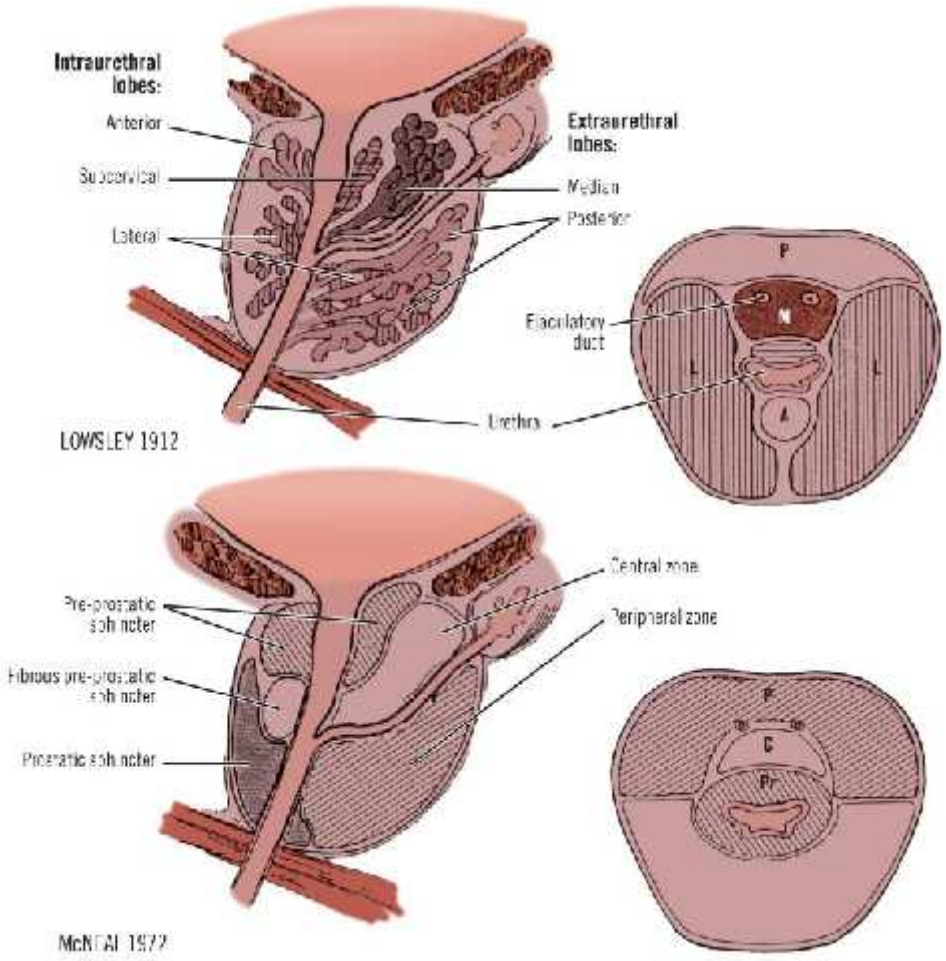


Figure 1: Structure of prostate gland

McNeal wrote that marked histologic differences exist between the peripheral and central zones, suggesting important differences in biologic function. This information and some of the other findings from McNeal's brilliant embryologic, anatomic, histologic, and pathologic observations are summarised below;

Embryology

- *Peripheral* - It is likely that the glands of this zone develop from the urogenital sinus and drain into the prostatic urethra.
- *Central* - Ducts of this zone are probably of Wolffian origin.
- *Transitional* - Glands in the transition zone are formed from the junction of the proximal and distal urethral segments.
- *Stroma* - This region is formed by nonglandular tissue.

Anatomy

Peripheral

Nearly 75% of the glandular prostate, the peripheral zone surrounds most of the central zone and much of the urethra; in other words, it surrounds the posterior and lateral areas of the prostate gland. Its glands drain into the prostatic urethra.

Central

The central zone, which is nearly 25% of the glandular prostatic parenchyma, envelops the ejaculatory ducts and extends toward the base of the urinary bladder.

Transitional

This zone is less than five percent of the glandular prostate. The transition zone is composed of two minute glandular regions which are lateral to the preprostatic sphincter and directly related to the proximal urethral segment. The periurethral region is related to this zone and to the junction of the proximal and distal urethral segments. Periurethral ducts, which are responsible for the genesis of BPH, are present in this zone.

Stroma

The anterior fibromuscular stroma is nonglandular. It constitutes one third of the prostatic tissue within the prostatic capsule but is in continuity with the detrusor muscle of the neck of the urinary bladder. It is heavily fixed with the anterior surfaces of the three glandular zones, and represents the periurethral gland region.

Histology

Peripheral

This zone is formed by multiple tubuloalveolar glands. The long, narrow ducts of this zone branch into small, round, regular acini with smooth, nonseptate walls. Epithelium is simple columnar; its pale cells have distinct borders and basally-placed small, dark nuclei.

Central

The central zone is continuous with the peripheral zone and, like the peripheral zone, is formed by several tubuloalveolar glands (mucosal,

submucosal, main prostatic) which are located around the urethra. The acinar tissue consists of large, irregularly shaped spaces; the walls have intraluminal ridges or septa. The cells of the central zone differ significantly from those of the peripheral zone. They have more opaque, granular cytoplasm and less distinct cell membranes. Their cell length varies, they have an irregular luminal border, and they appear more crowded. Their nuclei, which are slightly larger than those of the peripheral zone and stain paler, are displaced to variable levels from the basement membrane.

Transitional

In this zone one observes a minimal number of glands.

Stroma

The fibromuscular stroma is composed of striated and smooth muscles, as well as elastin and collagen.

Pathology

- *Peripheral* - Most carcinomas develop in the peripheral zone.
- *Central* - Carcinoma seldom arises in the central zone.
- *Transitional* - The transition zone and other periurethral glands are the exclusive site of origin of BPH. The area near or within the sphincter almost invariably produces the most numerous and largest nodules. Ten to twenty percent of carcinomas may develop in the transition zone.
- *Stroma* - This area is without importance for prostatic function or pathology.

Capsules of the Prostate

There are three capsules of the prostate; two (the true and false) are anatomic, the third is pathologic. The true capsule is a very thin covering surrounding the gland in toto. The false capsule (periprostatic fascia or prostatic sheath) is an extraperitoneal fascia (visceral layer of endopelvic fascia).

This capsule is continuous with four fasciae:

- Anterior: fascia of the bladder, puboprostatic ligament.
- Lateral: arcus tendineus of the fascia pelvis.
- Posterior: fascia of Denonvilliers.
- Inferior: superior fascia of the urogenital diaphragm.

Between the true and false capsules is a venous plexus, the prostatic or pudendal venous plexus. Part of the normal aging process is progressive prostatic growth due to BPH. The peripheral part of the prostate becomes compressed against the surrounding endopelvic connective tissue, forming a surgical capsule (pathologic capsule).

Vascular Supply

Arteries

There are three arterial zones within the prostatic parenchyma: anterior or capsular, intermediate, and urethral. Characteristically, the urethral vessels enter the prostatovesical junction at seven to eleven o'clock and at one to five o'clock. The two sides have few anastomoses.

The blood supply of the prostate is derived primarily from the inferior vesical artery. A branch of this artery enters the prostate laterally at the prostatovesical junction. This artery divides into two branches, the peripheral and the central. The peripheral branch serves the majority of the prostatic parenchyma; the central branch supplies the urethra and the periurethral tissues.

Veins

There is a rich venous plexus (prostatic plexus) between the prostate gland and the prostatic sheath. It communicates with the internal iliac venous system and the presacral veins. The prostatic venous plexus receives the deep dorsal penile vein and the veins of the base of the bladder. The vesical and internal iliac veins receive most of the venous blood.

Lymphatics

From the prostatic acinus, large intraprostatic trunks are formed. These penetrate the prostatic capsule and form the periprostatic lymphatic plexus. This plexus yields lymphatic vessels which follow the vascular network of the prostatovesical arteries.

The lymph vessels that follow the prostatovesical arteries travel to the internal iliac lymph nodes. The vessels also travel to the presacral lymph nodes and, occasionally, to the external iliac lymph nodes.

From a surgical standpoint, the primary sites of lymphatic drainage of the prostate are the obturator and external iliac nodes.

Innervation

The preganglionic sympathetic nerve supply to the smooth muscle of the seminal vesicles, ejaculatory ducts, and prostate gland arises in the intermediate gray area of spinal cord levels L1 and L2 (or L3). Postganglionic fibers arise in the preaortic or pelvic plexuses. The sympathetic fibers cause contraction of the smooth muscle and expulsion of seminal fluid.

Parasympathetic fibers from sacral cord levels S2, S3, and S4 synapse in pelvic ganglia and periprostatic ganglia. They act perhaps to dilate blood vessels and stimulate secretion from glands of the genital system, including the prostate.

Histology

70% of the weight of the prostatic mass is glandular epithelium. 30% is fibromuscular, mainly non-striated. The glandular part contains ducts and acini which are lined with columnar epithelium and drain in the posterior and lateral walls of the prostatic urethra.

Physiology

The prostate gland secretes a milklike alkaline fluid. This fluid is very important for the fertilization of the ovum, since sperm within both the ductus deferens and vaginal tissue produce fertilization-inhibiting acidity. Guyton[11] stated that prostatic fluid most likely neutralises the acidity of the fluids of the ductus deferens and vagina after ejaculation, enhancing the motility and fertility of the sperm. The prostatic fluid also contains citric acid, calcium, phosphorus, and other substances.

BENIGN PROSTATIC HYPERPLASIA AND CANCER OF THE PROSTATE

Benign prostatic hyperplasia

Incidence & epidemiology

BPH is the most common benign tumour in men, and its incidence is age related. The prevalence of histologic BPH in autopsy studies rises from approximately 20% in men aged 41 to 50, to 50% in men aged 51 to 60, and to more than 90% in men older than 80. Although clinical evidence of disease occurs less commonly, symptoms of prostatic obstruction are also age related. At age 55, approximately 25% of men report obstructive voiding symptoms. At age 75, 50% of men complain of a decrease in the force and caliber of their urinary stream.

Risk factors for the development of BPH are poorly understood. Some studies have suggested a genetic predisposition, and some have noted racial differences. Approximately 50% of men under the age of 60 who undergo surgery for BPH may have a heritable form of the disease. This form is most likely an autosomal dominant trait, and first-degree male relatives of such patients carry an increased relative risk of approximately fourfold.

Aetiology

The etiology of BPH is not completely understood, but it seems to be multifactorial and endocrine controlled. The prostate is composed of both stromal and epithelial elements, and each, either alone or in combination, can give rise to

hyperplastic nodules and the symptoms associated with BPH. Each element may be targeted in medical management schemes. Observations and clinical studies in men have clearly demonstrated that BPH is under endocrine control. Castration results in the regression of established BPH and improvement in urinary symptoms. Additional investigations have demonstrated a positive correlation between levels of free testosterone and oestrogen and the volume of BPH. The latter may suggest that the association between aging and BPH might result from the increased oestrogen levels of aging causing induction of the androgen receptor, which thereby sensitizes the prostate to free testosterone. However, no studies to date have been able to demonstrate elevated oestrogen receptor levels in human BPH.

Pathology

As discussed earlier, BPH develops in the transition zone. It is truly a hyperplastic process resulting from an increase in cell number. Microscopic evaluation reveals a nodular growth pattern that is composed of varying amounts of stroma and epithelium. Stroma is composed of varying amounts of collagen and smooth muscle. The differential representation of the histologic components of BPH explains, in part, the potential responsiveness to medical therapy. Thus alpha-blocker therapy may result in excellent responses in patients with BPH that has a significant component of smooth muscle, while those with BPH predominantly composed of epithelium might respond better to 5-alpha-reductase inhibitors. Patients with significant components of collagen in the stroma may not respond to either form of medical therapy.

As BPH nodules in the transition zone enlarge, they compress the outer zones of the prostate, resulting in the formation of a so-called surgical capsule. This boundary separates the transition zone from the peripheral zone and serves as a cleavage plane for open enucleation of the prostate during open simple prostatectomies performed for BPH.

Pathophysiology

One can relate the symptoms of BPH to either the obstructive component of the prostate or the secondary response of the bladder to the outlet resistance. The obstructive component can be subdivided into the mechanical and the dynamic obstruction. As prostatic enlargement occurs, mechanical obstruction may result from intrusion into the urethral lumen or bladder neck, leading to a higher bladder outlet resistance.

Prior to the zonal classification of the prostate, urologists often referred to the “three lobes” of the prostate, namely, the median and the 2 lateral lobes. Prostatic size on DRE correlates poorly with symptoms, in part, because the median lobe is not readily palpable. The dynamic component of prostatic obstruction explains the variable nature of the symptoms experienced by patients. The prostatic stroma, composed of smooth muscle and collagen, is rich in adrenergic nerve supply. The level of autonomic stimulation thus sets a tone to the prostatic urethra. Use of alpha-blocker therapy decreases this tone, resulting in a decrease in outlet resistance.

The irritative voiding complaints of BPH result from the secondary response of the bladder to the increased outlet resistance. Bladder outlet

obstruction leads to detrusor muscle hypertrophy and hyperplasia as well as collagen deposition. Although the latter is most likely responsible for a decrease in bladder compliance, detrusor instability is also a factor. On gross inspection, thickened detrusor muscle bundles are seen as trabeculation on cystoscopic examination. If left unchecked, mucosal herniation between detrusor muscle bundles ensues, causing diverticula formation (so-called false diverticula composed of only mucosa and serosa).

Clinical features

The symptoms of BPH can be divided into obstructive and irritative complaints. Obstructive symptoms include hesitancy, decreased force and calibre of stream, sensation of incomplete bladder emptying, double voiding (urinating a second time within 2 hours of the previous void), straining to urinate, and post-void dribbling. Irritative symptoms include urgency, frequency, and nocturia.

A detailed history focusing on the urinary tract excludes other possible causes of symptoms that may not result from the prostate, such as urinary tract infection, neurogenic bladder, urethral stricture, or prostate cancer.

A physical examination, DRE and focused neurologic examination are performed on all patients. The size and consistency of the prostate is noted, even though prostate size, as determined by DRE, does not correlate with severity of symptoms or degree of obstruction. BPH usually results in a smooth, firm, elastic enlargement of the prostate. Induration, if detected, must alert the physician to the possibility of cancer and the need for further evaluation (ie, PSA, transrectal ultrasound [TRUS], and biopsy).

Symptom scores

Self-administered questionnaire developed by the American Urological Association (AUA)/ International Prostate symptom score (IPSS) is both valid and reliable in identifying the need to treat patients and in monitoring their response to therapy.[12]

The IPSS questionnaire is the single most important tool used in the evaluation of patients with BPH and is recommended for all patients before the initiation of therapy. This assessment focuses on seven items that ask patients to quantify the severity of their obstructive or irritative complaints on a scale of zero to five. Thus, the score can range from zero to 35. A symptom score of zero to seven is considered mild, eight to 19 is considered moderate, and 20 to 35 is considered severe.

Table 1: International prostate symptom score (IPSS)

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	**Your score**
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times or more	**Your score**
Nocturia Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	
Total IPSS score							

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed – about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Investigations

Analysis of urine to exclude infection or haematuria and serum creatinine measurement to assess renal function is important. Renal insufficiency may be observed in 10% of patients with prostatism and warrants upper-tract imaging. Patients with renal insufficiency are at an increased risk of developing postoperative complications following surgical intervention for BPH. Serum PSA is included in the initial evaluation. PSA, compared with DRE alone, certainly increases the ability to detect PCa.

Cystoscopy is not recommended to determine the need for treatment but may assist in choosing the surgical approach in patients opting for invasive therapy.

Cystometrograms and urodynamic profiles are reserved for patients with suspected neurologic disease or those who have failed prostate surgery. Measurement of flow rate, determination of post-void residual urine, and pressure flow studies are considered optional.

Differential Diagnosis

- Urethral stricture
- Bladder neck contracture
- Bladder stone
- PCa
- Urinary tract infection

Treatment

Specific treatment recommendations can be offered for certain groups of patients. For those with mild symptoms, watchful waiting only is advised. On the other end of the therapeutic spectrum, absolute surgical indications include refractory urinary retention (failing at least one attempt at catheter removal), recurrent urinary tract infection from BPH, recurrent gross haematuria from BPH, bladder stones from BPH, renal insufficiency from BPH, or large bladder diverticula.[12]

Available treatment modalities include the following

- Watchful waiting
- Medical therapy
    - Alpha blockers
    - Five-Alpha reductase inhibitors
    - Combination therapy
    - Phytotherapy
- Conventional surgical therapy
    - Transurethral resection of prostate
    - Transurethral incision of prostate
    - Open simple prostatectomy
- Minimally invasive therapy
    - Laser therapy
    - Transurethral electro-vaporisation of the prostate
    - Microwave Hyperthermia

- Transurethral needle ablation of the prostate
- High-intensity focused ultrasound
- Intraurethral stents

Carcinoma of the Prostate

Incidence and epidemiology

PCa is the second leading cause of cancer death for men. According to the World health organization the total number of worldwide deaths due to PCa has shown an increase from 239,000 deaths in 1998 to 262,000 in 2002.[2] It is estimated that PCa was responsible for 11,700 deaths in India in 2005.[3] Of all cancers, the prevalence of PCa increases the most rapidly with age. However, unlike most cancers, which have a peak age of incidence, the incidence of PCa continues to increase with advancing age.[13]

Risk factors for prostate cancer

- Increasing age
- Race: African Americans are at a higher risk than whites
- Age of onset of prostate cancer: Age of disease onset in the family member with the diagnosis of PCa affects a patient's relative risk. Earlier the age of onset, higher is the relative risk
- Diet - Incidence is lower in populations with a low fat, high fiber diet

Molecular Genetics and Pathobiology

Molecular profiling of human tissues has identified differential expression of specific genes and proteins in the progression from normal precursor tissue to preneoplastic lesions to cancer (both androgen dependent and independent). In doing so diagnostic, prognostic, and therapeutic markers have been discovered. Chromosomal rearrangements or copy number abnormalities at 8p, 10q, 11q, 13q, 16q, 17p, and 18q have been described in PCa. Some of these such as specific loss at 8p23.2 and/or gain at 11q13.1 are predictive of PCa progression. The entire prostate microenvironment, not just the epithelial compartment, is important for both normal and neoplastic growth as significant epithelial-mesenchymal/ stromal interactions occur.[14,15]

Molecular events may not always be spontaneous, but the product of environmental influences. For instance, both epidemiologic and molecular data suggest that inflammation may be related to PCa development.[16]

Proliferative inflammatory atrophy lesions containing activated inflammatory cells and proliferating epithelial cells appear likely to be precursors to prostatic intraepithelial neoplastic (PIN) lesions and PCa.

The number of PCas attributable to heritable factors may be greater than once thought.[17] Although the loci 1p, 3q, 5q, and 22q have been identified as harboring potential predisposition genes in those with a family history of PCa, a multigene model may best explain familial clustering of this disease. In addition, men with a family history of breast and/or ovarian cancer may be offered a

predictive genetic test to determine whether or not they carry the family specific BRCA1/2 mutations as they are at increased risk of breast and PCa.

Pathology

Over 95% of the cancers of the prostate are adenocarcinomas. Of the other five percent, 90% are transitional cell carcinomas, and the remaining cancers are neuroendocrine ("small cell") carcinomas or sarcomas.

PIN and atypical small acinar proliferation are thought to be precursor lesions. Men found to have either lesion may be at an increased risk of PCa and warrant repeat biopsy certainly if an extended core biopsy was not performed initially. High-grade PIN (HGPIN) is characterized by cellular proliferations within preexisting ducts and glands, with nuclear and nucleolar enlargement similar to prostate cancer. However, unlike cancer, HGPIN retains a basal cell layer identifiable by immunohistochemistry.

Approximately, 60 to 70% of cases of PCa originate in the peripheral zone, 10 to 20% originate in the transition zone, and five to 10% in the central zone.

The histology of the remaining five percent of PCa is heterogenous, arising from stromal, epithelial, or ectopic cells. Non-adenocarcinoma variants can be categorized into two groups based on the cellular origin: epithelial and nonepithelial. Epithelial variants consist of endometrioid, mucinous, signet-ring, adenoid cystic, adenosquamous, squamous cell, transitional cell, neuroendocrine, and comedocarcinoma. Nonepithelial variants include rhabdomyosarcoma,

leiomyosarcoma, osteosarcoma, angiosarcoma, carcinosarcoma, malignant lymphoma, and metastatic neoplasms among others. It is becoming increasingly evident that neuroendocrine differentiation may occur in response to prolonged androgen deprivation. This can be recognized by staining such tissue for neuroendocrine markers (chromogranin A, neuron-specific enolase) and/or by measuring such markers in serum.

Grading and staging

The Gleason grading system is the most commonly employed grading system. It is truly a system that relies upon the low-power appearance of the glandular architecture under the microscope. In assigning a grade to a given tumour, pathologists assign a primary grade to the pattern of cancer that is most commonly observed and a secondary grade to the second most commonly observed pattern in the specimen.

Grades range from one to five. If the entire specimen has only one pattern present, then both the primary and secondary grade are reported as the same grade. The Gleason score or Gleason sum is obtained by adding the primary and secondary grades together. As Gleason grades range from one to five, Gleason scores or sums thus range from two to 10.

Well-differentiated tumours have a Gleason sum of two to four, moderately differentiated tumours have a Gleason sum of five to six, and poorly differentiated tumours have a Gleason sum of eight to 10.

TNM Staging

The TNM system was first adopted in 1975 by the American Joint Committee for Cancer Staging and End Results Reporting (AJCC).[4]

Primary Tumour (T)

Clinical

- TX - Primary tumour cannot be assessed.
- T0 - No evidence of primary tumour.
- T1 - Clinically inapparent tumour neither palpable nor visible by imaging.
- T1a - Tumour incidental histologic finding in five percent or less of tissue resected.
- T1b - Tumour incidental histologic finding in more than five percent of tissue resected.
- T1c - Tumour identified by needle biopsy (e.g., because of elevated PSA).
- T2 Tumour confined within prostate.
- T2a Tumour involves one-half of one lobe or less.
- T2b Tumour involves more than one-half of one lobe but not both lobes.
- T2c Tumour involves both lobes.
- T3 Tumour extends through the prostate capsule.
- 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, and/or pelvic wall.

Pathologic (pT)

- pT2 Organ confined.
- pT2a Unilateral, one-half of one lobe or less.
- pT2b Unilateral, involving more than one-half of lobe but not both lobes
- pT2c Bilateral disease.
- pT3 Extraprostatic extension.
- pT3a Extraprostatic extension.
- pT3b Seminal vesicle invasion.
- pT4 Invasion of bladder, rectum.

Regional Lymph Nodes (N)

Clinical

- NX Regional lymph nodes were not assessed.
- N0 No regional lymph node metastasis.
- N1 Metastasis in regional lymph node(s).

Pathologic

- pNX Regional nodes not sampled.
- pN0 No positive regional nodes.
- pN1 Metastases in regional node(s).

Distant Metastasis (M).

- MX Distant metastasis cannot be assessed (not evaluated by any modality).
- M0 No distant metastasis.
- M1 Distant metastasis
- M1a Nonregional lymph node(s)
- M1b Bone(s)
- M1c Other site(s) with or without bone disease

Stage Grouping

I	T1a	N0	M0	G1
II	T1a	N0	M0	G2,3–4
T1b	N0	M0		Any G
T1c	N0	M0		Any G
T1	N0	M0		Any G
T2	N0	M0		Any G
III	T3	N0	M0	Any G
IV	T4	N0	M0	Any G
Any T	N1	M0		Any G
Any T	Any N	M1		Any G

Patterns of Progression

The likelihood of local extension outside the prostate (extracapsular extension) or seminal vesicle invasion and distant metastases increases with increasing tumour volume and more poorly differentiated cancers. Small and well-differentiated cancers (grades one and two) are usually confined to the prostate, whereas large-volume (>four cm3) or poorly differentiated (grades four and five) cancers are more often locally extensive or metastatic to regional lymph nodes or bone. Penetration of the prostatic capsule by cancer is a common event and often occurs along perineural spaces. Seminal vesicle invasion is associated with a high likelihood of regional or distant disease. Locally advanced PCa may invade the bladder trigone, resulting in ureteral obstruction. Of note, rectal involvement is rare as Denonvilliers' fascia represents a strong barrier.

Lymphatic metastases are most often identified in the obturator lymph node chain. Other sites of nodal involvement include the common iliac, presacral, and periaortic lymph nodes. The axial skeleton is the most usual site of distant metastases, with the lumbar spine being most frequently implicated. The next most common sites in decreasing order are proximal femur, pelvis, thoracic spine, ribs, sternum, skull, and humerus. The bone lesions of metastatic PCa are typically osteoblastic. Involvement of long bones can lead to pathologic fractures. Vertebral body involvement with significant tumour masses extending into the epidural space can result in cord compression. Visceral metastases most commonly involve the lung, liver, and adrenal gland. Central nervous system involvement is usually a result of direct extension from skull metastasis.

Clinical features

Symptoms

Most patients with early PCa are asymptomatic. The presence of symptoms indicates locally advanced or metastatic disease. Obstructive or irritative voiding complaints can result from local growth of the tumour into the urethra or bladder neck or from its direct extension into the trigone of the bladder. Metastatic disease to the bones may cause bone pain. Metastatic disease to the vertebral column with impingement on the spinal cord may be associated with symptoms of cord compression, including paresthesias and weakness of the lower extremities and urinary or faecal incontinence.

Signs

A physical examination, including a DRE, is needed. Induration, if detected, must alert the physician to the possibility of cancer and the need for further evaluation (i.e., PSA, TRUS, and biopsy). Locally advanced disease with bulky regional lymphaedenopathy may lead to lymphoedema of the lower extremities. Specific signs of cord compression relate to the level of the compression and may include weakness or spasticity of the lower extremities and a hyperreflexic bulbocavernosus reflex.

Laboratory findings

Azotemia can result from bilateral ureteral obstruction either from direct extension into the trigone or from retroperitoneal lymphaedenopathy. Anaemia may be present in metastatic disease. Alkaline phosphatase may be elevated in

the presence of bone metastases. Serum acid phosphatase may be elevated with disease outside the confines of the prostate.

Prostate cancer tumour markers

The discovery and utilisation of tumour markers have positively affected early detection, diagnosis, and staging for many malignancies. By improving early detection, tumour markers contribute to improved curative success rates. Optimal treatment and cure depend not only on accurate and early diagnosis but also on reliable follow-up for efficient detection of clinical recurrence.

Among urologic malignancies, PCa has greatly benefited from the discovery and application of tumour markers. Since its discovery in 1979 to clinical application in the late 1980s through 1990s, PSA has evolved into an invaluable tool for the detection, staging, and monitoring of men diagnosed with PCa.[18,19] The widespread use of PSA screening has generated greater awareness about prostate cancer. During the PSA era, identification of cancers while confined to the prostate has improved curability with either radical prostatectomy or radiation therapy. Whereas the majority of PCas in the 1980s and early 1990s commonly arose with an abnormal DRE or elevated PSA, or both, today most PCa arises as clinically nonpalpable (stage T1c) disease with PSA between 2.5 and 10 ng/mL. The evolving demographics and natural history of PCa have resulted in a stage migration to nonpalpable, clinically localized (stage T1c) disease and a parallel reduction in mortality.[20] Although PSA screening has improved survival, outcomes are not the same for all T1c detected disease as some of these cancers may not pose a threat to survival.[21]

A source of PCa markers has been identified among the protein products of the human kallikrein gene family. The serine proteases encoded by the three originally described genes have been identified as KLK1 (hk1 or hPRK), KLK2 (hK2 or hGK-1), and KLK3 (hK3 or PSA). The amino acid sequence has been demonstrated to be similar among these serine proteases, with hK1 expressing 60% and hK2 expressing 78% homology with PSA.[22]

Prostate-Specific Antigen (PSA or hK3)

The most notable marker in the kallikrein family is hK3, also known as PSA. It was first identified and purified in the late 1970s, but widespread use in clinical urology did not occur for another decade.[23] PSA is a 33-kD glycoprotein that acts as a serine protease. The ectopic expression of PSA has been reported in smaller concentrations in the tissue of malignant breast tumours, normal breast tissue, breast milk, female serum, and adrenal and renal carcinomas. However, for practical and clinical purposes PSA is organ specific, primarily produced by the prostatic luminal epithelial cells.[24] Although it is organ specific, PSA is not cancer specific, as demonstrated by the substantial overlap in values between men with benign versus malignant prostate disease.[25] The function of this androgen-regulated protease is to liquefy semen through its action on the gel-forming proteins semenogelin and fibronectin within the semen following ejaculation.[26]

PSA is normally found in low concentration in sera (ng/mL). Within sera, PSA circulates in both bound and unbound forms. The concentrations found in seminal plasma range from 0.5 to 5.0 mg/mL, whereas the normal serum

concentration in men aged 50 to 80 years without prostate disease ranges between 1.0 and 4.0 ng/mL.[27]

PSA is probably cleared from the blood through the liver as the size of the complexed structure is too large for glomerular filtration.[28] The serum half-life of PSA, calculated after removal of all prostate tissue, is two to three days.[29]

Prostate cancer cells do not necessarily make more PSA than do normal prostate cells, and elevated serum levels are probably a result of cancer progression and destabilization of the prostate histologic architecture.[29]

Studies have demonstrated that prostate cancer cells do not make more PSA but rather make less PSA than normal prostatic tissue.[30]

Factors Influencing the Serum Level of Prostate Specific Antigen

Prostate specific antigen expression is strongly influenced by androgens.[31] Immunohistochemical detection of PSA within the prostate is characterized by bimodal peaks between zero and six months and after 10 years, correlating directly with testosterone levels. Serum PSA becomes detectable at puberty with increases in luteinizing hormone and testosterone. In the absence of prostate cancer, serum PSA levels vary with age, race, and prostate volume. In men without BPH, the rate of change in PSA is 0.04 ng/mL per year, compared with 0.07 to 0.27 ng/mL per year in men with BPH who are between the ages of 60 and 85 years. On a volume/volume basis that the benign prostatic tissue of black men contributes more PSA to sera than does the benign prostatic tissue of white men a difference that increases with age. Elevated serum PSA levels are probably

a product of disruption of cellular architecture within the prostate gland. The loss of the barrier afforded by the basal layer and basement membranes within the normal gland is a likely site for the egress of PSA into the circulation. This can occur in the setting of prostate disease (BPH, prostatitis, PCa) and with prostate manipulation (prostate massage, prostate biopsy). Prostatic inflammation (acute and chronic) and urinary retention can cause PSA elevations to variable degrees.

PSA elevations may not be related to the histologic finding of inflammation in men without clinical prostatitis. Prostatic trauma such as occurs after prostatic biopsy can result in a leak of PSA into the circulation that may require more than 4 weeks for return to baseline values. DRE as performed in an outpatient setting can lead to increases in serum PSA. However, the change in PSA after DRE would not appear to be clinically significant.

The presence of prostate disease (PCa, BPH, and prostatitis) is the most important factor affecting serum levels of PSA. PSA elevations may indicate the presence of prostate disease, but not all men with prostate disease have elevated PSA levels. Furthermore, PSA elevations are not always specific for PCa.

Prostate-directed treatment (for both BPH and cancer) can lower serum PSA by decreasing the volume of prostatic epithelium available for PSA production and by decreasing the amount of PSA produced per cell. Manipulation of the hormonal environment for treatment of cancer and BPH with orchiectomy, luteinizing hormone–releasing hormone analogues, and 5α-reductase inhibition; radiotherapy; and surgery for BPH or cancer can all lead to reductions in serum PSA. Finasteride (five mg) and other 5α-reductase inhibitors for treatment of

BPH have been shown to lower PSA levels by an average of 50% after six months of treatment.[32] Thus, one can multiply the PSA level by two to obtain the "expected" PSA level of a patient who has been taking finasteride for six months or more. Men who are to be treated with Finasteride should have a baseline PSA measurement before initiation of treatment and should be observed with serial PSA measurements as this drug may decrease PSA serum levels by up to 50%. If PSA does not decrease by 50% or if there is a rise in PSA when the patient is taking Finasteride, the patient should be suspected of having occult prostate cancer and undergo further testing.

Clinical Use of Serum Prostate-Specific Antigen Levels

Early studies had established the reference range of 0 to 4.0 ng/mL to define normal serum PSA levels. The choice of a PSA threshold or cut point above which one would recommend further evaluation to rule out PCa is controversial.[33] Although the PSA threshold of 4 ng/mL has been most commonly used, the PSA threshold that most efficiently balances the dual goal of reducing cancer mortality and reducing unnecessary testing (PSA measurements and biopsies) is not known.

Gann and co-workers (1995) evaluated the ability of a single PSA measurement to predict the later development of prostate cancer among men in the Physicians Health Study observed for a decade after serum donation. This evaluation demonstrated that maximum validity (consideration of both sensitivity and specificity together) occurred at a PSA threshold of 3.3 ng/mL and that overall validity was not statistically significantly different when comparing PSA

thresholds of 3.3 and 4 ng/mL. The determination of sensitivity and specificity at given PSA thresholds does not provide information on the biologic characteristics of the cancers detected.

Early studies recognized that the positive predictive value of PSA testing for cancer detection increased from 12% to 32% for PSA levels of 4 to 10 ng/mL and as high as 60% to 80% for levels above 10 and 20 ng/mL.[34]

Thus, men with PSA levels greater than 10 ng/mL and benign DRE have up to a 60% likelihood of being diagnosed with cancer and are unlikely to benefit from further improvement of PSA sensitivity and specificity. These percentages are even more pronounced for levels greater than 20 ng/mL or when DRE is suspicious for PCa.

Following surgery, many of these cancers are discovered to have escaped the prostate. Thus, men with PSA levels above 10 ng/mL should undergo biopsy regardless of PSA derivative values.

PSA derivatives

Numerous strategies to refine PSA for cancer detection have been explored. Their common goal is to decrease the number of false-positive test results. This would increase the specificity and positive predictive value of the test and lead to fewer unnecessary biopsies, lower costs, and reduced morbidity of cancer detection. Attempts at refining PSA have included PSA velocity (change of PSA over time), PSAD (standardizing levels in relation to the size of the prostate), age-adjusted PSA reference ranges (accounting for age-dependent

prostate growth and occult prostatic disease), and PSA forms (free versus protein bound molecular forms of PSA).

PSA velocity

PSA velocity refers to the rate of change of serum PSA. A retrospective study has shown that men with prostate cancer have a more rapidly rising serum PSA in the years before diagnosis than do men without PCa. Patients whose serum PSA increases by 0.75 ng/mL/y appear to be at an increased risk of harboring cancer. However, PSA velocity must be interpreted with caution. An elevated PSA velocity should be considered significant only when several serum PSA assays are carried out by the same laboratory over a period of at least 18 months. As a screening tool in large population based studies, PSA velocity appeared to add little to enhance early detection of PCa. However, it is becoming increasingly clear that those with rapid PSA velocity (that is, PSA doubling times less than six months) both before diagnosis and/or after treatment are at an increased risk of failure of initial treatment, the development of metastases and PCa specific mortality.[35,36]

PSA density

The majority of men with PSA elevations greater than 80% have serum levels in the range of 4 to 10 ng/mL.[27] In these men, the most likely reason for the PSA elevation is prostate enlargement, not PCa, because of the high prevalence of BPH in this population. Benson and colleagues[37] introduced a method to correlate more directly the degree to which cancer contributes to the serum PSA and to compensate for BPH and prostate size as determined from transrectal

ultrasonography. A direct relationship between PSAD and the likelihood of cancer has been documented. For patients with a PSA value between 4.0 and 10.0 ng/mL and a normal DRE, a PSAD greater than 0.15 has been suggested as discriminatory for the presence of cancer.

The usefulness of PSAD in prostate cancer detection has not been confirmed in all studies. Catalona and colleagues (1994) found that PSAD failed to detect up to 50% of cancers in men with PSA values within the diagnostic gray zone of four to 10 ng/mL. Higher PSAD may be found among groups of men with positive biopsies compared with men with negative biopsies because PCa are more likely to be found when a constant number of biopsies are obtained in men with smaller prostate volumes than in men with larger prostate volumes.[38]

Age-adjusted reference ranges for PSA

Age adjusted PSA values for normal men are presented in Table 1. It is thought that the rise in PSA with increasing age results from prostate gland growth from BPH, the higher incidence of subclinical prostatitis, and the growing prevalence of microscopic, clinically insignificant PCa. Age-adjusted reference ranges increase the sensitivity in younger patients and increase the specificity in older patients. Concerns over the general applicability of these reference ranges have been raised because they were derived from American Midwestern white men.

Table 2: Age-adjusted reference ranges for PSA

Age (Years)	PSA – Normal Ranges (ng/L)
40-49	0-2.5
50-59	0-3.5
60-69	0-4.5
70-79	0-6.5

Racial variations in PCa detection

Previously, it was noted that in men without PCa, African American men presented with higher baseline serum PSA and PSAD. In addition, African American men had worse outcomes (cancer recurrence and mortality) compared to Caucasian, Hispanic, and Asian American men. Differential screening practices were recommended based on these results.[39] However, more contemporary analyses suggest that these discrepancies are disappearing. In addition, much of any variation noted may be more strongly related to education, insurance status, and access to health care than ethnicity.[40]

Molecular forms of PSA

The most recent refinement in PSA has been the recognition of the various molecular forms of PSA—free and protein-bound. Approximately 90% of the serum PSA is bound to alpha-1-antichymotrypsin, and lesser amounts are free or are bound to alpha-2-macroglobulins. In the latter form, no epitopes to the antibodies used in the current assays are available, while PSA bound to alpha-1-

antichymotrypsin may have 3 of its 5 epitopes masked. Early studies suggest that PCa patients demonstrate a lower percentage of free PSA than do patients with benign disease. A large multicenter study has reported that in men with a normal DRE and a total PSA level between four and 10 ng/ mL, a 25% free PSA cutoff would detect 95% of cancers while avoiding 20% of unnecessary biopsies. The cancers associated with more than 25% free PSA were more prevalent in older patients and generally were less threatening in terms of tumour grade and volume.[27]

The role for percent free PSA is more applicable to PSA levels less than 10 ng/mL as the positive predictive rate of total PSA above 10 to 20 ng/mL has been demonstrated to be as high as 80%.[41] Currently, percent free PSA is approved by the Food and Drug Administration for use to aid PSA testing in men with benign DRE and minimal PSA elevations, within the diagnostic grey zone of 4 to 10 ng/mL.[42]

Imaging in carcinoma of prostate

Gray Scale transrectal Ultrasonography (TRUS)

Gray-scale TRUS has become the most common imaging modality for the prostate. Most commonly used for PCa detection, TRUS may also be used in the evaluation of other conditions such as infertility. Although the role of TRUS is expanding in directing the biopsy PCa, the role of staging localized prostate cancer using TRUS is very limited.[43]

TRUS is useful in performing prostatic biopsies and in providing some useful local staging information if cancer is detected. Almost all prostate needle biopsies are performed under TRUS guidance. This allows uniform spatial separation and sampling of the regions of the prostate and also makes lesion-directed biopsies possible.

Commercially available endorectal probes come in both side- and end-fire models and transmit frequencies of six to 10 MHz. Most modern ultrasound machines have optimized self-programming for TRUS and biopsy. Some newer biplane probes provide simultaneous sagittal and transverse imaging modes. Probes provide a scanning angle approaching 180 degrees to allow simultaneous visualization of the entire gland in both the transverse and sagittal planes. Increasing frequency yields increased resolution. As the frequency of the probe is increased, the portion of the image that is in focus (focal range) is closer to the transducer.[44]

The commonly used 7-MHz transducer produces a high resolution image with a focal range from one to four cm from the transducer (best for Peripheral Zone where most cancers arise).

Acoustic properties of soft tissue are similar to those of water, but clinically useful ultrasound energy does not propagate through air. For this reason, a water-density substance, termed a coupling medium, is used. The coupling medium, usually sonographic jelly or lubricant, is placed between the probe and the rectal surface. If the probe is covered with a protective condom, the

coupling medium is placed between the probe and the condom, as well as between the condom and the rectal surface.

Prostate cancer imaging on TRUS

TRUS provides more accurate local staging than does DRE. The sonographic criteria for extracapsular extension are bulging of the prostate contour or angulated appearance of the lateral margin. The criteria for seminal vesicle invasion are a posterior bulge at the base of the seminal vesicle or asymmetry in echogenicity of the seminal vesicle associated with hypoechoic areas at the base of the prostate.

All hypoechoic lesions within the Peripheral zone should be noted and included in the biopsy material. The lack of a distinct hypoechoic focus does not preclude proceeding with biopsy because 39% of all cancers are isoechoic and up to 1% of tumours may be hyperechoic on conventional gray-scale TRUS[45]. Despite the higher prevalence of cancers discovered in prostates with hypoechoic areas, the hypoechoic lesion itself was not associated with increased cancer prevalence compared with biopsy cores from isoechoic areas in a contemporary series of almost 4000 patients.[43] Furthermore, other disease processes such as granulomatous prostatitis, prostatic infarct, and lymphoma may all produce hypoechoic lesions. Transitional zone BPH nodules are typically hypoechoic but may contain isoechoic or even hyperechoic foci. A hypoechoic lesion is malignant in 17% to 57% of cases[46] highlighting the need to biopsy these lesions but recognizing that they are not pathognomonic for cancer as was once thought.

TRUS also enables measurement of the prostate volume, which is needed in the calculation of PSAD.

Endorectal magnetic resonance imaging (MRI)

Use of an endorectal coil improves cancer detection and staging compared to the use of a standard body coil. While rendering high image quality, the use of an endorectal coil appears to be operator dependent, requiring education and expertise. Routine use of this technology may not alter treatment decisions compared to the information gained by assessment of more standard clinopathologic information. Use of magnetic resonance spectroscopy (MRS) in conjunction with MRI may improve the accuracy of imaging. PCa is associated with proportionately lower levels of citrate and higher levels of choline and creatine compared to BPH or normal prostate tissue. The combined metabolic and anatomic information provided by MRI and MRS may allow for a more accurate assessment of cancer location and stage. The reported staging accuracy of endorectal MRI varies from 51% to 92%. It appears to add novel information to the assessment of some patients over the use of nomograms alone, but may be best utilized in high-risk patients where it is most accurate and helpful.[47]

Axial imaging (CT, MRI)

Cross-sectional imaging of the pelvis in patients with PCa is selectively performed to exclude lymph node metastases in high-risk patients who are thought to be candidates for definitive local therapy, whether it be surgery or irradiation. Both MRI and computed tomography (CT) are used for this purpose. Patients identified as having lymphaedenopathy on imaging may undergo CT-

guided fine-needle aspiration. If lymph node metastases are confirmed, such patients may be candidates for alternative treatment regimens. However, the incidence of lymph node metastases in contemporary radical prostatectomy series is low (<10%). In addition, imaging is costly and its sensitivity is limited (30 to 40%). Various criteria can be used to identify patients for axial imaging, including negative bone scans and either T3 cancers or a PSA >20 ng/mL and primary Gleason grade four or five cancers. Intravenous administration of superparamagnetic nanoparticles, which gain access to lymph nodes by means of interstitial-lymphatic fluid transport, at the time of high-resolution MRI, appears to improve visualization of small nodal metastases. Analyses of several contemporary series of patients with clinically localized PCa suggest that the risk of lymph node metastases is low and that its risk can be quantified on the basis of serum PSA, local tumour stage, and tumour grade.

Bone scan

When PCa metastasizes, it most commonly does so to the bone. Soft tissue metastases (eg, lung and liver) are rare at the time of initial presentation. Although a bone scan has been considered a standard part of the initial evaluation of men with newly diagnosed PCa, good evidence has been accumulated that it can be excluded in most of these men on the basis of serum PSA. Several investigators have shown that bone scans can be omitted in patients with newly diagnosed, untreated PCa who are asymptomatic, have T1 and T2 disease, and have serum PSA concentrations <15 ng/mL. However, patients with PSA 15 ng/mL or greater, locally advanced disease (T3b, T4) are at higher risk for bone metastases and should be considered for bone scan.

Antibody imaging

ProstaScint[48] is a murine monoclonal antibody to an intracellular component of the prostate-specific membrane antigen (PSMA), which is conjugated to 111 Indium. After infusion of the antibody, single photon emission computed tomography (SPECT) images are usually obtained at 30 minutes to access vasculature and at 72–120 hours. It has been approved by the U.S. Food and Drug Administration for use in the evaluation of patients prior to treatment and for detecting the site of recurrent disease in patients who have biochemical relapse after initial treatment. However, this antibody recognizes the intracellular domain of PSMA; only soft tissues are imaged and the test may suffer from both false-positive and negative results in both clinical situations described above. Use of new antibodies, which recognize the extracellular domain of PSMA, appear to allow for recognition of both bone and soft tissue metastases and could be used as agents for therapy, not only improved imaging.

Prostate Biopsy

Indications for prostate biopsy

Before TRUS improvements and serum PSA testing became widespread, clinicians relied mainly on digital rectal examination to establish a suspicion of PCa and performed digitally directed lesional biopsies. Nowadays, PSA-based screening of asymptomatic men has resulted in the adaptation of TRUS biopsy as the standard of care for routine prostate biopsy. The presence of focal nodules on DRE still will prompt a biopsy using the TRUS technique regardless of PSA

levels. TRUS-directed prostate needle biopsy remains the gold standard for diagnosis of PCa.

Although most clinicians recommend biopsy once a patient's serum PSA rises above 4.0 ng/mL, significant research efforts are ongoing to identify the optimal PSA threshold to recommend prostate biopsy in the asymptomatic patient. Evidence for lowering the PSA threshold from work by Catalona's group showed higher rates of organ-confined disease at the time of radical retropubic prostatectomy in men sampled with PSAs in the 2.6- to 4.0-ng/mL range.[49]

The indications for TRUS and prostate biopsy are rapidly evolving and being continually refined.

Indications for TRUS-Directed Biopsy

Diagnosis of suspected symptomatic prostate cancer

- Screening for PCa in asymptomatic patient > age 50 with > a 10-year life expectancy
- Prior to intervention in symptomatic BPH
- Prior to cystoprostatectomy or orthotopic urinary diversion
- To diagnose failed radiation therapy before use of second-line therapy
- Follow-up biopsy (three to six months) after diagnosis of high-grade PIN

Complications of Prostate biopsy

Prostate biopsy is usually performed using local anesthesia and pre-procedure antibiotic prophylaxis. Although prostate biopsy is usually very well

tolerated by patients, approximately 10–24% of those undergoing the procedure will find it very painful. The use of local anesthesia, either applied topically along the anterior rectal wall, injected into or adjacent to the prostate, or a combination of the two, decreases pain associated with the procedure. Haematospermia and haematuria are common occurring in approximately 40–50% of patients. Minor rectal bleeding may occur, as well. High fever is rare occurring in 2.9–4.2% of patients.

Treatment of Carcinoma of Prostate

Early disease

Curative treatment can only be offered to patients with early disease (T1a, T1b, T1c and T2). T1a disease found incidentally at TURP is by definition low volume and usually well differentiated. This stage can usually be managed by active surveillance, with three to six monthly DRE and PSA measurement, considering treatment if there is disease progression. The options available need to take into account patient age, performance status and lifestyle preferences.

Radical prostatectomy

Radical prostatectomy is only suitable for localised disease (T1 and T2) and should only be carried out in men with a life expectancy of more than ten years. Exclusion of metastasis should include a bone scan, chest radiograph and a PSA of less than 20ng/ml. It results in a high incidence of impotence, but a low incidence of severe stress incontinence, which might require the fitment of an artificial urinary sphincter. It involves removal of the prostate down to the distal

sphincter mechanism in addition to the seminal vesicles. The bladder neck is reconstituted and reanastomosed to the urethra. Careful dissection in cases of early stage disease has lead to preservation of the neurovascular bundles that lie behind the prostate. This has resulted in preservation of erectile function in 60-70% of the cases. Recently robotic guided laparoscopic techniques of radical prostatectomy have been introduced.[50]

Radical radiotherapy for early PCa

External beam radiotherapy (EBRT) can be administered in fields that conform to the contours of the prostate, thereby limiting exposure of adjacent tissues. Survival rates following treatment of T1 and low volume T2 disease are not greatly different from those following radical prostatectomy, although histological evidence of persistent tumour is found within the prostate within the prostate in about 30% of treated patients.[51] Patients with locally advanced disease (T3) may be treated by radiotherapy, but most urologists tend to treat such patients by means of androgen ablation therapy. The treatment requires the patient to attend the hospital on a daily basis for four to six weeks. Common complications include irritation of the bladder, urinary frequency, urgency and sometimes urge incontinence and similar problems affecting the rectum with diarrhoea and, occasionally radiation proctitis. Loss of erectile dysfunction is less common, usually affecting upto 30% of the patients.

Brachytherapy

Under transrectal ultrasound guidance, radioactive seeds are permanently implanted into the prostate. A computer programme converts accurate ultrasound

measurements of the prostate gland to construct a plan for the gland. Under anaesthesia, the patient is placed in the lithotomy position and, according the template plan, seeds are placed through transperineal needles. The radioisotopes commonly used are Iodine-125 and Palladium-103. The isotopes deliver an intense, confined radiation dose, which falls off rapidly to spare the surrounding tissues. Brachytherapy is ideal for low volume low grade T1 disease. A major factor for its increasing popularity is reduced pre-operative complications and generally low morbidity. Long term results are encouraging.

Advanced disease

There is still debate about the timing of androgen ablation treatment in patients with locally advanced or metastatic disease without symptoms. The options are androgen deprivation at diagnosis or careful review, reserving active treatment for the later development of symptoms. Patients with poorly differentiated carcinoma have a risk of catastrophic events such as spinal cord compression; in these patients early androgen ablation can prolong time to complications. Also, patients with local and or general symptoms should be offered androgen deprivation.

Orchidectomy is performed to carry out androgen ablation in the treatment of locally advanced (T3 or T4) disease, or of metastatic disease. Bilateral orchidectomy, whether total or sub-capsular will eliminate the major source of testosterone production.

Since death due to PCa is almost invariably a result of failure to control metastatic disease, a great deal of research has concentrated on efforts to improve

control of distant disease. It is well known that most prostatic carcinomas are hormone dependent and that approximately 70–80% of men with metastatic PCa respond to various forms of androgen deprivation. Testosterone, the major circulating androgen, is produced by the Leydig cells in the testes (95%), with a smaller amount being produced by peripheral conversion of other steroids. Although 98% of serum testosterone is protein bound, free testosterone enters prostate cells and is converted to dihydrotestosterone (DHT), the major intracellular androgen. DHT binds to a cytoplasmic receptor protein and the complex moves to the cell nucleus, where it modulates transcription. Androgen deprivation may be induced at several levels along the pituitary-gonadal axis using a variety of methods or agents. Use of a class of drugs (LHRH agonists) has allowed induction of androgen deprivation without orchiectomy or administration of diethylstilbestrol. There are four LHRH agonists currently approved for the treatment of prostate cancer: goserelin acetate, triptorelin pamoate, histrelin acetate, and leuprolide acetate. These can be delivered by injection monthly or as depot preparations lasting three to six months. A subcutaneous implant that releases leuprolide acetate at a constant rate for one year is also available. Agonists would avoid the “flare” phenomenon associated with antagonists where serum testosterone concentrations increase before falling. Such an increase could cause symptoms in those with advanced cancer. Currently, administration of LHRH agonists is the most common form of primary androgen blockade used. Because of its rapid onset of action, ketoconazole should be considered in patients with advanced prostate cancer who present with spinal cord compression or disseminated intravascular coagulation. Although

testosterone is the major circulating androgen, the adrenal gland secretes the androgens dehydroepiandrosterone, dehydroepiandrosterone sulfate, and androstenedione. Some investigators believe that suppressing both testicular and adrenal androgens (complete androgen blockade) allows for a better initial and a longer response compared with those methods that inhibit production of only testicular androgens. Complete androgen blockade can be achieved by combining an antiandrogen with the use of an LHRH agonist or orchidectomy. Antiandrogens[52] appear to act by competitively binding the receptor for DHT, the intracellular androgen responsible for prostatic cell growth and development.

High-dose antiandrogen monotherapy (bicalutamide 150 mg/day) is an alternative to castration both in patients with locally advanced and metastatic disease who are interested in maintaining libido and erectile function. In those with locally advanced disease, no significant difference in overall survival has been demonstrated between bicalutamide monotherapy and castration. However in those with metastatic disease, castration is associated with better survival.

Table 3: Androgen ablation therapy for prostate cancer

Level	Agent	Route	Dose(mg)	Frequency
Pituitary				
	Diethystilbesterol	Oral	1-3	Daily
	Goserelin	Subcutaneous	10.8	Every 3 months
	Goserelin	Subcutaneous	3.6	Every month
	Leuprolide	Intramuscular	22.5	Every 3 months
	Leuprolide	Intramuscular	7.5	Every month
Adrenal				
	Ketoconazole	Oral	400	Daily
Testicle				
	Orchidectomy			
Prostate cell				
	Bicalutamide	Oral	50	Daily
	Flutamide	Oral	250	TID
	Nilutamide	Oral	150	Daily

METHODOLOGY

This study was conducted at the KLES' Prabhakar Kore Hospital and Research centre, Belgaum between October 2007 and September 2008. After obtaining approval from the institutional ethics committee, written informed consent was taken from all the patients who were included in the study.

The participants in the study were male patients who presented with lower urinary tract symptoms and were over forty five years of age.

A pre-designed and pre-tested pro forma was used for this study.

Study design

This study was designed as a pilot study.

Sample size

As the proposed study was a pilot study, a sample size of 50 patients was chosen arbitrarily.

Selection criteria

Inclusion criteria

1. Males aged above 45 years.
2. Presenting with Lower urinary tract symptoms which would include.
    i) Incomplete emptying.
    ii) Nocturia.
    iii) Frequency.

iv) Intermittency.

v) Urgency.

vi) Weak stream.

vii) Straining.

Exclusion criteria

1. Urinary catheterisation within the last 15 days.
2. Urinary tract infection.
3. Prostatic biopsy within the last 12 weeks.
4. Trans urethral resection of the prostate within the last 16 weeks.
5. Prostatic massage within the past 48 hours.
6. Vesical calculus
7. Bladder malignancy
8. Known prostatic malignancy

Methodology

The pilot study was conducted on patients who presented to the department of Urology at the KLES' Dr. Prabhakar Kore hospital, Belgaum. The patients presented with symptoms of lower urinary tract symptoms as mentioned above. Their consent was obtained on a consent form as per the hospital protocol. The patients were then supplied with a questionnaire which included questions on the demographic variables. They were also asked to objectively quantify the symptoms that they were experiencing, these were tabulated according to the international prostate symptom score.

In the next step the patients' pertinent history was recorded on the proforma, which included additional symptoms like haematuria, burning micturition, fever, nausea and vomiting, breathlessness, history of significant weight loss and back pain.

A clinical examination was then carried out to note some important aspects. This included examination for pallor and generalised lymphaedenopathy. The respiratory system was examined for the presence of any added sounds. Bony tenderness over the spine, hips and the lower limbs was also noted. Examination of the abdomen included the palpation for any organomegaly, a palpable urinary bladder and the condition of the external genitalia.

A per-rectal examination was then performed by an experienced clinician to note the tone of the anal sphincter, the size of the prostate was noted clinically, its consistency, the nature of its surface and the state of the mucosa.

Laboratory examination

Following the initial clinical examination, blood and urine samples were collected. The blood samples were sent for serum PSA analysis to the central lab at the KLES' Dr. Prabhakar Kore hospital. A radiometric assay technique was used (Diagnostic system Laboratory, Texas, USA). The standard reference range for this assay was 0.0 to 4.0 ng/mL.

Urine was sent for routine urinalysis which included examination for red blood cells, pus cells and casts.

Prostatic Biopsy

Those patients who were included for the study were subjected to the prostatic biopsy after taking an informed written consent.

Following the PR examination, the patient was subjected to a trans-rectal ultrasound scan with a simultaneous biplanar trans-rectal ultrasound probe (Probe 8818, 4-12 MHz, B.K Medical, Mileparken, Denmark).

The patients were placed in left lateral decubitus position. TRUS was performed in both the transverse and sagittal planes. With the biplanar probe used in this study, advancing the probe cephalad into the rectum imaged the base of the prostate, the seminal vesicles and the bladder neck. Pulling the probe out towards the anal verge demonstrated the prostatic apex and the proximal urethra. Transverse imaging was achieved by sideways movement of the probe, with the anal sphincter as a point of fulcrum. Sagittal imaging was accomplished by angling the probe up or down using the anal sphincter as a fulcrum. The ultrasonographic characteristics of the prostate were noted.

Figure 2: Ultrasound probe

Figure 3: Ultrasound machine

Figure 4: Trans rectal ultrasound image of prostate

Prior to biopsy, the patient was administered adequate analgesics and one dose of intravenous Ciprofloxacin 500mg. The antibiotic regime (Tab. Ciprofloxacin 500mg BD P.O) was continued per orally for three days following the biopsy procedure.

A spring-driven 18-gauge needle core biopsy gun, which could be passed through the needle guide attached to the ultrasound probe, was used for the biopsy. Images were superimposed with a ruled puncture path that corresponded to the needle guide of the TRUS unit. The biopsy gun advanced the needle 0.5 cm and sampled the subsequent 1.5 cm of tissue with the tip extending 0.5 cm beyond the area sampled. The biopsy samples were placed in 10% formalin and sent to the histopathology lab for analysis.

The Presti[53] 10 core biopsy technique was used to take the samples from different regions of the prostate.

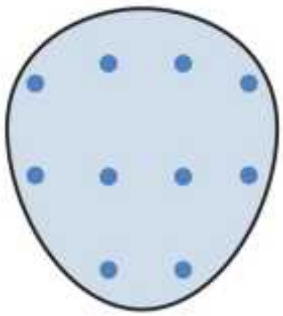


Figure 5: Presti 10 core biopsy

The volumetric assessment of the prostate was made according to a preloaded formula (Volume of an ellipse equals π/6 × transverse diameter × AP diameter × longitudinal diameter).

Laboratory examination

Following clinical examination, blood and urine samples were collected.

The blood samples were sent for serum PSA analysis to the central lab at the KLES' Dr. Prabhakar Kore hospital. A radiometric assay technique was used (Diagnostic system Laboratory, Texas, USA). The standard reference range for this assay was 0.0 to 4.0 ng/mL.

Urine was sent for routine urinalysis which included examination for red blood cells, pus cells and casts.

PSA density

The PSA density was calculated with the data obtained from the prostate volume measurement by TRUS and the serum PSA levels.

PSA Density = Serum PSA (ng/mL) ÷ Prostate volume (cc)

Statistical analysis

The demographic data was analysed using descriptive statistical analysis. The sensitivity, specificity, the positive predictive value and the negative predictive value was calculated for outcomes from both the PSA and PSA density values. SPSS version 17 (IBM corp. Chicago, IL, USA) was used for statistical analysis.

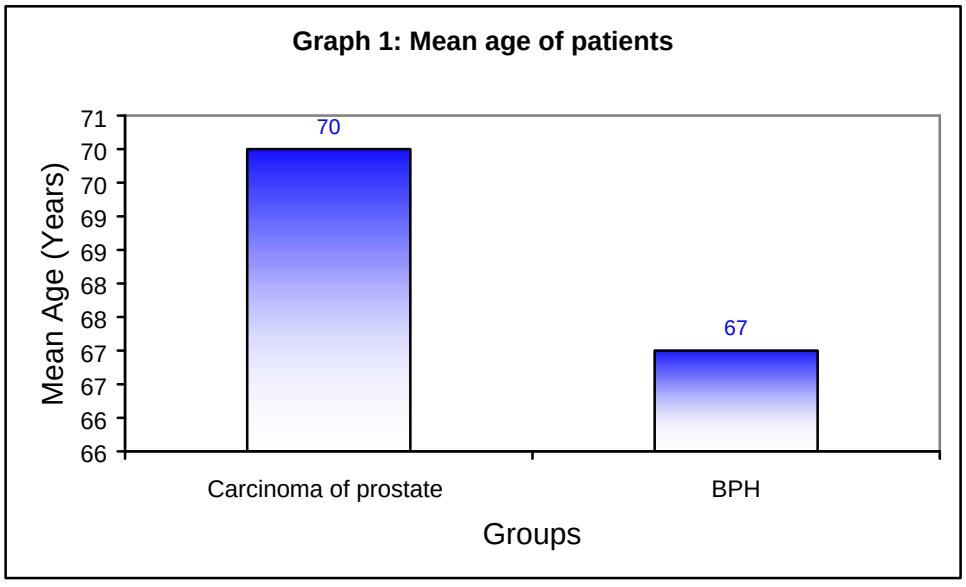
RESULTS

The study was conducted between October 2007 and September 2008. Amongst the 249 patients aged more than 45 years who presented to the Department of Urology, KLES' Dr Prabhakar Kore Hospital, Belgaum, Karnataka; 50 patients were included in this study after subjecting them to the initial inclusion and exclusion criteria.

The patients were worked up according to the pre-tested pro forma and the data was tabulated and analysed with statistical software (SPSS ver. 17, IBM Corporation, Chicago, IL, USA).

Table 4: Mean age of patients

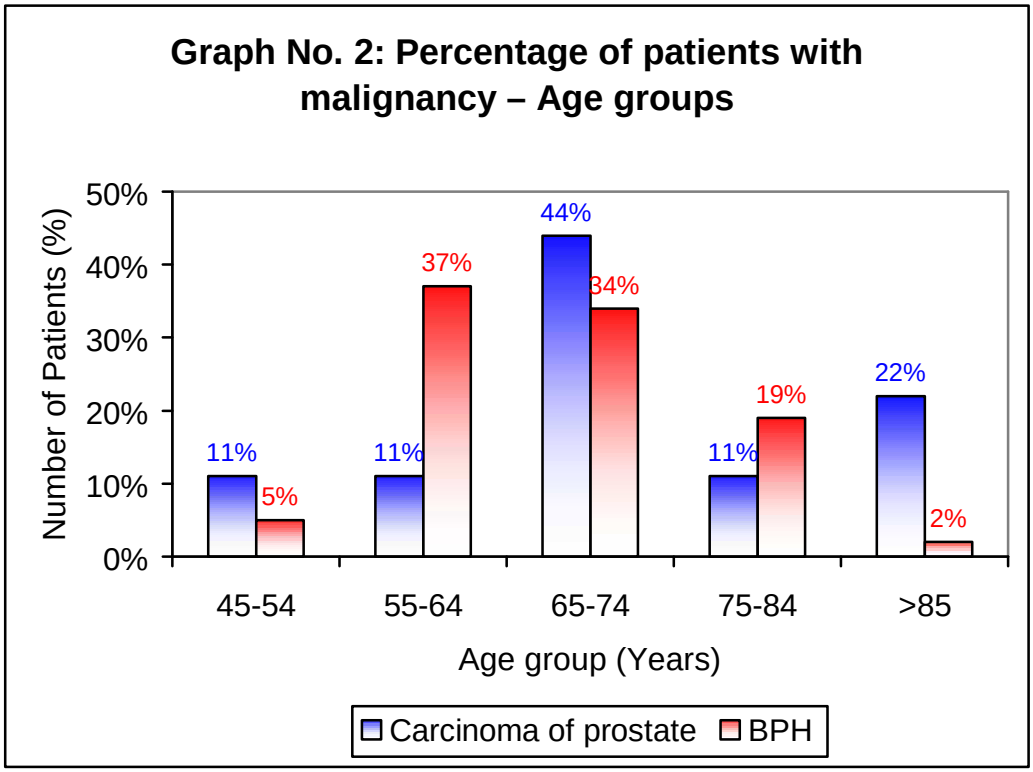
	Carcinoma of prostate	BPH
Mean age (Years)	70±13.37	67±10.18
Median age (Years)	68	65



The mean age for patients in this study was 68 (standard deviation was 10.61) years. The oldest patient was 106 years old and the youngest was 45 years. The mean age of patients with Carcinoma of Prostate was 70 years, and the median age was 68 years. The mean age of patients with BPH was 67, whereas the median age was 65 years.

Table 5: Percentage of patients with malignancy – Age groups

Age	Carcinoma of prostate		BPH		Total
	Number	Percentage	Number	Percentage	
45-54	01	11%	02	5%	03
55-64	01	11%	15	37%	16
65-74	04	44%	14	34%	18
75-84	01	11%	08	19%	09
Above 85	02	22%	01	2%	03



In this study of 50 patients with lower urinary tract symptoms, who were above 45 years of age, the prevalence of the disease in different age groups was compared as per the charts shown below. It was noted that the majority of cases of BPH were present in the 55 to 74 age interval, while the cases of carcinoma of prostate were clustered more closely in the 65 to 74 age group.

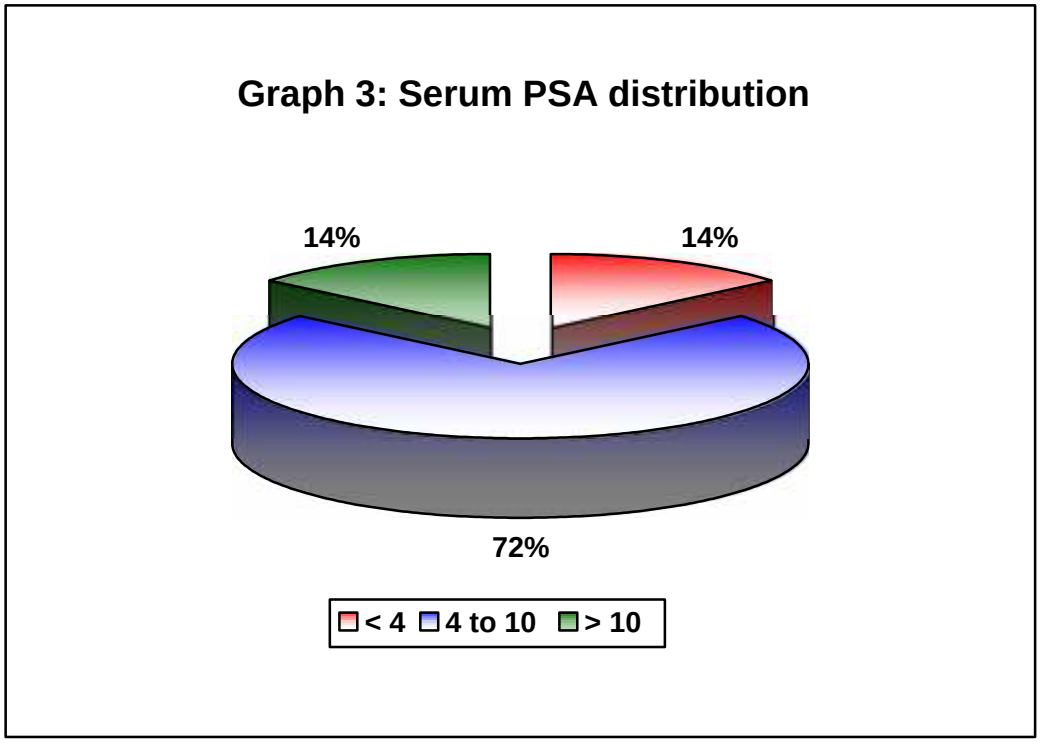
Table 6: Mean Volume, PSA and PSA density across different age groups

Age Group	PSA	Average Prostate volume	Average PSA Density	Total cases
45-54 yrs	48.07	57.1	0.568	3
55-64 yrs	6.06	36	0.184	16
65-74 yrs	20.8	42.4	0.482	18
75-84 yrs	8.7	43	0.284	9
Above 85 yrs	31.63	44	0.476	3

The mean prostate volume, PSA and PSA density were calculated for different age groups. There was a progressive increase in the size of the prostate gland as age advanced. The PSA and PSA density values did not correlate with this increase in size. The lowest average PSA, PSA density and volume was noted in the 55-64 year old group.

Table 7: Serum PSA distribution

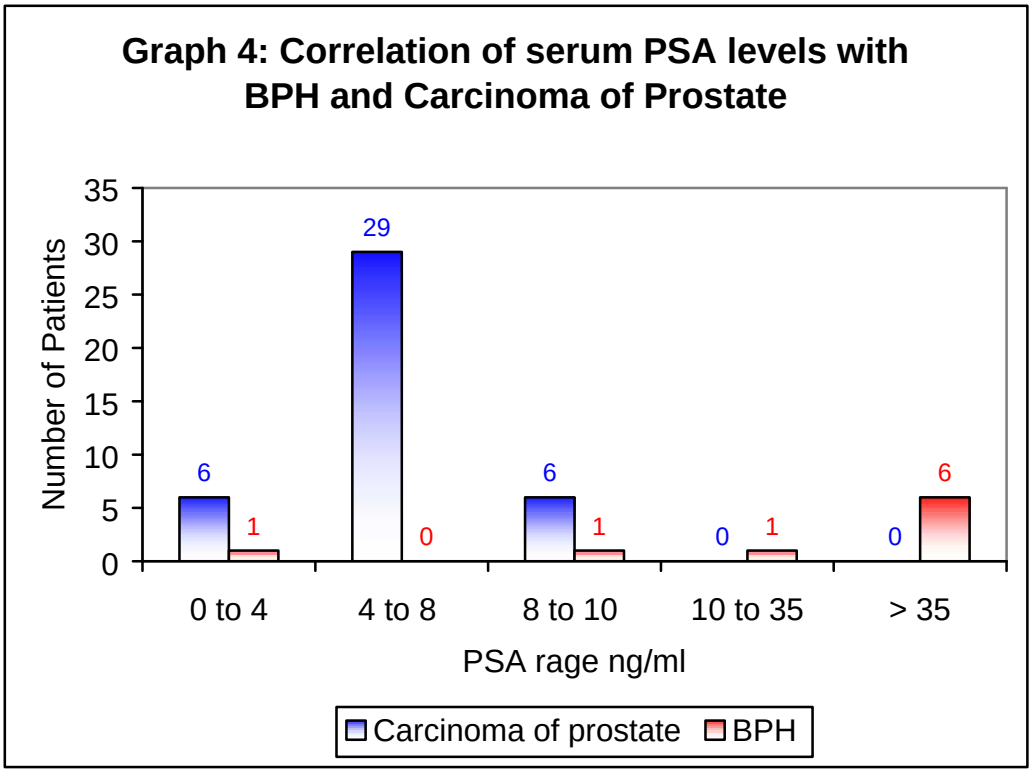
PSA (ng/ml)	Patients	
	Number	Percentage
< 4	7	14
4 – 10	36	72
> 10	7	14



On performing serum PSA estimation only 7 cases (14%) were found to have a PSA level below 4 ng/mL. The majority of cases were in the grey area where their PSA levels were between 4 and 10 ng/mL. (n= 36, 72%). There were 7 cases with PSA level above 10 ng/mL. (14%).

Table 8: Correlation of serum PSA levels with BPH and Carcinoma of Prostate

PSA Range	BPH	Carcinoma of Prostate	Total
0-4 ng/ml	6	1	7
4-8 ng/ml	29	0	29
8-10 ng/ml	6	1	7
10-35 ng/ml	0	1	1
above 35 ng/ml	0	6	6



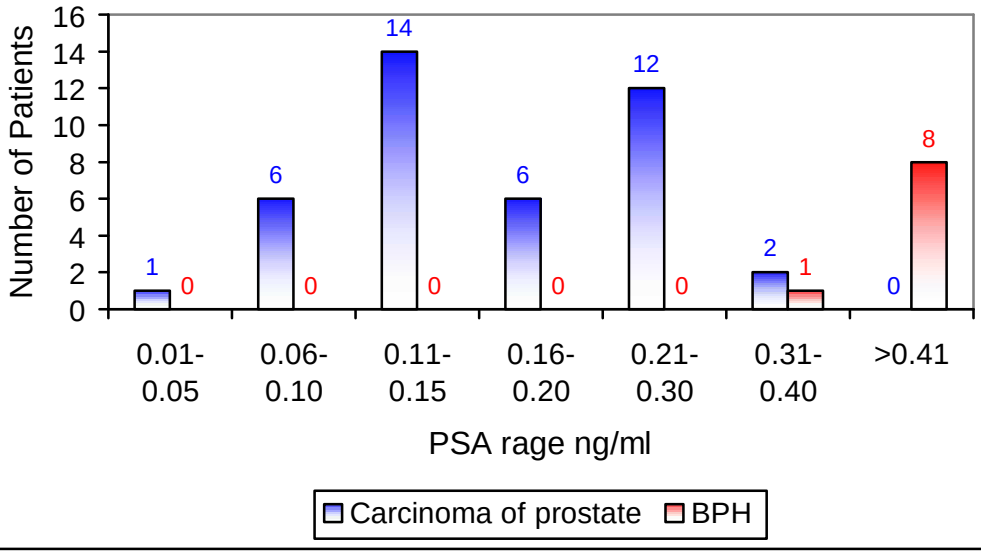
On tabulating the PSA ranges it was noted that there was clustering of BPH cases (n=29) in the 4-8 ng/ml group where there were no Carcinoma of

prostate cases. In patients with PSA level above 35, no cases of BPH were noted in our study. All six patients in this group had a diagnosis of carcinoma.

Table 9: Correlation of PSA density with BPH and carcinoma of the prostate

PSA density range	BPH	Carcinoma of prostate	Total
0.01-0.05	1	0	1
0.06-0.10	6	0	6
0.11-0.15	14	0	14
0.16-0.20	6	0	6
0.21-0.30	12	0	12
0.31-0.40	2	1	3
>0.41	0	8	8
Total Cases	41	9	**50**

Graph 5: Correlation of PSA density with BPH and carcinoma of the prostate



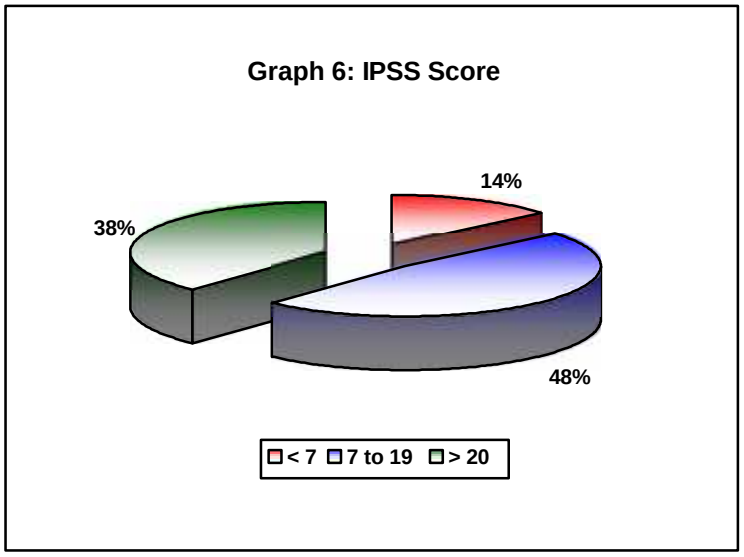
PSA density ranges were tabulated as shown in the table, and the number of cases of BPH and prostatic cancer were noted for each PSA density interval. It was noted that below PSA density range of 0.30, there were no cases of PCa. A PSA density of over 0.41 showed a majority of the PCa cases (n=8).

Duration of symptoms

The average duration of symptoms for cases with BPH was 10.6 months, while patients with PCa had been suffering from symptoms for a 10.1 months on an average.

Table 10: IPSS Score

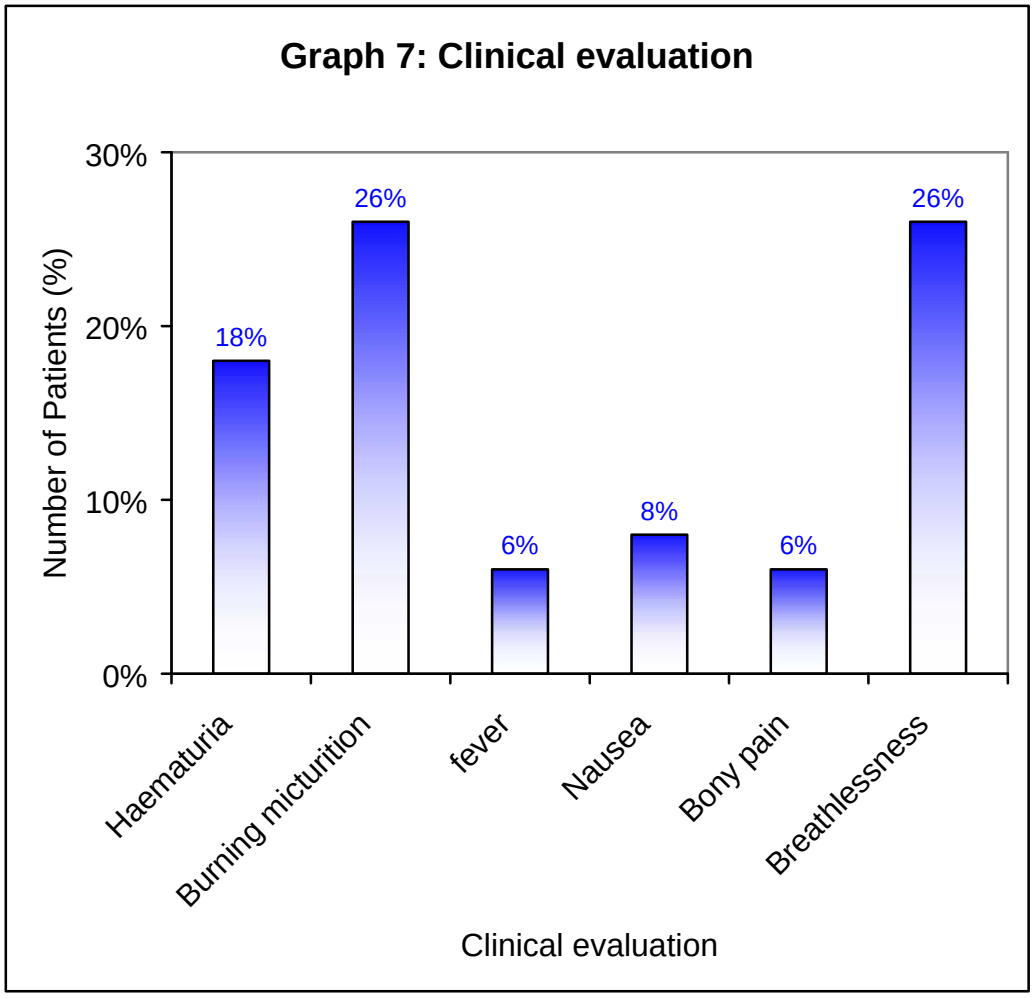
IPSS Score	Patients	
	Number	Percentage
< 7	7	14%
7 – 19	24	48%
> 20	19	38%



The IPSS was calculated in all the patients. The symptom score was calculated according to the pro forma. Scores below 7 signified mild symptoms, 7-19 they were considered moderate and patients with scores between 20 and 30, were considered to have severe symptoms. Of the 50 patients, 7 (14%) patients had mild symptoms, 24 (48%) had moderate symptoms and 19 (38%) had severe symptoms.

Table 11: Clinical evaluation

Clinical evaluation	Patients	
	Number	**Percentage**
Haematuria	9	18
Burning micturation	13	26
Fever	3	6
Nausea	4	8
Bony pain	3	6
Breathlessness	13	26

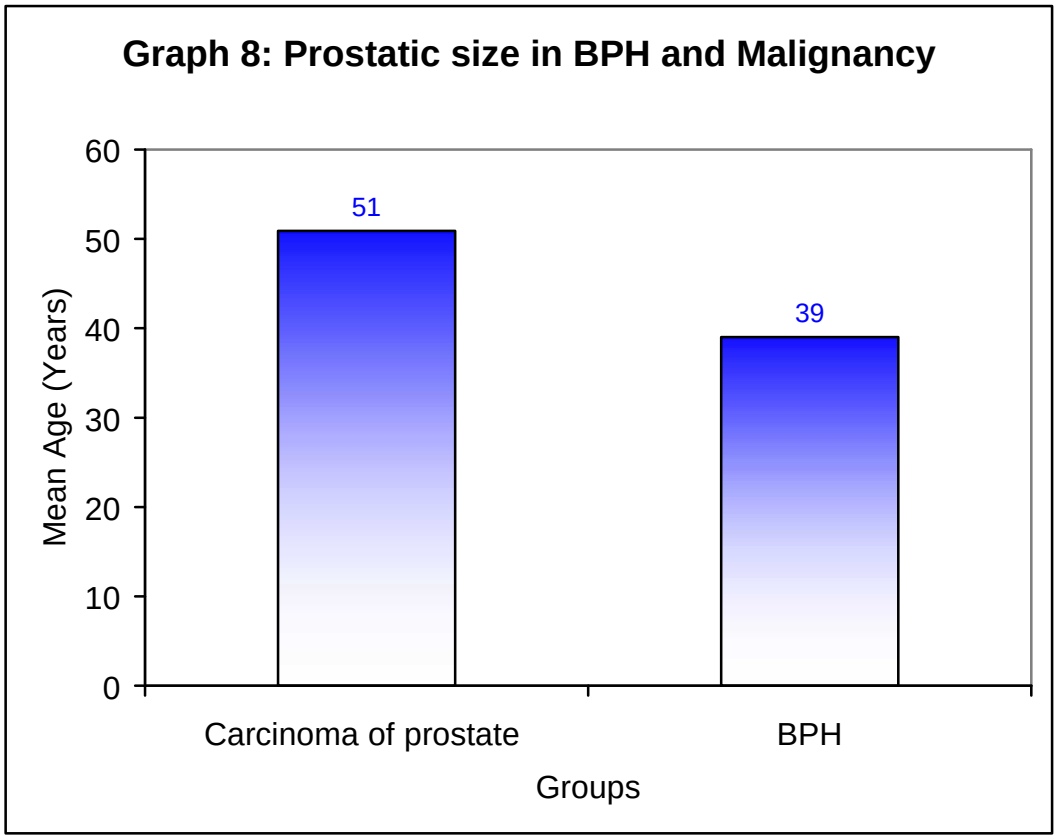


The clinical symptoms of the patients were noted on the pro forma. Haematuria was present in three (33%) patients with PCa and in five (12.19%) patients with BPH. Two (22.2%) patients with PCa had burning micturition, whereas 26% (n=26.4%) patients with BPH had similar symptoms. None of the patients with PCa had a history of fever in contrast to 7% of patients with BPH.

Bony pain was present in three (33%) of patients with PCa, and in none of the patients with BPH. Breathlessness was present in four (44%) patients with PCa and nine (21%) patients with BPH.

Table 12: Prostatic size in BPH and Malignancy

	Carcinoma of prostate	BPH
Mean size (cc)	50.9±31.73	39.0±14.1
Median size (cc)	42.0	37.0



The average size of the prostate in patients with BPH was 39.14 cc. The patients with prostate cancer had a mean volume of 50.9 cc. The median prostate volume in BPH was 37 cc. The median prostate volume size in PCa was 42.0 cc.

Sensitivity and specificity of PSA and PSA density

Table 13: Sensitivity and specificity for serum PSA

PSA	Patients	
	Ca prostate on HPR	BPH on HPR
Test positive (> 4ng/ml)	8	35
Test Negative (4 ng/ml)	1	6

When serum PSA levels were estimated to calculate the probability of malignancy in patients with LUTS aged over 45 years. A cut off point of 4ng/mL was taken. Values under 4ng/mL were considered as negative for malignancy and values over the threshold were considered as positive for Carcinoma of the prostate. The results from the test were compared with the histopathology report. The sensitivity and specificity were calculated. The positive and negative predictive values were also determined.

Sensitivity = 88.89%

Specificity = 14.63%

Positive predictive value = (8÷43) × 100 = 18.60%

Negative predictive value = (6÷7) × 100 = 85.71%

Diagnostic accuracy of the test = {(8+6) ÷ 50} × 100 = 28%

Table 14: Sensitivity and specificity for PSA density

PSAD	Sensitivity	Specificity	PPV	NPV
0.04	100%	0%	100%	0%
0.15	100%	46%	29%	100%
0.21	100%	65%	39%	100%
0.3	100%	95%	81%	100%
0.6	78%	100%	100%	95%

PSA	Patients	
	Ca prostate on HPR	BPH on HPR
Test positive (PSAD >0.3)	9	2
Test negative (PSAD <0.3)	0	39

The PSA density was calculated by dividing the PSA by the volume of the prostate. The value of 0.3 was chosen as the most suitable value in view of the available data. Similar methodology was used by Gafoori et al in their study[54]. PSAD values which were lower than 0.3 were considered negative for malignancy, while values higher than 0.3 were considered to be suggestive of PCa.

Sensitivity	= 100%
Specificity	= 95.12%
Positive predictive value	= (9÷11) × 100 = 81.82%
Negative predictive value	= (39÷39) × 100 = 100%
Diagnostic accuracy of the test	= {(9+39) ÷ 50} × 100 = 96%

Table 15: Comparison between the sensitivity and specificity of PSA and PSA density

Variables	Sensitivity	Specificity	PPV	NPV
PSA	88.9%	14.63%	18.6%	85.7%
PSA density	100%	95.12%	100%	96%

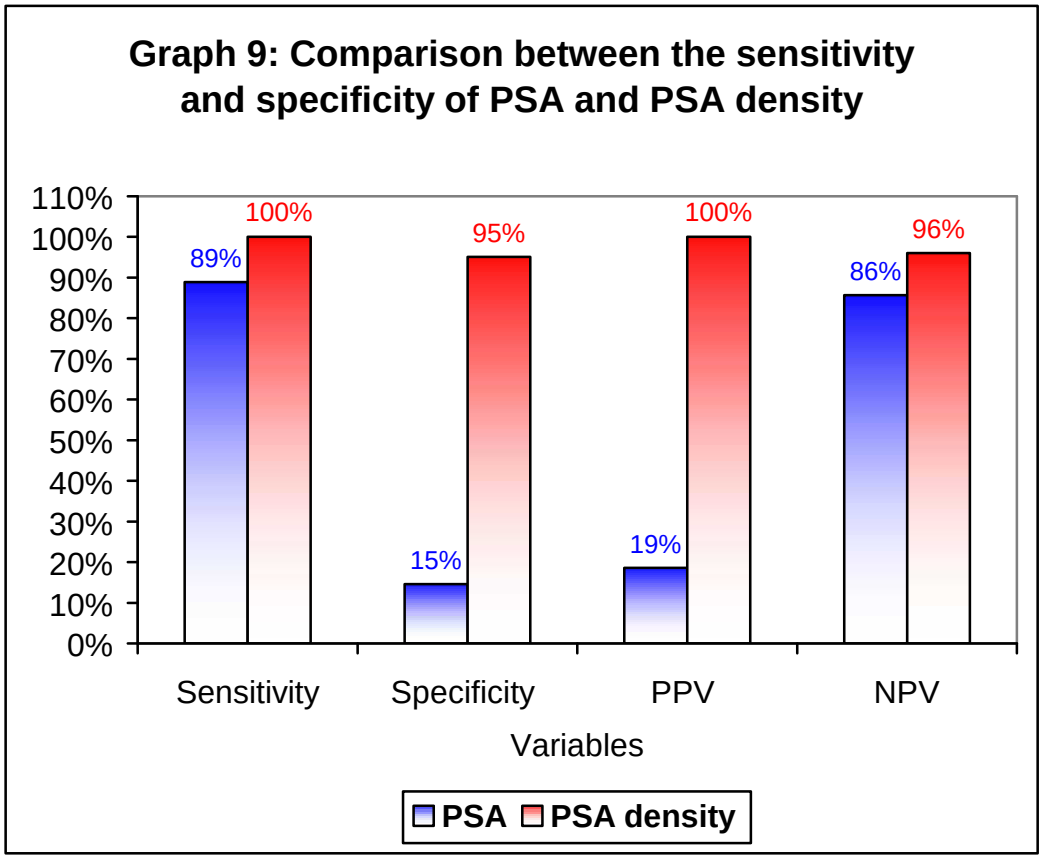
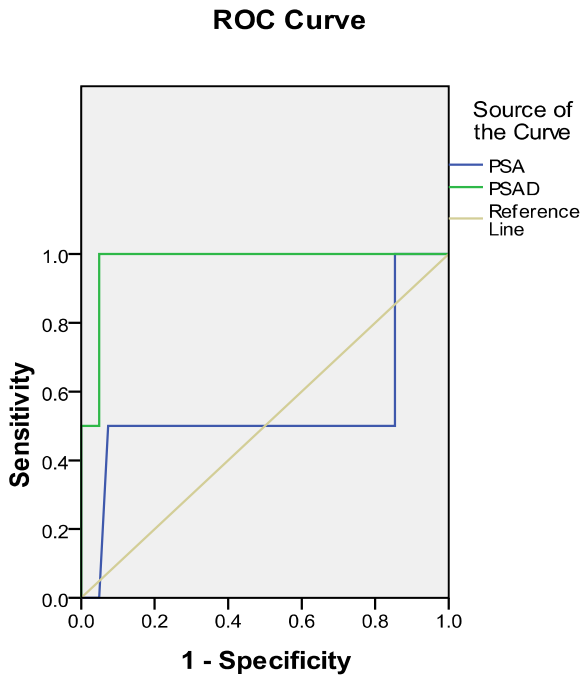


Table 16: Receiver operating characteristic curves for PSA (4-10ng/ml/cc) and PSAD



Diagonal segments are produced by ties.

Area Under the Curve

Test Result Variable(s)	Area	Std. Error[a]	Asymptotic Sig.[b]	Asymptotic 95% Confidence Interval	
				Lower Bound	Upper Bound
PSA	0.543	0.283	0.840	0.000	1.000
PSAD	0.976	0.027	0.025	0.000	1.000

The test result variable(s): PSA has at least one tie between the positive actual state group and the negative actual state group. Statistics may be biased.

a. Under the nonparametric assumption

b. Null hypothesis: true area = 0.5

When a ROC curve analysis for the traditional grey area for PSA between 4 and 10ng/ml and PSAD was plotted; it showed that PSAD area under curve was 0.976 versus 0.543 and that this difference was significant. The p value was 0.027, which was statistically significant.

DISCUSSION

The detection of PCa in the population continues to be a vexing problem for clinicians. An ideal screening test should have high sensitivity, high specificity, the disease entity tested for should have had an important impact on the social and economic indicators and there should be appropriate curative modalities available to treat the condition once it is detected. PCa is the most common visceral malignancy in the western world, and there were over 11,000 deaths recorded in India in 2005.

The fact that the disease generally affects the elderly population, and is a slow growing malignancy has lead to it not being accorded as much significance as other malignancies like carcinoma of breast and uterine cervix.

The need for a non-invasive, cost effective screening strategy for detection of PCa at an early stage has been felt in the past, and an effort has been made in this pilot study to identify whether PSA density testing holds any promise.

The mean age of diagnosis of PCa in this study was 70 years and the median age was 68 years. This indicated that in our study group, the age at which PCa was detected at a later stage in comparison with published data, where the mean and median age were 67 years and 65.2 years respectively.[55] There could be many factors which lead to this, namely the small sample size in our study, the racial variation, and the lack of patient education.

The largest percentage of cancer patients were found to be clustered in the 65 to 74 year age group. This correlated well with a study[56] where the maximum detected cases were in the 70 to 74 year age group.

BPH was found to be clustered over a much wider age range where over 71 percent of the BPH cases were present in this age group. There is no study in literature which has indicated the age clustering due to the large scale prevalence of this condition, and the relatively greater proportion of asymptomatic cases in this group.

A study[57] in 1991 showed that serum PSA with a cut off value of 4.0ng/ml was useful for screening for prostate cancer. Seven years later the same group suggested a cut off value of 2.5ng/ml, which was widely accepted after demonstrating a detection rate of prostate cancer in the PSA range of 2.5 to 4 ng/ml of 22%.[58] In our study only seven patients had a PSA level lower than 4 ng/ml, and only one of these patients had a diagnosis of Prostatic carcinoma. 36 patients in this study had a PSA level between four and 10 ng/ml and this was the grey area where the greatest number of PCa and BPH cases was interspersed. Because of the small sample size of our study, and the racial variation between the subjects who were part of both these studies, a definitive verdict based on this data cannot be reached.

The IPSS scores were ascertained for all the subjects in this study and were clubbed as mild, moderate and severe. The vast majority of the patients presented to the clinic only when their symptoms were moderately severe (86%). Clearly, symptom scores alone do not capture the complete picture of a prostate

problem as perceived by the individual patient. Symptom impact on a patient's lifestyle should be considered as well. Any intervention may make more sense for a moderately symptomatic patient who finds his symptoms very bothersome than for a severely symptomatic patient who finds his symptoms tolerable.[59]

On evaluating the symptoms other than the ones which were determined, it was found that 26% of the patients with BPH also presented with symptoms of burning micturition. There was no data available in literature indicating the percentage of patients who were suffering from urinary tract infections and its association with BPH.

It has been stated that cancer secretes 12 times more serum PSA per volume than BPH.[60] Therefore the volume of patients with PCa is presumed to be smaller than those with BPH. In our study, contrary to previous studies the average and median size of the scanned prostate glands was larger in patients with prostatic malignancy than in patients with BPH.

In our study, statistical analyses showed that there was a significant difference in serum PSA and PSAD levels between the patients with and without prostate cancer. This finding is compatible with previous reports.[61,62]

A serum PSA threshold of 4ng/ml is usually an indication for prostate biopsy, and PSA levels between 4ng/ml and 10ng/ml, which is considered a grey zone, are shown to have a low sensitivity, but values above 10 ng/ml have a high sensitivity for prostate cancer. The sensitivity even reaches 100% if we consider values higher than 15 ng/ml[63,64].

In our study, a lower cut off point of 4 ng/ml had a sensitivity of 88.89% and specificity of 14.63%. We had one patient diagnosed with prostate cancer who had a PSA level below 4 ng/ml. This means that if we do not continue to follow up patients with PSA levels less than 4ng/ml, we will miss some patients with prostate cancer.

A study on Arab men[63] reported benign disease with the PSA levels up to 50ng/mL. There were a few studies in Asian populations as well[65,66] which showed that the prostate specific antigen levels were higher due to the presence of prostatitis in these subjects. This could not be verified or refuted in our study as we did not have any cases of BPH with PSA over 10ng/ml. Our tentative findings are in line with western reports.[64]

In order to eliminate the effect of other diseases like BPH, Benson and colleagues introduced PSAD as a useful tool to increase specificity in the detection of prostate cancer.[67] Some studies have however not confirmed this advantage and reported that PSAD could not surpass PSA[68,69]. In our study, in all given thresholds the sensitivity and the specificity of PSAD was more than PSA. For instance at the PSAD threshold of 0.15ng/ml/cc the sensitivity is 100% and the specificity is 46% for detecting prostate cancer. A threshold of 0.3ng/ml/cc showed a sensitivity of 100%, specificity of 95%. The diagnostic accuracy of the test using PSAD was 96% compared to 28% when PSA was used to test for malignancy. The ROC curve analysis of the traditional grey area showed that the AUC for PSA was 0.543 compared to 0.976 for PSAD for the same range (p value 0.027). This indicated that there was a considerable improvement in diagnosis of malignancy when PSAD was utilised.

CONCLUSION

- Serum PSA per se does not have sufficient sensitivity and specificity to be useful in the routine evaluation of patients with lower urinary tract symptoms.
- It is not accurate enough to include or exclude patients with prostate cancer.
- The use of PSAD, however, increases the accuracy and improves the sensitivity and specificity for detection of cancer.
- In our pilot study the PSA density of 0.3 ng/ml/cc was found to be highly specific and sensitive for detection of prostate cancer.
- We need to have a larger cohort of patients to determine the PSA density threshold for identifying Carcinoma of prostate

SUMMARY

A total of 50 consecutive patients who were aged above 45 years were included in this study. They had presented with lower urinary tract symptoms and were recruited in this study between October 2007 and September 2008. The study was conducted at the Department of Urology, KLES' Prabhakar Kore Hospital, Belgaum.

- The mean age for patients in this study was 68 years.
- The mean age of patients with Carcinoma of Prostate was 70 years, and the median age was 68 years.
- The mean age of patients with BPH was 67, whereas the median age was 65 years.
- 71% of cases of BPH were present in the 55 to 74 age interval, while 44% cases of carcinoma of prostate were clustered more closely in the 65 to 74 age group.
- 72% of the patients came with a PSA level between 4ng/ml and 10ng/ml
- Of the 50 patients, seven (14%) patients had mild symptoms, 24 (48%) had moderate symptoms and 19 (38%) had severe symptoms.
- Haematuria was present in three (33%) patients with PCa and in five (12.19%) patients with BPH. Two (22.2%) patients with PCa had burning micturition, whereas 26% (n=13) patients with BPH had similar symptoms. None of the patients with PCa had a history of fever in contrast to 7% of patients with BPH.

- Bony pain was present in three (33%) of patients with PCa, and in none of the patients with BPH. Breathlessness was present in four (44%) patients with PCa and nine (21%) patients with BPH.
- The median prostate volume in BPH was 37 cc. The median prostate volume size in PCa was 42.0 cc.
- When serum PSA cut-off value of 4ng/ml was used to detect PCa, the sensitivity was 88.8%, specificity was 14.6% and the diagnostic accuracy of the test was 28%.
- When a PSA density threshold of 0.3 was utilised to detect PCa, the sensitivity was 100%, the specificity was 95.1% and the diagnostic accuracy of the test was 96%.
- When a ROC curve analysis for the traditional grey area for PSA between 4 and 10ng/ml and PSA density was plotted; it showed that PSAD area under curve was 0.976 versus 0.543 and that this difference was significant.

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ANNEXURE I

CONSENT FORM

Dear Mr. _____ we are requesting you to enroll yourself in the study entitled **"THE ROLE OF PROSTATE SPECIFIC ANTIGEN LEVELS AND PROSTATE SPECIFIC ANTIGEN DENSITY IN PATIENTS WITH LOWER URINARY TRACT SYMPTOMS AGED OVER FORTY FIVE YEARS – A ONE YEAR HOSPITAL BASED PILOT STUDY"** conducted by **Dr. Vivek Anilkumar Saraf,** a post graduate student under the Guidance of **Dr. A. C. Pangi** in the department of General Surgery at the JN Medical College, Belgaum under the KLE University, Belgaum.

You have been asked to participate in this study as you suffer from Lower urinary tract symptoms and because you are in the age category for this study. During the course of this study you will be asked some questions and it is pertinent that you answer them to the best of your knowledge. You are free to refrain from answering any of the questions if you feel they are irrelevant.

Your participation in this project is voluntary. A decision made by you to terminate involvement in this study would not alter your relationship with either the institution where you are undergoing treatment or the doctors who are looking after you and.

The purpose of this research project is to determine the occurrence of Prostatic carcinoma in patients who are aged above 45 years and who present with Lower urinary tract symptoms.

Procedure involved

On enrolling into the study group, an initial blood sample would be taken to estimate the serum PSA levels (which is a marker for prostate cancer), following which a Trans Rectal Ultrasound would be performed to visualise the prostate and a small biopsy of the prostate would be taken during this procedure to come to a definitive diagnosis of the condition. The data would then be analysed.

Risks and benefits

The estimation of the PSA levels and its correlation with the size of the prostate has been shown to increase the accuracy of diagnosis and pick up cancers at an earlier stage than previously possible.

There is an increased risk of urinary tract infections following the biopsy of the prostate. A prophylactic course of antibiotics would be given to safeguard you against this.

Alternatives

If you wish not to be part of this study, you will be treated in the routine manner without any bias.

Privacy and confidentiality

The only members who know that you are a research subject are members of the research team. No information about you, or provided by you during the

course of this study would be disclosed to others without your written permission except:

1. In an emergency to protect your rights and welfare
2. If required by law

Compensation in case of complications

In the unlikely event that you suffer from any complications of the investigations/ procedures that are part of this study, you would be managed as per the current norm. The cost of treatment would have to be borne by you; the institution or the doctors treating you are not liable for any compensation for the same.

Financial incentives/ cost of treatment

The Trans-rectal ultrasound scan would be performed free of cost. The cost of the histopathology examination and the blood PSA estimation would have to be borne by the patient.

There are no financial incentives for participation in this study.

Right to publish data from this study

The doctors and the institution conducting this study reserve the right to publish data from this study. The data would not contain any elements which could lead to personal identification of the subjects.

Signature or left thumb print of participant or legally authorized representative

_____ Participant's name _____Participant's signature /thumb print

_____ Experimenters' name _____ Experimenters' signature

_____ Witness' name _____ Witness' signature

_____ Date

ANNEXURE II

PROFOMA

"THE ROLE OF PROSTATE SPECIFIC ANTIGEN LEVELS AND PROSTATE SPECIFIC ANTIGEN DENSITY IN DETECTION OF PROSTATIC CARCINOMA IN SYMPTOMATIC PATIENTS AGED OVER FORTY FIVE YEARS – A ONE YEAR HOSPITAL BASED PILOT STUDY"

Dr. Vivek Anilkumar Saraf
Department of General Surgery
J. N. Medical College, Belgaum

Date:

Demographic Data

Name:

Age:

Address:

Religion:

Marital Status:

Occupation:

History

Duration of onset of symptoms in days:

Any history of haematuria (if yes, then for how long):

Symptoms (tick the boxes)

Fever ( ) Nausea/ Vomiting ( ) Breathlessness ( )

Burning micturition ( ) Weight loss – more than 10% over the last 6 months ( )

Painful back/ hip/ upper thigh ( )

International prostate symptom score (IPSS)

	Not at all	Less than 1 time in 5	Less than half the time	About half the time	More than half the time	Almost always	**Your score**
Incomplete emptying Over the past month, how often have you had a sensation of not emptying your bladder completely after you finish urinating?	0	1	2	3	4	5	
Frequency Over the past month, how often have you had to urinate again less than two hours after you finished urinating?	0	1	2	3	4	5	
Intermittency Over the past month, how often have you found you stopped and started again several times when you urinated?	0	1	2	3	4	5	
Urgency Over the last month, how difficult have you found it to postpone urination?	0	1	2	3	4	5	
Weak stream Over the past month, how often have you had a weak urinary stream?	0	1	2	3	4	5	
Straining Over the past month, how often have you had to push or strain to begin urination?	0	1	2	3	4	5	
	None	1 time	2 times	3 times	4 times	5 times or more	**Your score**
Nocturia Over the past month, many times did you most typically get up to urinate from the time you went to bed until the time you got up in the morning?	0	1	2	3	4	5	

Total IPSS score

Quality of life due to urinary symptoms	Delighted	Pleased	Mostly satisfied	Mixed – about equally satisfied and dissatisfied	Mostly dissatisfied	Unhappy	Terrible
If you were to spend the rest of your life with your urinary condition the way it is now, how would you feel about that?	0	1	2	3	4	5	6

Total score: 0-7 mildly symptomatic; 8-19 moderately symptomatic; 20-35 severely symptomatic.

Examination findings

General Physical examination

Pallor ( )

Lymphaedenopathy ( )

Systemic examination

Respiratory system

Bony Pain over spine/ Hips/ Lower limbs ( )

Abdominal examination

Organomegaly ( )

If present anatomic location _____

Bladder palpable ( )

External genitalia normal ( )

If not describe changes_____

Per Rectal examination

Anal sphincter tone: normal ( ) lax ( )

in spasm ( )

State of mucosa: free ( ) fixed ( )

Approximate prostate size: _____ cc

Consistency of prostate: _____

Surface: _____

Laboratory findings

Urinalysis

RBCs Nil ( ) if yes no: _____/ HPF

Pus cells Nil ( ) if yes no: _____/ HPF

Casts if any _____

PSA level: _____ ngm/mL

Trans-rectal Ultrasound scan

Echo- texture of prostate: _____

Volume: _____cc

Calculated PSA density: _____

Histopathology Report of Prostate biopsy

Report number:

Result:

ANNEXURE III - MASTER CHART

IP Number	Age (Years)	Occupation	Marital Status	Religion	Lymphaedenopathy	Weightloss	Painfulhipback	IPSSScore	Pallor	Onset Duration	Haematuria	Fever	Nausea	Bonypain	Breathlessness	Burningmicturition	RespExam	Organomegaly	Bladderpalpable	Externalgenitalia	PRtone	Mucosa	Consistency	Surface	Approx size Pron examination	UrineRBC	PUScells	Prostatevolume	PSA	PSAD	HPRREPORT
326366	75	UNE	MR	H	-	-	-	MD	-	18	+	-	-	-	-	-	CL	-	-	NR	NR	FR	NR	SMT	25	-	+	27.8	3.00	0.108	BPH
324752	65	EMP	MR	H	-	-	-	ML	-	12	-	-	-	-	-	-	CL	-	-	NR	NR	FR	NR	SMT	25	-	+	29.7	3.00	0.101	BPH
314854	60	EMP	MR	H	-	-	-	ML	-	12	-	-	-	-	-	-	CL	-	-	ABN	NR	FR	HD	MSL	25	-	-	26.3	3.00	0.114	BPH
311848	106	UNE	WD	MS	-	-	-	MD	+	4	-	+	-	-	+	+	CL	-	-	NR	LX	FR	NR	SMT	25	+	-	31.6	3.00	0.095	BPH
1122667	76	UNE	MR	H	-	-	-	SV	-	15	-	-	-	-	+	-	CR	-	+	NR	LX	FR	NR	SMT	25	-	-	71.1	3.20	0.045	BPH
315724	58	EMP	MR	H	-	-	-	ML	-	36	-	-	-	-	-	-	CL	-	+	NR	SP	FR	NR	SMT	25	+	-	32.1	3.50	0.109	BPH
311922	86	UNE	MR	H	-	-	-	MD	-	24	-	-	-	-	+	-	CR	-	-	NR	LX	FR	NR	SMT	20	-	-	12.6	3.90	0.310	CAP
324536	65	EMP	MR	H	-	-	-	MD	-	18	-	-	-	-	-	-	CL	-	-	NR	LX	FR	NR	MSL	30	-	-	43.2	4.23	0.098	BPH
325142	71	UNE	MR	H	-	-	+	SV	+	24	+	-	-	-	-	+	CL	-	+	NR	NR	FR	HD	MSL	25	+	+	31.2	4.90	0.157	BPH
321728	61	EMP	MR	H	-	-	+	ML	-	12	-	-	-	-	-	+	CL	-	-	NR	NR	FR	NR	SMT	30	-	+	39.2	4.90	0.125	BPH
319249	61	EMP	MR	H	-	-	-	MD	-	4	-	-	-	-	-	-	CR	-	-	NR	NR	FR	NR	SMT	25	-	-	23.3	4.90	0.210	BPH
319315	78	UNE	WD	H	-	-	-	MD	+	2	-	-	-	-	-	-	CR	-	-	NR	LX	FR	NR	MSL	25	-	+	17.3	5.00	0.289	BPH
326071	64	EMP	MR	H	-	-	-	MD	-	7	-	-	-	-	-	-	CL	-	+	NR	NR	FR	HD	SMT	30	+	+	44.8	5.20	0.116	BPH
313290	73	UNE	MR	H	-	-	-	MD	-	4	+	-	-	-	+	-	CL	-	-	NR	NR	FR	NR	SMT	25	-	-	24.1	5.20	0.216	BPH
308739	63	EMP	MR	MS	-	-	-	MD	-	4	-	-	-	-	-	-	CL	-	-	NR	NR	FR	NR	SMT	40	-	+	43.2	5.40	0.125	BPH
321869	58	EMP	MR	H	-	-	-	ML	-	24	-	-	-	-	-	-	CL	-	+	NR	NR	FR	NR	SMT	25	-	+	32.2	5.80	0.180	BPH
319168	65	UNE	MR	H	-	-	-	SV	-	3	-	+	-	-	-	-	CL	-	-	ABN	NR	FR	NR	SMT	35	-	+	27.1	5.80	0.214	BPH
316579	68	UNE	MR	MS	-	-	-	ML	-	15	-	-	-	-	+	-	CL	-	+	NR	LX	FR	NR	SMT	20	-	-	47.0	5.90	0.125	BPH
311914	62	EMP	MR	H	-	-	-	SV	-	12	-	-	-	-	-	+	CL	-	-	NR	NR	FR	NR	SMT	45	-	-	53.6	5.90	0.110	BPH
321061	55	EMP	MR	H	-	-	-	MD	-	12	-	-	+	-	-	-	CL	-	+	NR	LX	FR	HD	SMT	25	-	+	31.7	6.00	0.189	BPH
1102199	74	UNE	MR	H	-	-	-	MD	-	6	-	-	-	-	-	-	CL	-	-	NR	NR	FR	NR	MSL	55	+	+	54.5	6.00	0.110	BPH
313280	60	EMP	MR	H	-	-	-	SV	-	12	+	-	-	-	-	+	CL	-	-	NR	NR	FR	NR	SMT	25	-	-	23.1	6.00	0.260	BPH
312912	65	EMP	MR	H	-	-	-	SV	-	18	+	-	-	-	-	-	CR	-	-	NR	NR	FR	NR	SMT	30	-	-	27.1	6.00	0.221	BPH
309205	61	EMP	MR	H	-	-	+	SV	-	6	-	-	-	-	-	-	CL	-	-	NR	NR	FR	NR	SMT	35	-	+	52.6	6.00	0.114	BPH
320143	84	UNE	WD	H	-	-	-	MD	+	24	-	-	-	-	+	+	CL	-	-	NR	NR	FR	NR	SMT	65	-	+	59.6	6.20	0.104	BPH
313332	76	UNE	MR	H	-	-	-	MD	-	2	-	-	-	-	-	-	CL	-	-	NR	LX	FR	NR	SMT	25	-	-	19.4	6.30	0.325	BPH

IP Number	Age (Years)	Occupation	Marital Status	Religion	Lymphaedenopathy	Weightloss	Painfulhipback	IPSSScore	Pallor	Onset Duration	Haematuria	Fever	Nausea	Bonypain	Breathlessness	Burningmicturition	RespExam	Organomegaly	Bladderpalpable	Externalgenitalia	PRtone	Mucosa	Consistency	Surface	Approx size Pron examination	UrineRBC	PUScells	Prostatevolume	PSA	PSAD	HPRREPORT
321963	53	EMP	MR	H	-	-	-	MD	-	12	-	-	-	-	-	-	CL	-	-	NR	NR	FR	NR	SMT	20	-	+	26.7	6.40	0.240	BPH
323849	70	UNE	MR	MS	-	-	+	SV	-	24	-	-	-	-	-	-	CL	-	-	NR	NR	FR	NR	SMT	40	-	-	36.8	7.00	0.190	BPH
321254	57	UNE	WD	H	-	-	+	MD	-	9	-	-	-	-	-	-	CR	-	-	ABN	NR	FR	NR	SMT	40	-	+	36.8	7.00	0.190	BPH
319620	59	UNE	MR	H	-	-	-	MD	-	9	+	-	-	-	-	-	CL	-	-	NR	NR	FR	NR	SMT	35	+	+	44.0	7.00	0.159	BPH
318949	72	UNE	MR	H	-	-	-	MD	-	5	-	-	-	-	-	+	CL	-	+	NR	NR	FR	NR	SMT	40	-	-	54.3	7.00	0.129	BPH
317989	78	UNE	MR	H	-	-	-	MD	-	4	-	-	-	-	+	+	CL	-	-	NR	NR	FR	NR	SMT	45	-	-	58.8	7.00	0.119	BPH
317814	58	EMP	MR	H	-	-	-	MD	-	9	-	-	-	-	-	+	CR	-	-	NR	NR	FR	NR	NOD	25	+	-	32.7	7.00	0.214	BPH
312945	66	UNE	MR	H	-	-	-	SV	-	5	-	-	-	-	-	-	CL	-	-	NR	NR	FR	NR	SMT	30	-	-	27.8	7.80	0.281	BPH
313481	76	UNE	MR	H	-	-	-	SV	+	9	-	-	-	-	+	-	CL	-	-	NR	LX	FR	NR	SMT	40	-	-	54.4	8.00	0.147	BPH
309967	61	EMP	MR	H	-	-	-	SV	-	3	-	-	+	-	-	-	CL	-	-	NR	NR	FR	NR	SMT	20	-	+	24.5	8.00	0.326	BPH
319856	70	UNE	MR	H	-	-	-	SV	-	6	-	-	-	-	+	-	CL	-	-	NR	NR	FR	NR	SMT	30	-	+	39.0	8.20	0.210	BPH
309675	65	UNE	MR	H	-	-	-	SV	-	7	-	-	-	-	-	+	CR	-	-	NR	NR	FR	NR	SMT	30	-	-	32.8	8.50	0.259	BPH
1114288	62	UNE	MR	H	-	-	-	ML	-	6	-	-	-	-	-	-	CL	-	-	NR	NR	FR	NR	MSL	45	-	+	51.5	8.70	0.169	BPH
318334	54	EMP	MR	H	-	-	-	MD	+	7	-	+	-	-	-	-	CL	-	-	NR	NR	FR	NR	SMT	30	-	-	41.9	8.80	0.210	BPH
311693	62	EMP	MR	CH	+	+	+	MD	-	3	+	-	-	-	-	-	CR	HPSP	+	NR	NR	INV	HD	MSL	25	-	-	20.7	8.80	0.425	CAP
310583	84	UNE	WD	H	-	-	-	SV	-	9	-	-	-	-	+	-	CL	-	-	ABN	SP	FR	NR	SMT	35	-	-	53.9	8.90	0.165	BPH
317395	70	EMP	MR	H	-	-	-	MD	-	6	-	-	+	-	-	+	CL	-		NR	NR	FR	NR	MSL	75	-	-	76.3	9.00	0.118	BPH
324247	81	UNE	WD	H	-	+	+	MD	-	15	+	-	-	-	+	-	CR	-	-	NR	LX	FR	HD	NOD	30	-	-	24.4	30.70	1.256	CAP
312146	68	UNE	MR	H	-	-	-	SV	-	2	-	-	-	+	-	+	CR	-	-	NR	NR	FR	HD	NOD	35	-	-	42.0	44.00	1.047	CAP
315146	70	UNE	MR	H	-	-	+	SV	+	6	-	-	-	-	-	-	CL	-	-	NR	NR	FR	HD	MSL	70	-	-	61.1	59.90	0.981	CAP
321475	67	UNE	MR	H	+	-	-	SV	+	8	+	-	-	-	-	+	CR	-	-	NR	NR	INV	HD	MSL	65	-	+	74.8	72.00	0.962	CAP
313043	85	UNE	WD	H	-	+	-	MD	-	3	-	-	-	-	+	-	CR	-	+	NR	LX	INV	NR	NOD	70	-	-	85.9	88.00	1.024	CAP
316003	65	EMP	MR	H	+	-	+	SV	+	18	-	-	-	+	+	-	CL	-	-	NR	NR	FR	HD	NOD	40	-	+	33.8	110.00	3.250	CAP
314183	43	EMP	MR	H	-	+	-	SV	-	12	-	-	+	+	-	-	CR	-	-	NR	NR	INV	NR	NOD	80	-	-	102.9	129.00	1.254	CAP

ANNEXURE IV

KEY TO MASTER CHART

-	-	Absent
+	-	Present
ABN	-	Abnormal
BPH	-	Benign prostatic hyperplasia
CAP	-	BPH, Ca. Prostate
CH	-	Christian
CL	-	Clear
CR	-	Crepts
EMP	-	Employed
H	-	Hindu
HPSP	-	Hepatosplenomegaly
LX	-	Lax
MD	-	Moderate
ML	-	Mild
MR	-	Married
MS	-	Muslim
NR	-	Normal
SP	-	Spasm
SV	-	Severe
UNE	-	Unemployed
WD	-	Widowed