Sudan University of Science and Technology
College of Graduate Studies

Correlation Between Bone Scan by Gamma Camera and Prostatic Specific Antigen Level in Prostate Cancer in National Cancer Institute

العلاقة الارتباطية بين مسح العظام بواسطة كاميرا قاما ومستوى قياس مضاد البروستات النوعي في سرطان البروستات في المعهد القومي للسرطان

A thesis Submitted for Partial Fulfillment of Academic Requirements for the Degree of Master of Sciences in Nuclear Medicine Technology

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استهـــلال

بسم الله الرحمن الرحيم

قَالَ تَعَالَىٰ:

﴿ وَإِذَا مَرِضْتُ فَهُوَ يَشْفِينِ ﴾

صدق الله العظيم

سورة الشعراء: الآية (٨٠)

Dedication

To my father

To my Mother soul

To my husband

To all cancer patients

With much Love

Acknowledgment

My acknowledgments and gratefulness at the beginning and at end to Allah who gave me the gift of the mind. Profound, thanks and gratitude goes to everyone who encouraged me to complete this thesis. My gratitude is extended to my supervisor ***Prof. Mohamed Elfadil Mohamed*** **Gar-elnabi.my thanks also extend to** ***Mr. Yousif Abdalhmeed Mohmed*** **for unlimited assistance during the course of preparing thesis work** and all employees at National Cancer Institute (NCI) for their helps their works have stimulated and fostered my efforts in producing this research .

Many thanks to my friends and colleagues in Radiotherapy and Nuclear Medicine department College of medical radiological Sciences, Sudan University of Sciences and Technology for their continuous encouragement.

Finally I would like to warmly thank my long-suffering family for their endless support. May almighty God bless them all.

Abstract

Prostate cancer is the one of the major medical problems in adult males. According to National cancer Institute (NCI) medical information and research center annual reports it is the first male cancer in Gezira state. The main objective of this study is to find the correlation between PSA level and bone Metastasis in prostate cancer patients. The sample of this study consisted of 50 cases of prostate cancer patients that were diagnosed and referred to(NCI) for further investigations and treatment. Bone scan and serum PSA levels were done to assess the treatment response and for follow up for prostate cancer in the period between febuaray2020 to march 2021. Serum PSA was determined by Immune Radiometric Assay (IRMA). Results showed a significant difference between PSA level and bone scan according to *t*-test ($p<0.0001$) for the prostate cancer patients. Also there were significant relation between PAS level before Treatment and after treatment according to a verge, PSA level before treatment (*p* =.003) PSA level after treatment (0 .014) and decrease of PSA after treatment by0.23 show diaghram1. And also the results show the region of metastasis there was 12% at the skull and lumber spine.

المستخلص

يعتبر سرطان البروستات من السرطانات التي تسبب مشاكل صحيه كثيره في الرجال الذين تجاوزت اعمارهم 40 سنه او اكثر وحسب التقارير الإحصائية بقسم علاج الاورام بالمعهد القومي للسرطان بجامعه الجزيره يعتبر سرطان البروستات الاول من السرطانات التي تصيب الرجال في ولاية الجزيرة . الهدف الاساسي لهذه الدراسة توضيح العلاقة الارتباطية بين المستضد النوعي للبروستات ونتائج فحص العظام لمرضي سرطان البروستات .اشتملت الدراسة علي 50 مريض بسرطان البروستات تم تحويلهم لقسم علاج الاورام بالمعهد القومي للسرطان للعلاج والمتابعة بسرطان البروستات تم تحويلهم لقسم علاج الاورام بالمعهد القومي للسرطان للعلاج والمتابعة بعد تشخيصهم بمعمل الجامعةللأنسجةالمريضة ثم عمل مسح للعظام وقياس المستضد النوعي للبروستات وذلك ففي الفترة ما بين فبراير2020 وحتي مارس 2021 وقياس المستضد النوعي للبروستات بواسطة القياس المناعي الاشعاعي .يعتبر مسح العظام واحد من الوسائل المستعملة في تشخيص انتشار سرطان البروستات في العظام .من نتائج هذه الدراسة فقد وجد هنالك علاقه قويه بين المستضد البروستاتي النوعي ونتائج مسح العظام حيث وجد ان مستوي الثقة($p_{=}$0.000) وكذلك وجدت ان هنالك علاقه بين مستويات المستضدالنوعي البروستاتي قبل العلاج وبعده مع انتشار المرض في العظام حيث وجد ان مستوي الثقة($p_{=}$0.003) و ($p_{=}$0.014.)،كما وجد ان مستوي المستضد البروستاتي ينقص بعد العلاج بمعدل 0.23 . وكذلك وجدت الدراسة ان اكثر المناطق التي يمكن ان ينتشر اليها السرطان هي منطقة الراس والفقرات البطنية والتي تمثل 23%من جملة المناطق التي ينتشر اليها المرض

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List of abbreviation

Ab	Anti-body
BPH	Beign Prostate Hyperplasia
CaP	Cancer of Prostate
CT	Computed Tomography
DHT	Di Hydro Testostrone
DRE	Digital Rectal Examination
EDs	Endocrine Disruptors
H MDP	Hydroxy Methylene Di Phosphate
Mci	Millicurie
MRI	Magnetic Resonance Image
NCI	National Cancer Institute
IRMA	Immuno Radio Metric Assay
PSA	Prostate Specific Antigen
TC^{99}-MDP	Technisium –Methylene Diphosphate
TRUS	Trans Rectal Ultra Sound

Chapter One
Introduction

1.1 Introduction:

Prostate cancer is a form of cancer that develops in the prostate, a gland in the male reproductive system. Most prostate cancers are slow growing; however, there are cases of aggressive prostate cancers. The cancer cells may metastasize (spread) from the prostate to other parts of the body, particularly the bones and lymph nodes. Prostate cancer may cause pain, difficulty in urinating, problems during sexual intercourse, or erectile dysfunction. Other symptoms can potentially develop during later stages of the disease.

Prostate cancer tends to develop in men over the age of fifty and although it is one of the most prevalent types of cancer in men, many never have symptoms, undergo no therapy, and eventually die of other causes. This is because cancer of the prostate is, in most cases, slow-growing, symptom-free, and since men with the condition are older they often die of causes unrelated to the prostate cancer, such as heart/circulatory disease, pneumonia, other unconnected cancers, or old age. About 2/3 of cases are slow growing, the other third more aggressive and fast developing

The presence of prostate cancer may be indicated by symptoms, physical examination, prostate-specific antigen (PSA), or biopsy. The PSA test increases cancer detection but does not decrease mortality. Suspected prostate cancer is typically confirmed by taking a biopsy of the prostate and examining it under a microscope. Further tests, such as CT scans and bone scans, may be performed to determine whether prostate cancer has spread.

1.2 Problem of the study

Prostate cancer is the most common male cancer in Sudanese. According to National Cancer Institute medical information and research center, annual report it is the first male cancer in Sudan majority of patient present with bone metastasis.

1.3 Objectives of the study:

The main Objective of this study was to find out the Correlation between PSA level and Bone metastasis; to relate the elevation of prostate specific antigen to bone metastasis.

1.4 Specific objectives

- To estimate the PSA level in patients with prostate cancer.
- To determine the correlation between PSA elevation and presence of bone metastasis.
- To find the relationship between the age and PSA level before and after the treatment.
- To find the common site of metastasis.
- To determine the significance of difference in means of PSA before and after treatment as a measure of response to treatment.

1.5 Significance of the study

This study will provide information about the relation of PSA level in respect to metastasis as well as it can gives an indication of response to treatment.

1.6 Overview of the study

This study consisted of five chapters; with Chapter One is an introduction which includes; general introduction, statement of the problems, Objectives of the study and important of the study. Chapter two included theoretical background information, which includes anatomy, physiology, pathology

of the prostate, as well as a comprehensive literature review, which includes diagnosis of the prostate cancer. Chapter three includes the material used to collect the data and the method of data collection. Chapter four presents the results of the study using tables and figures. Finally Chapter five gives elaborative discussions of the result, Conclusions and Recommendations.

Chapter Two

Literature review

2.1 Theoretical background:

2.1.1: Anatomy and physiology of the prostate:

The prostate is fibro muscular glandular organ that encircles the proximal part of the male urethra. It is about 1.25 in (3 cm) long and lies between bladder above and urogenital diaphragm below (fig 2-1).

The prostate is surrounded by a fibrous capsule. The somewhat conical prostate has a base, which lies against the bladder neck above, and an apex, which lies against urogenital diaphragm below. The periurethral glands are embedded in the longitudinal smooth muscle of the proximal urethra (prostatic portion of the urethra). The levatorani muscles are located at the sides of the gland. The two ejaculatory ducts pierce the upper part of the posterior surface of the prostate to open into prostatic urethra at the lateral margins of prostatic utricle (fig 2-2).**2.1.1a Relations:**

Superiorly: The base of the prostate is continuous with the neck of the bladder, the smooth muscle passing without interruption from one organ to other. The urethra enters the center of the prostate (fig 2-2).

Inferiorly: The apex of the prostate lies on the upper surface of the urogenital diaphragm. The urethra leaves the prostate just above the apex on the anterior surface (fig 2-2).

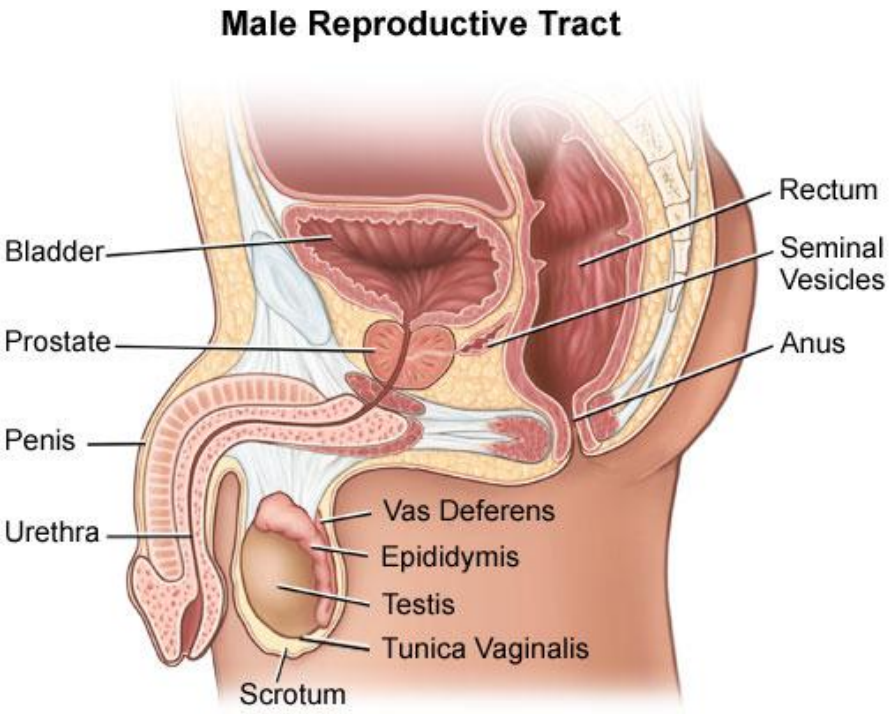


Figure (2.1)

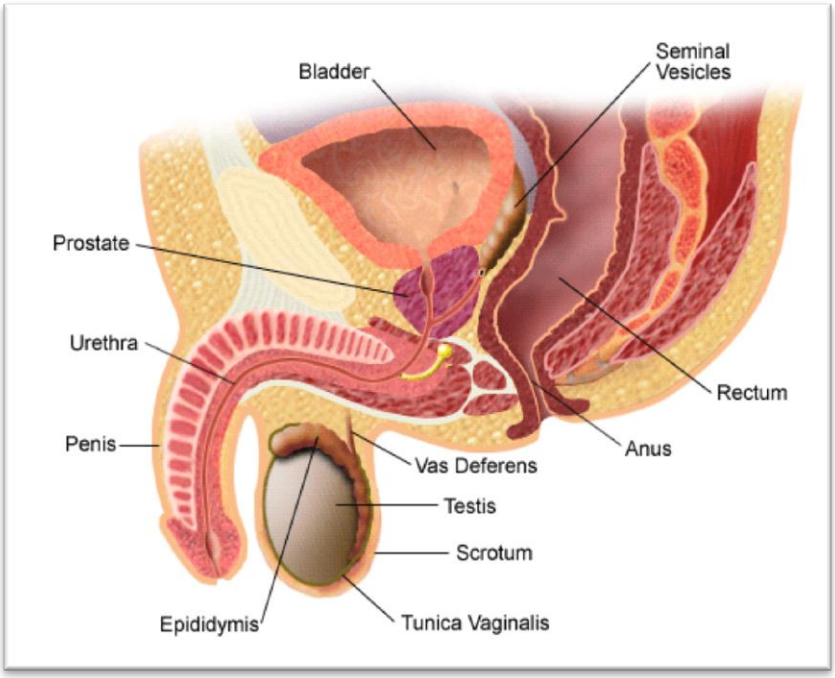


Figure (2- 2) shows: Sagittal view of The prostate

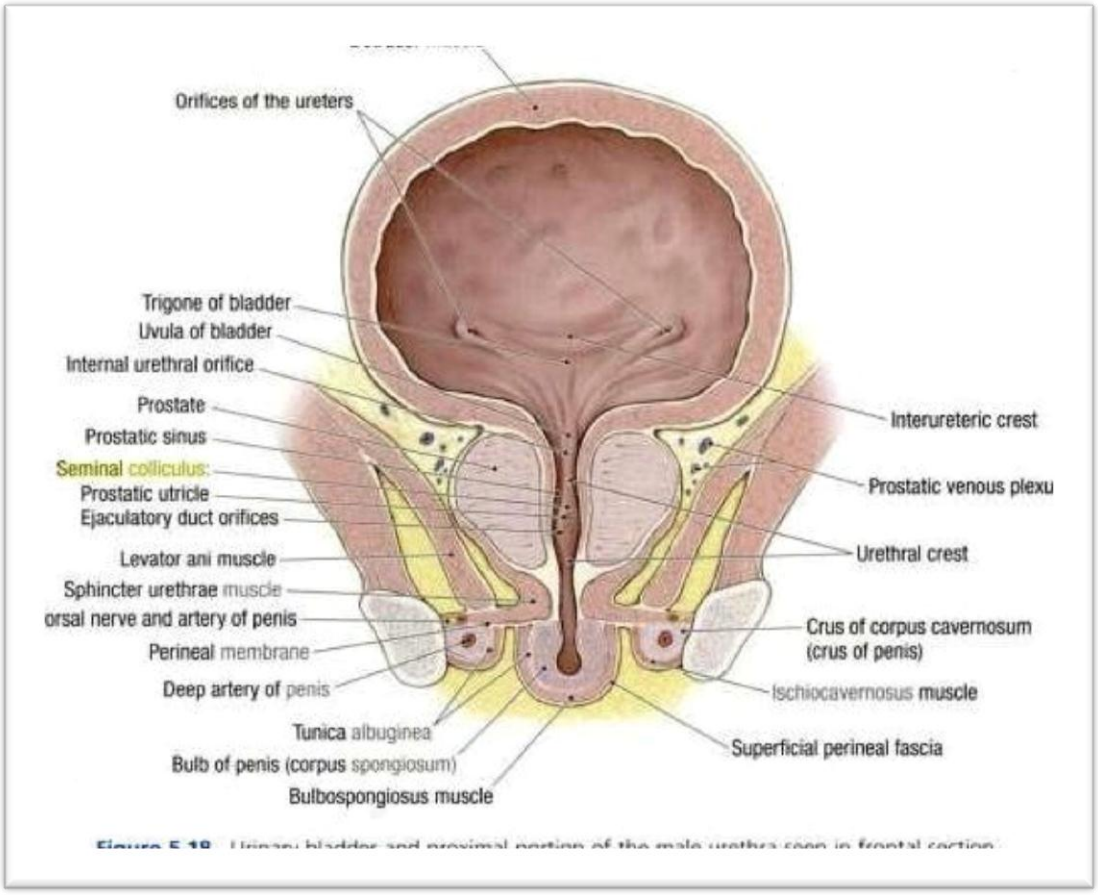


Figure (2- 3) shows: Coronal view of the prostate .

Anteriorly: The prostate is related to the symphysis pubis, separated from it by the extraperitoneal fat in the retropubic space (cave Retzius). The prostate is connected to the posterior aspect of the pubic bone by the fascialpuboprostatic ligament.

Posteriorly: The prostate is closely related to anterior surface of the rectal ampulla and is separated from it by the recovesical septum (fascia of Denonvilliers). This septum is formed in fetal life by the fusion of the wall end of the rectovesical pouch of peritoneum, which originally extended down to the perineal body .

Laterally: The prostate embraced by the anterior fibers of the levatorani as they run posteriorly from the pubis .

2.1.1b: Surface of the prostate:

The numerous gland of the prostate are embedded in a mixture of smooth muscle and connective tissue, and their ducts open into prostatic urethra. The prostate is incompletely divided into five lobes: The anterior lobe lies in front of the urethra and is devoid of glandular tissue. The median, or middle, lobe is the wedge of the gland situated between the urethra and the ejaculatory duct. Its upper surface is related to the trigone of the bladder: it is rich in glands. The posterior lobe is situated behind the urethra and below the ejaculatory ducts and also contains glandular tissue. The right and left lateral lobes lie on either side of the urethra and are separated from one another by a shallow vertical groove on the posterior surface of the prostate. The lateral lobes contain many glands .

2.1.1c: Prostatic zones:

The prostate is divided into four glandular zones surrounding the prostatic urethra; the peripheral zone, transition zone, central zone, and periurethral glandular area.

The peripheral zone, the largest of the glandular zones, contains approximately 70% of the prostatic glandular tissue and is the source of most prostate cancer. It surrounds the distal urethral segment and is separated from the transition zone and central zone by the surgical capsule, which is often hyperechoic as a result of corpora amylacea or calcification. The peripheral zone occupies the posterior, lateral, apical regions of the prostate, extending somewhat anteriorly. The ducts of the peripheral zone enter the distal urethra.

The transition zone, in normal patient contains approximately 5% of the prostatic glandular tissue. It is seen as two small glandular area located adjacent to the proximal urethra segment. It is the site of origin of benign prostatic hyperplasia. The ducts of the transition zone end in the proximal

urethra at the level of the verumontanum, which bounds the transition zone caudally .

The central zone constitutes approximately 5% of the glandular tissue. It is located the prostatic base. The ducts of the vas deferens and seminal vesicles enter the central zone, and ejaculatory ducts pass through it. The central zone is relatively resistant to disease processes and is the site origin of only 5% of prostate cancer. Central zone ducts terminate in the proximal urethra near the verumonatnum .

The periurethral glands form about 1% of the glandular volume. They are embedded in longitudinal smooth muscle of the proximal urethra, also known as the internal prostatic sphincter .

2.1.1d.:Arterial Supply of Prostate:

The arteries are derived mainly from the inferior vesical and middle rectal arteries, branches of internal iliac artery (fig 2-4).

Venous Drainage of Prostate:

The veins of prostate from the prostatic venous plexus around the sides and base of the prostate. This plexus, located between the capsule of the prostate and its fascial sheath, drains into internal iliac veins, but it communicate with vesical venous plexus and the vertebral venous plexuses

Lymphatic Drainage of the Prostate:

Parasympathetic fibers arise from the pelvis splanchnic nerves. The sympathetic fibers are derived from the inferior hypogastric plexuses (fig 2- 4).

2.1.1e :Prostatic urethra:

The prostatic urethra about 1.25 in. (3) cm long and begin at the neck of the bladder. It passes through the prostate from the base to the apex, where it becomes continuous with the membranous part of the urethra. The prostatic urethra is the widest and most dilatable portion of the entire urethra. On the posterior wall is a longitudinal ridge is a groove called the

prostatic sinus; the prostatic gland open into these groove. On the summit of the urethra crest is a depression, the prostatic utricle, which is an analog of the urethra and vagina in female. On the edge of the mouth of the utricle are the openings of the two ejaculatory ducts.

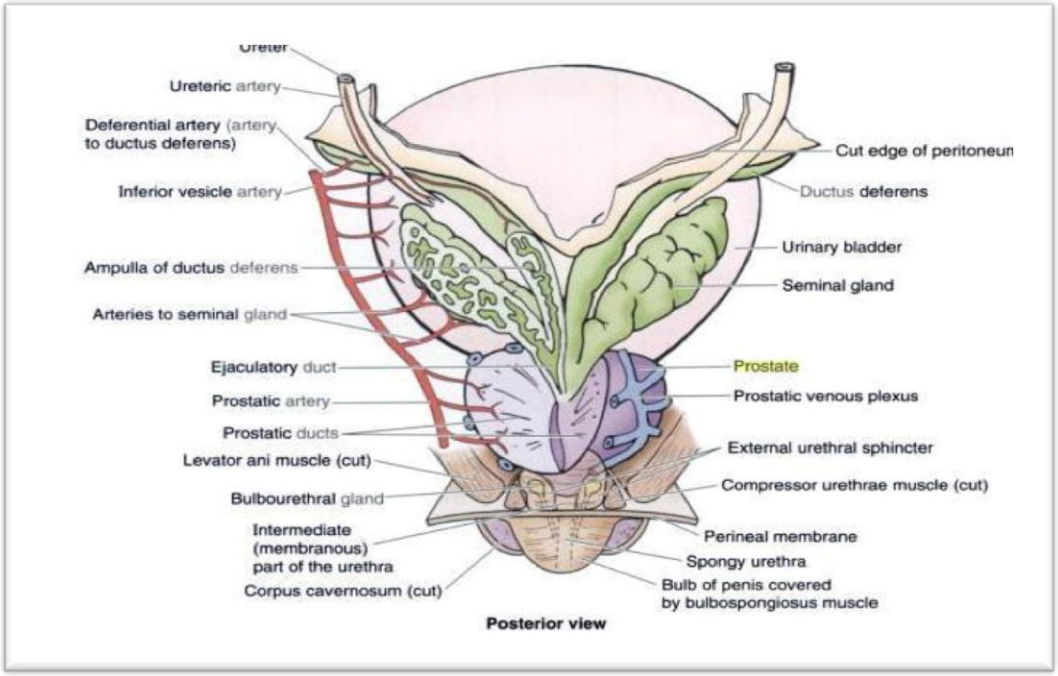


Figure (2- 4) shows: Arterial supply, veinous drainage, and Lymphatic drainage of the prostate.

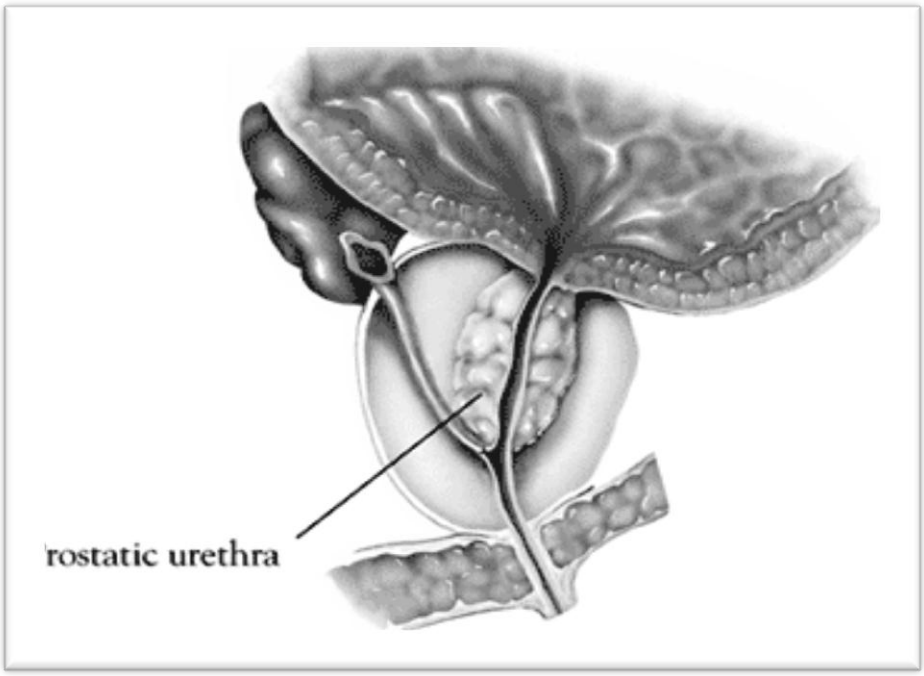


Figure (2- 5) shows: prostatic urethra in sagittal view .

Seminal vesicles:

Each vesicle is a thin-walled, pear-shaped structure, about 5cm long, actually it consists of a tube (10-15) cm long), which is coiled to form the vesicle-like mass that lies between the fundus of the bladder and rectum. The seminal vesicles obliquely placed superior to the prostate, do not store sperms as their name implies. They secret a thick alkaline fluid that mixes with sperms as they pass into the ejaculatory ducts and urethra. These secretions, expelled when the seminal vesicles contract during orgasm, provide most of the volume of the semen or seminal fluid. The seminal vesicles and ampulla of the ductus deferens have a similar structure; they are a thin-walled and their mucous membranes have a honeycombed appearance. The superior ends of the seminal vesicles are covered with peritoneum and lie posterior to the ureters, where they are separated from the rectum by peritoneum of the rectovesical pouch.

The inferior ends of the seminal vesicles are closely related to the rectum and are separated from it by only the rectovesical septum. The duct of each seminal vesicle joins the ductus deferens to form the ejaculatory duct, which opens into the posterior wall of the prostatic urethra near the opening of the prostatic utricle.

2.1.2 Pathology of the Prostate:

Diseases of prostatic are common cause of urinary problem in men, the incidence of which increases with age, particularly beyond 60 years. Most prostatic disease cause enlargement of the organ resulting in compression of the intraprostatic portion of urethra; this leads to impaired urine flow, and increase risk of urinary infections, and, in some cases, cause retention of urine requiring urgent relief by catheterization. The most important and common causes of these sign and symptoms are prostatic hyperplasia and prostatic carcinoma. Inflammation of prostate gland

(prostatitis) is also common, but it less often gives rise to serious clinical problem; indeed small foci of prostatic inflammation are not uncommon coincidental finding in prostatic tissue removed because of hyperplasia or carcinoma.

2-1-2a: Prostatitis

A variable inflammatory infiltrated is commonly seen the prostatic stroma in glands enlarged by benign nodular hyperplasia. Its significance is sometimes uncertain; it may simply be associated with leakage of material from distended ducts into the stroma. A marked degree of stromal edema and periductal inflammation may, however, contribute to urethral obstruction.

Prostatitis implies a more prominent inflammatory lesion of the gland, often associated with a specific infective cause. Prostatitis may be:

2-1-2b: Acute suppurativeprostatits

Acute prostatits usually results from spread of infection along the prostatic ducts secondary to urethritis or cystitis. Common causative micro-organisms include coliforms, staphylococci and gonococci. Acute prostatitis may occasionally follow urethral catheterization or endoscopy; more rarely, the infection is blood-borne.

The lesion is characterized by difficulty in micturition with perineal or rectal pain. There is general malaise and pyrexia and prostate is palpably enlarged, soft and tender. Histology reveals acute inflammation with acini distended by polymorphs macrophages and damaged epithelial cells. There may be necrosis with formation of an abscess which may eventually discharge into urethra.

2.1.2c: Granulomatous prostatitis

Granulomatous prostatitis is a heterogeneous group of lesion, all of which may cause enlargement of the gland and urethral obstruction. The inflammatory component and associated fibrosis produce a firm, indurated gland on rectal examination which may mimic a neoplasm clinically; thus the importance of correctly diagnosing this uncommon group of conditions.
Idiopathic prostatitis may result from leakage of material from distended duct in gland enlarged by nodular hyperplasia. There is periductal inflammatory infiltrate which includes macrophages, multinucleated giant cells, lymphocytes and plasma cells, with associated fibrosis.
The prostate is often involved in cases of genitourinary tuberculosis. This condition is usually secondary to tuberculous cystitis or epididymitis, the infection spreading along the prostatic duct or vas deferens. The histological features are of caseating granulomas distributed among the prostatic glands and through the stroma. Some patients may require a second transurethral resection for benign nodular hyperplasia or carcinoma if the first operation fails to relieve the obstructive symptoms. The second biopsy often contains granulomas with necrosis; this lesion may be ischaemic, related to damage blood vessels.
Allergic (eosinophilic) prostatitis is a rare lesion, occurring usually in men with bronchial asthma. There may be a sudden onset of prostatic symptoms. The gland contains granulomas with areas of fibrinoid necrosis and a surrounding zone of histiocytes, giant cells and numerous eosinophils.

2.1.2d Nodular Hyperplasia of the Prostate

The normal prostate consists of glandular and stromal elements surrounding the urethra. The prostatic parenchyma can be divided into several biologically distinct regions, the most important of which are the

peripheral, central, transitional, and periurethral zones. The types of proliferative lesions are different in each region. For example, more hyperplastic lesion arise in the inner transitional and zones of the prostate, while most carcinoma (70% to 80%) arise in the peripheral zones.

Nodular hyperplasia, also termed glandular and stromal hyperplasia, is an extremely common abnormality of the prostate. It is present in a significant number of men by the age of 40, and its frequency rises progressively with age, reaching 90% by the eighth decade. Prostatic hyperplasia is characterized by proliferation of both stromal and epithelial elements, with resultant enlargement of the gland and, in some cases, urinary obstruction. Benign prostatic hypertrophy (BPH), a time-honored synonym for nodular hyperplasia of the prostate, is both redundant and a misnomer, because all hypertrophies are benign and the fundamental lesion is hyperplasia rather than a hypertrophy.

Although the cause of nodular hyperplasia remains incompletely understood, it is clear that androgens have a central role in its development. Nodular hyperplasia does not occur in male castrated before the onset of puberty nor in men with genetic diseases that block androgen activity.

Dihydrotestosterone (DHT), an androgen derived from testosterone through the action of 5α-reductase, and metabolite, 3α-androstanediol, seem to be major hormonal stimuli for stromal and glandular proliferation in men with nodular hyperplasia. DHT binds to nuclear androgen receptors and, in turn, simulates synthesis of DNA, RNA, growth factors, and other cytoplasmic proteins, leading to hyperplasia. This form the basis for the current use of 5α-reductase inhibitors in the treatment of symptomatic nodular hyperplasia. Because no study has shown conclusive association between circulating androgen levels and the development of nodular hyperplasia, it follows that local, intraprostatic concentrations of androgens and androgen receptors contribute to the pathogenesis of this condition.

Experimental work has also identified age-related increase in estrogen levels that may increase the expression of DHT receptors on prostatic parenchymal cells, thereby functioning in the pathogenesis of nodular hyperplasi.

2-1-2e : Carcinoma of the Prostate:

Carcinoma of the prostate is most common visceral cancer in males, ranking as the second most common cause of cancer-related deaths in men older than 50 years of age, after carcinoma of lung. It is predominantly a disease of older males, with a peak incidence between the ages of 65 and 75 years. Latent cancers of the prostate are even more common than those that are clinically apparent, with an overall frequency of more than 50% in men older than 80% years of age.

Although the cause of carcinoma of the prostate remain unknown, clinical and experimental observations suggest that hormones, genes, and environment all have a role in its pathogenesis. Cancer of the prostate does not developed in males castrated before puberty, indicating that androgens probably contribute to its development. A hormonal influence is further suggested by the observation that the growth of many carcinoma of the prostate can be inhibited by orchiectomy or by the administration of estrogen such as dithylstibestrol. As in the case of nodular hyperplasia of the prostate, however, the function of hormones in the pathogenesis of carcinoma of the prostate is not fully understood. ***Hereditary***contributions have also been implicated in light of the increased risk of disease among first-degree relatives of patients with prostate cancer. Symptomatic carcinoma of the prostate is more common and occurs at an earlier age in American blacks than the whites, Asians, or Hispanics. Whether such racial differences occur as a consequence of genetic influences, environmental factors, or some combination of the two remains unknown. However, the frequency of incidental prostatic cancer is comparable in all races,

suggesting that race fingers more importantly in the growth of established lesions that in the initial development of carcinoma. Much effort is focused on finding prostate cancer genes, but no definitive data are available. In the studies of familial cases, several susceptibility loci on chromosome 1 have been identified. In sporadic cases, hypermethylation of glutathione S-transferase p1 (GSTP1), a genome caretaker gene on chromosome 11, and telomere shortening are relatively common genetic alterations. Recent studies implicate overexpression of two ETS family transcription factors in the pathogenesis of prostate cancer. Recall that these transcription factors are also involved in Ewing sarcoma. Interestingly, racial variations in the number of CAG repeats in the androgen receptor gene seem to be linked to the higher incidence of prostate cancer in African American. Perhaps these polymorphisms influence the action of androgens on epithelium.

A possible role for environmental influences is suggested by the increased frequency of prostatic carcinoma in certain industrial settings and by significant geographic differences in the incidence of disease. Males emigrating from low-risk to high-risk areas maintain a lower risk of prostate cancer; the risk of disease is intermediate in subsequent generations, in keeping with an environmental influence on the development of this disease. Among environmental influence, a diet high fat has been suggested as a risk factor.

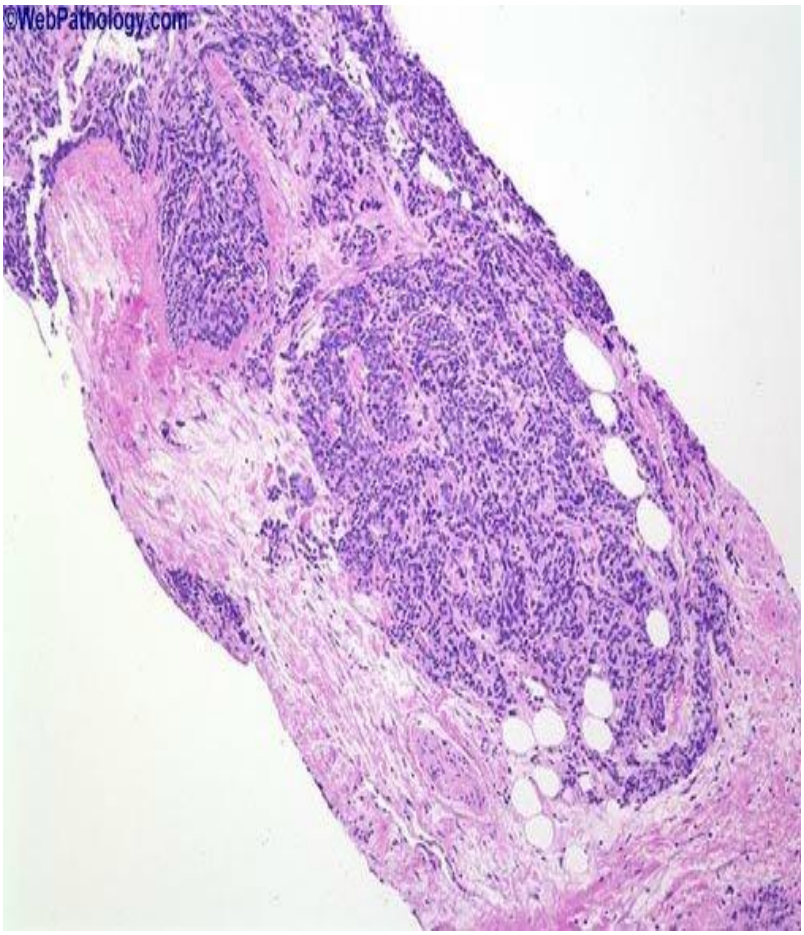


Figure (2-6) shown Prostate - Small Cell Carcinoma .

Histologic type of Prostate cancer

Adenocarcinoma	95%	
Others		
Transitional cell cancer		5%
Squamous cell cancer		
Sarcoma		
Carcinosarcoma		
Endometroid cancer		
Small cell anaplastic cancer		

Clinical features:

Carcinomas of the prostate are often clinically silent, particularly during their early stages. Approximately 10% of localize carcinomas are discovered unexpectedly, during histologic examination of prostate tissue removed for nodular hyperplasia. In autopsy studies, the incidence approaches 30% in men between 30 and 40 years of age.

Because most cancers begin in the peripheral regions of the prostate, they may be discovered during routine digital examination. More extensive disease may produce signs and symptoms of "prostatism," including local discomfort and evidence of lower urinary tract obstruction similar to that encountered in patients with nodular hyperplasia. Physical examination in such cases typically reveals evidence of locally advanced disease, in the form of a hard, fixed prostate. More aggressive carcinoma of the prostate may first come to clinical attention because of the presence of metastases.

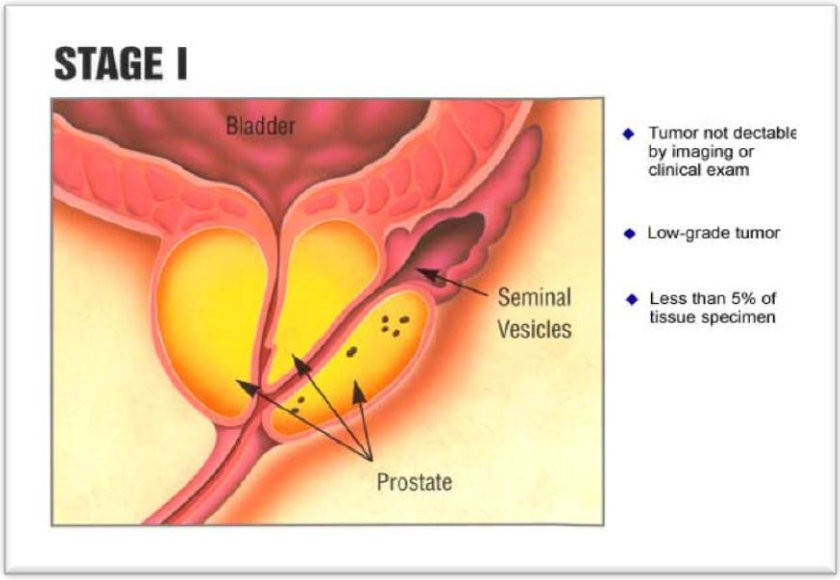
Regrettably, this is not an uncommon mode of presentation. Bone metastases, particularly to the axial skeleton, are common and may cause either osteolytic or, more commonly, osteoblasticlesions. The presence of osteoblastic metastases in an older male is strongly suggestive of advanced prostatic carcinoma.

2.1.3. ***Clinical Staging of Prostate Cancer*** (fig 2-6a,b,c,d).

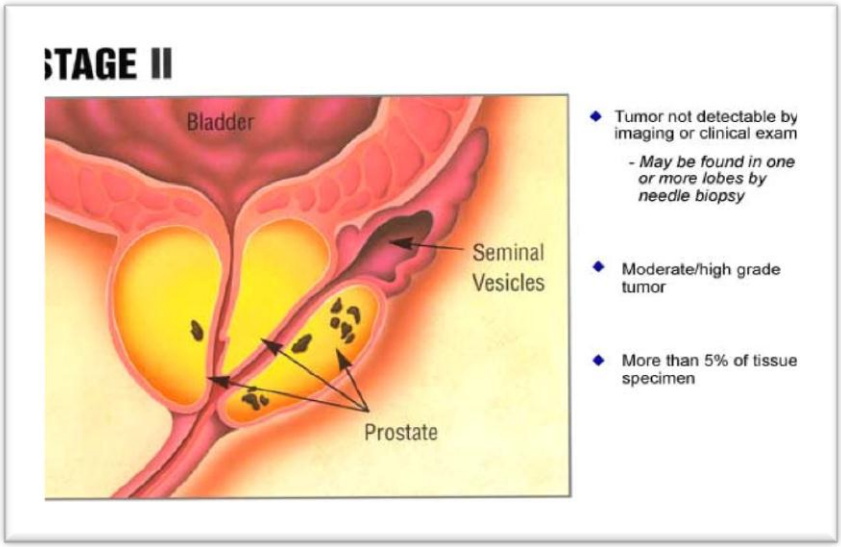
MTN Staging:

- **T1** : Tumor is an incidental histologic finding
- **1a** :There or fewer microscopic foci carcinoma
- **1b** :More than three microscopic foci
- **T2** : Tumor present clinically or grossly limited to the gland
- **2a** **:**Tumor ≤ 1.5 cm greatest dimension, with normal tissue on at least three sides
- **2b** :Tumor > 1.5 cm greatest dimension, in more than one lobe

- **T3** : Tumor invade in to prostatic apex or into or beyond the capsule or bladder neck or seminal vesicle, but is not fixed
- **T4** : Tumor is fixed or invades adjacent structures other than those listed for T3
- **N0** : No abnormal nodes
- **N1** : Metastasis in a single node ≤ 2 cm
- **N2** : Metastasis in a single node > 2 cm but no more than 5 cm or multiple nodes with none > 5 cm
- **N3** : Metastasis in lymph node, > 5 cm in greatest dimension



(A)



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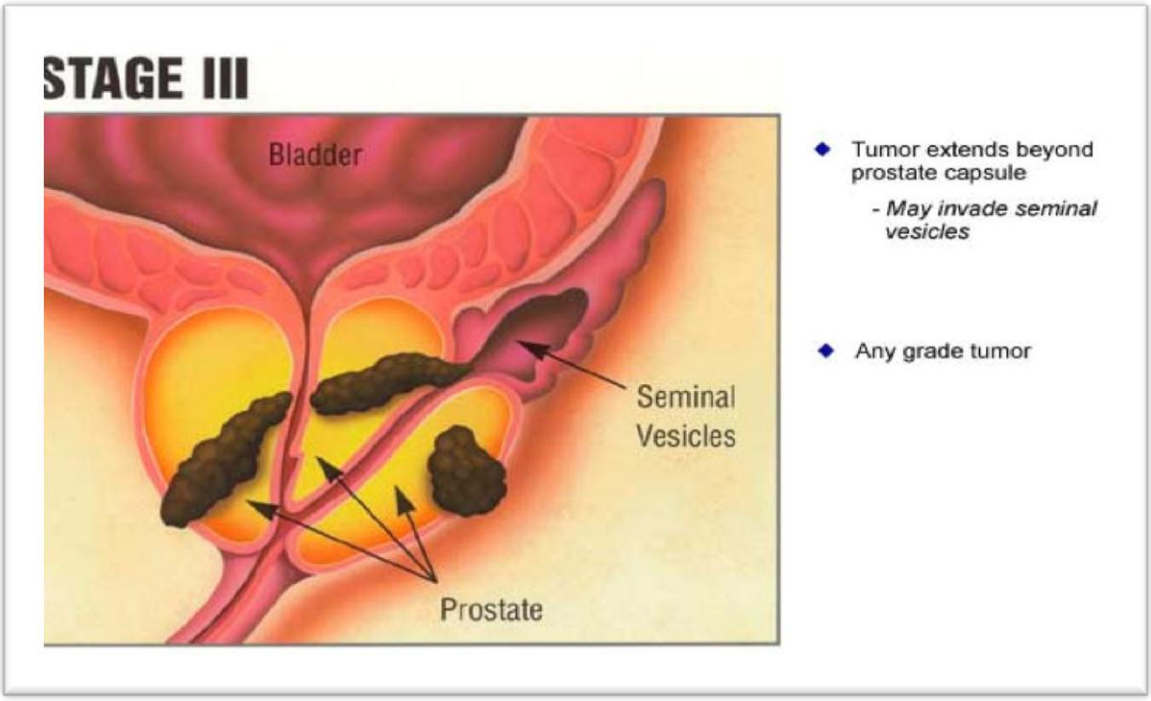

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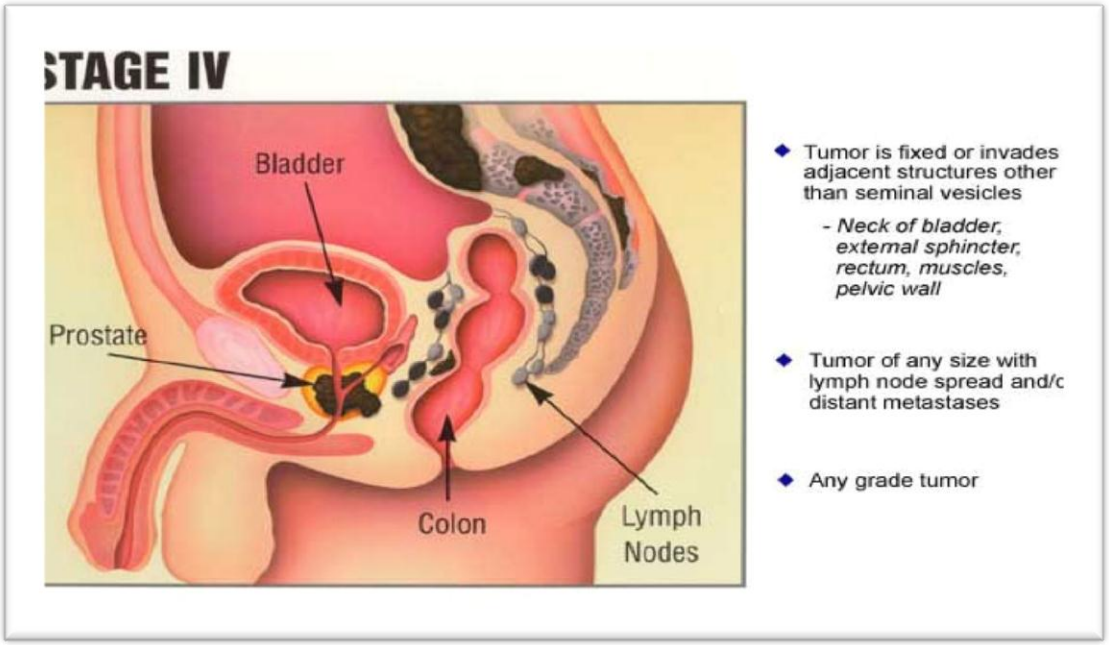

(D)

Figure 2-7 (A,B,C,D) Shows: staging of prostate cancer .

2.1.4 .Signs and symptoms:

Early prostate cancer usually causes no symptoms. Sometimes, however, prostate cancer does cause symptoms, often similar to those of diseases such as benign prostatic hyperplasia. These include frequent urination, nocturia (increased urination at night), difficulty starting and maintaining a steady stream of urine, hematuria (blood in the urine), and dysuria (painful urination).

Prostate cancer is associated with urinary dysfunction as the prostate gland surrounds the prostatic urethra. Changes within the gland, therefore, directly affect urinary function. Because the vas deferens deposits seminal fluid into the prostatic urethra, and secretions from the prostate gland itself are included in semen content, prostate cancer may also cause problems with sexual function and performance, such as difficulty achieving erection or painful ejaculation. Advanced prostate cancer can spread to other parts of the body, possibly causing additional symptoms. The most common symptom is bone pain, often in the vertebrae (bones of the spine), pelvis, or ribs. Spread of cancer into other bones such as the femur is usually to the proximal part of the bone. Prostate cancer in the spine can also compress the spinal cord, causing leg weakness and urinary and fecal incontinence.

2.1.5. Diagnosis

Most often, prostate cancer diagnosis relies on screening tests, because the cancer typically does not produce symptoms in its early stages. In fact, about 40 percent of prostate cancer cases aren't detected until the cancer has spread beyond the prostate gland.

Screening tests are often part of a routine physical exam, especially in men over age 40. Your doctor may also recommend screening tests because of symptoms pointing to a prostate problem. Screening tests include:

- Digital Rectal Exam (DRE) — The doctor gently inserts a gloved, lubricated finger into the patient's rectum and by pressing against the

rectal wall can feel the back wall of the prostate gland. About 70 percent of cancerous tumors develop near the outer portion of the prostate and can be detected through a DRE.

- Prostate-Specific Antigen (PSA) Test — A sample of blood is analyzed for PSA, a substance produced in the prostate gland that helps liquefy semen. A small amount of PSA always circulates in the blood. High PSA levels, or levels that rise over time, could indicate prostate inflammation, enlargement, or cancer.
- Biopsy — Depending on the result of a digital rectal exam and/or PSA, the doctor may recommend a biopsy. Small tissue samples from several different areas of the prostate are removed — usually using a needle inserted through the perineum, located between the scrotum and anus. A doctor administers a local anesthetic to minimize any pain and discomfort. The tissue is then examined under a microscope for the presence of cancerous cells. A biopsy is usually done in the clinic as an outpatient procedure and generally does not require hospital admission.
- Grading and Staging — If cancer cells are found, doctors will determine how quickly the cancer is growing and whether it has spread beyond the prostate. Additional blood or imaging tests may be necessary to determine the extent of the cancer.
- Bone Scan — Currently, this test is the most effective imaging procedure to determine the spread of cancer to bone. A low-grade radioactive solution is injected into a vein and is selectively taken up or absorbed by areas of new or rapid bone growth, possibly indicating cancer. The need for a bone scan test depends on a man's prostate cancer type and stage.
- Ultrasound — This test is generally performed in conjunction with prostate biopsy. Sometimes, prostate cancer can appear different from normal prostate tissue. The best way to determine the presence of

prostate cancer is the combination of digital rectal exam, PSA level, and biopsied tissue.

- Chest X-ray — An X-ray can indicate if the cancer has spread to the lungs. Although less than 5 percent of prostate cancer spreads this far, lung cancer develops in about 25 percent of men with advanced prostate cancer.
- Computed Tomography (CT) Scan — CT scans are most useful when combined with other tests. A CT scan can show abnormal lymph nodes in the pelvis and abdomen where prostate cancer tends to spread. But the test is not sensitive enough to identify microscopic or individual cancer cells in lymph nodes. CT scans, at this time, do not provide reliable enough information about the condition of the prostate or the stage of prostate cancer.
- Magnetic Resonance Imaging (MRI) — Magnetic resonance imaging does not require radiation. It produces a detailed, three-dimensional picture of the body that can detect the spread of cancer to lymph nodes and bone and is better suited for detecting cancer in soft tissues than a CT scan and some other imaging tests. During a specialized form of MRI, called endorectal coil MRI, part of the device is inserted into the rectum to discern details that may determine if the cancer has spread beyond the prostate.
- Lymph Node Biopsy (lymphadenectomy) — During this surgical procedure, a urologist removes some of the nodes near the prostate and examines them under a microscope. The procedure typically takes place during prostate removal surgery, but not always. If other tests, such as a bone or CT scan, show the cancer has spread, this procedure usually is not needed. Lymph node biopsy is most often used to confirm test results indicating the cancer is confined to the prostate, and is part of prostate cancer staging.

If the doctor suspects a patient may have prostate cancer, additional prostate-specific antigen (PSA) and digital rectal exam (DRE) tests are usually performed. A biopsy can help determine a cancer's extent and aggressiveness.

Prostate Specific Antigen

Prostate specific antigen is a blood test that measures the level of PSA in serum. PSA is a serine protease discovered in 1979 by Wang. The normal level is 0 to 4 ng/mL using the Hybritech monoclonal antibody method. Although it is secreted only by epithelial cells in the prostate, it not specific for prostate cancer; it become elevated with any significant derangement of prostate architecture and subsequent leakage of PSA. A variety of pathologic conditions cause a leakage of PSA into the stroma of the gland. From there, it enters the circulation by thelymphatic and capillaries.

Cause of elevated PSA include benign prostatic hyperplasia (BPH), prostate cancer, prostatic intraepithelial neoplasm, instrumentation, prostatitis, infarction, biopsy, and transurethral prostatic resection (TURP). Other factors affecting the PSA level including antiandrogen therapy, sexual activity, ambulation, and exercise. The incidence of prostate cancer is significantly higher in black men. The PSA often is elevated in these men at an earlier age and may provide an early warning mechanism for prostate cancer. To confound matters, approximately 20% of men with prostatic carcinoma have normal PSA levels.

Serial PSA testing reveals a direct correspondence of the PSA level with the tumor volume and growth rate. PSA levels do not increase significantly until the tumor reaches a volume of 1 cc. Stamey and coworkers discovered that 1 g of BPH elevates the PSA by only 0.3 ng/mL, whereas 1 g of cancer generates 10 times more PSA, elevating the to 0.3 ng/mL. Continued

elevation or significant interval increases in PSA over time may be more important indicators of cancer than absolute PSA values.

The PPV of PSA varies from 17% to 28% and depends on the degree of elevation. Most men with PSA volumes above 10 ng/mL have prostate cancers that are extracapsular and much less likely to be curable. Elevation of the PSA is a better indicator of clinically significant tumor with extracapsular spread than is provided by DRE. Elevated level of PSA are correlated with increasing clinical stage and the pathologic grade of prostate cancer.

Velocity (PSAV), PSA density (PSAD), predicted PSA (PPSA), age-specific PSA, and investigation of different circulating forms of PSA molecules.

Bone scintigraphy

^{99m}Tc bone scintigraphy is an effective method for screening the whole body for bone metastases.[51, 52] ^{99m}Tcdiphosphonates, most commonly ^{99m}Tc methylene diphosphonate (MDP), is the most frequently used isotope. ^{99m}Tc planar bone scintiscans help in detecting metastatic bone deposits by the increased osteoblastic activity they induce; this finding is considered to be an indirect marker of tumor.

Indications for bone scintiscanning include staging in asymptomatic patients, evaluating persistent pain in the presence of equivocal or negative radiographic findings, determining the extent of bone metastases in patients with positive radiograph findings, differentiating metastatic from traumatic fractures by assessing the pattern of involvement, and determining the therapeutic response to metastases.

2.1.6. Treatment of prostate cancer:

The most common treatment for prostate cancer is *surgery,* which can remove the cancerous prostate from the body. Surgery is generally recommended for men with early stage or low-grade cancers but is sometimes used at advanced stages to relieve symptoms. The most common surgical procedure is *radical prostatectomy,* the removal of the entire prostate gland.

Radiation therapy can be used to treat men with small tumors confined to the prostate, as well as to relieve symptoms in advanced tumors. In one type of radiation therapy, *brachytherapy,* a surgeon implants radioactive pellets inside the prostate. Over time, the pellets radiate the prostate and surrounding tissue, killing the cancer cells. Another kind of radiation therapy is *external beam radiation* in which high-energy beams pinpoint and kill cancer cells. Radiation therapy generally creates fewer side effects than surgery; for this reason, it is often the preferred treatment for older men.

Physicians use *hormonal therapy* to reduce the amount of testosterone, which prostate cancers need to grow. Hormone therapy cannot cure cancer but can delay its growth and provide relief.

If the cancer has spread (usually to bones) and is no longer responsive to hormonal therapy, *chemotherapy* can be considered. This treatment delivers drugs throughout the body, slows the cancer's progression, and reduces pain.

2.2.1. Incidence and Mortality

The American Cancer Society predictions placed prostate cancer as the most common cancer in American men, with 234,460 new cases expected in 2012

This is nearly 3 times higher than the number of new cases that occurred in 1985. Mortality from prostate cancer increased by 20% between 1978 and

1994 and showed stabilization and then a downward trend since2000.5,6 An estimated 27,350 deaths due to prostate cancer are expected in 2010. Many studies have shown the increased incidence of prostate cancer.7,8 Suggestions for possible causes include a longer life expectancy, increased disease prevalence resulting from environmental carcinogens and the availability of novel diagnostic modalities. Furthermore the advancement in the disease detection using PSA testing and systematic biopsy procedures may also partially explain this increase.

The reasons for the decrease in prostate cancer mortality are not clear. The relationship between the decrease in mortality and the increase in early detection

has not been proven, but the impact of early detection is highly suggested by the decreasing rate of advanced prostate cancer at diagnosis.9,10 While increasing mortality trends are observed in some countries like Australia where PSA screening is high, mortality rates have declined in other countries like the United Kingdom where screening rates are relatively low.11,12 Nevertheless, there is now evidence that PSA screening and extended biopsy sampling of the prostate has led to a downward stage migration and a decrease in postoperative PSA failure.13,14 Decreased mortality may also be explained by other factors such as improvement of treatment of advanced disease, standardization of radical prostatectomy technique,and improvements in radiotherapy. The prostate arm of the Prostate, Lung, Colon and Ovary Cancer Screening Trial, together with the European Randomized Study of Screening for Prostate Cancer, is expected to establish whether screening has an effect on prostate cancer mortality.15,16 In this trial, 38,350 men were randomly assigned to the screening arm from November 1998 through June 2010. Diagnostic follow-up was obtained from their primary care provider. Screening was based on digital rectal examination (DRE) and serum PSA level, using a threshold

of4 ng/mL. Of the men with positive screening tests, 74.2% underwent additional diagnostic testing, and31.5% underwent prostate biopsies within 1 year. Overall, 1.4% of the men in the screening arm were diagnosed with prostate cancer, the majority of whom had clinically localized cancer. The European Randomized Study of Screening for Prostate Cancer, a large randomized, controlled trial of screening vs control, is being conducted in eight European countries (Belgium, Finland, France, Italy, The Netherlands, Spain, Sweden, and Switzerland). Definitive endpoint-related data from these two studies are expected between 2010 and2014 depending on the differences in prostate cancer mortality that may be shown between the screening and control arms. Whether such screening will result in a reduction of prostate cancer mortality cannot be results are available for review.

2.2.2. Worldwide Epidemiology

Global cancer incidence rates show that prostate cancer has become the third most common cancer in men. Half a million new cases occur each year, representing

almost 10% of all cancers in men (Fig 1).17,18 In most industrial countries, prostate cancer incidence rates are increasing,whereas mortality rates are declining. In 2009, Baade et al19 reported significant reductions in prostate cancer mortality in the United Kingdom, Austria, Canada, Italy, France, Germany, Australia, and Spain, and downward trends in The Netherlands, Ireland, and Sweden. However, the recorded incidence of prostate cancer varies enormously around the world. Obvious reasons for these disparities are access to medical care and prostate cancer screening policies. In countries where no screening is available, information is sparse regarding the incidence and management of the disease. Moreover, because of economic and social factors, some populations have limited access to health care. In China, for example, the reported incidence rate of160

Cancer Control July 2011, Vol. 13, No. 3 prostate cancer in 1995 was 26-fold lower than in the United States.20 A retrospective analysis of 431 consecutive patients treated for prostatecancer at six Chinese institutions showed that median patient age at diagnosis was 72 years and the median PSA was 46.1 ng/mL.21 Most prostate cancer cases were symptomatic with urinary symptoms (76%) or bone pain (13%). Surgical castration was the standard treatment,and only 24 patients underwent radical prostatectomy. Among the patients treated by medical or surgical castration, nearly two thirds had experienced biological recurrence at a median follow-up of 16.8 months.21 Despite the relatively low incidence of prostate cancer in China, screening probably could help detect earlier-stage tumors and improve outcomes. Recently, the prostate cancer incidence has been reported to be increasing rapidly in China and other Asian countries.22 This evolution cannot simply be attributed to screening practices. Therefore, some authors have suggested that environmentaland/or genetic changes also may be responsible of the increasing incidence of prostate cancer. Cook et al23 analyzed the incidences of prostate cancer in Chinese, Japanese and Filipino immigrants and their descendantsin the United States. They found that prostate cancer incidences in the native immigrants were approximately half that of US-born Chinese, Japanese, and Filipino men. These findings corroborate results of similar studies by Shimizu et al24 and Tsugane et al,25 who studied prostate cancer incidence rates in Japanese men relocated to the United States or other countries. It appears that when individuals from a low-incidence region move to a high-incidence region, the disease becomes more common within their own generation. These findings highlight the significance of environmental and genetic risk factors.

2.2.3. Previous study

Prostate cancer is the most common solid cancer in males and is the second leading cause of cancer deaths in American men (Jemal*et al*. 2008.While rates today are markedly higher than rates observed three decades ago, the most recent statistics show that prostate cancer incidence rates have now stabilized which is thought to reflect changes in utilization of prostate-specific antigen (PSA) testing. In addition, benign prostatic hyperplasia (BPH) is the most common benign neoplasm, occurring in ∼50% of all men by the age of 60. Despite extensive research, the basis for these high rates of abnormal prostatic growth is not well understood. It is recognized, however, that steroids play a role in the initiation and progression of prostate cancer which is the basis for hormonal treatment strategies. Eunuchs do not develop prostatic carcinoma (Moore 1947) and regression of the cancer can be initially achieved by castration and androgen blockade (Huggins & Hodges 1941). In addition to androgens, estrogen involvement in the etiology of BPH and prostatic cancer has been postulated and the use of anti-estrogens has been recently recognized to have a therapeutic role in prostate cancer management (Prins&Korach 2010, Raghow*et al*. 2012, Steiner & Pound 2013, Smith *et al*. 2014). Human and rodent prostates express both estrogen receptor α (ERα) and ERβ during development and into adulthood with ERα primarily found in stromal cells (Schulze & Claus 1990, Prins& Birch 1997) and ERβ in differentiated epithelium (Enmark*et al*. 1997, Prins*et al*. 1998). Furthermore, it is believed that early prostatic developmental events which are regulated by steroids may be linked to the predisposition of this structure to high rates of disease in adult men (Henderson *et al*. 1988, 1991). It is noteworthy that relative to adult estrogenic responses, the prostate gland is particularly sensitive to estrogen exposures during the critical developmental period (Prins et al. 200 9).

The established risk factors for prostate cancer are age and race with African American men possessing the highest incidence of prostate cancer worldwide, at rates twofold of those for Caucasian-American counterparts. It is also recognized that genetics (family history), diet, and environmental factors can impact prostate cancer risk. In the human population, direct connections between endocrine disruptors (EDs) and prostate cancer risk have not been established. Nonetheless, due to the hormonal basis of this disease and the evidence that dietary compounds high in isoflavones (e.g., red clover, genistein) can control prostate cancer growth in humans (Jarred *et al*. 2005, Lakshman*et al*. 2011) and animal models (McCormick *et al*. 2009), there is reasonable cause to evaluate and understand any potential relationship between environmental EDs and prostate cancer risk. In addition to epidemiologic studies, there are *in vitro* studies with human prostate cells and *in vivo* studies in animal models that indicate associations between EDs and prostate cancer, carcinogenesis, and/or susceptibility. Due to difficulties in directly associating prostate cancer risk in humans with ED exposures, potential risk(s) will have to include research with animal models, particularly those that that are responsive to environmentally relevant exposures.

One consequence of the steep rise of the incidence age is that increase reported numbers of cases will arise in the absence of any other temporal trend in populationwith increasing proportion of older people. To monitor corresponding trends in age –adjusted mortality rate; the literature has two Striking example: mortality rate almost constant across the Noric countries but incidence in Iceland exceeding that in Denmark by factor of all most three(Trtli et al , 1999). In the incidence rate in US whites were 2.2-2.4times those in UK for 1968-1987 then raised by 80% between 1983-1987 and 1988-1992 so that the ratio rose to 3.4. Yet mortility rates were

similar between the two countries and by time (Shibata, 1998) There has been study rise in incidence rates in most Western countries and an Explosive rise in US at time when PSA testing become wide spread. More recently There has been decline in incidence rates in the US so that rates are below those predicted by previous study trend. This, too unlikely to indicate underlying changes in risk since advancing diagnosis by screening will deplete the reservoir of new cases(Brawley et al, 2000).

In US from mid-1980 there was an initial sharp rise in mortality rates, this was followed by decrease in prostate cancer mortality rates. Age-adjusted prostate cancerMortality rates have risen quite consistently in most countries from the 1950 until the1980 (Tominaga et al, 1997) however they are now falling or stable in many countries with wide spread PSA testing e.g. USA, Canada (Skarsgard et al, 2005) and withoutUK and Australia (Oliver 2006).

Several authors have interpreted recent descriptive data on prostate cancer mortality As evidence that PSA screening is effective in causing its reduction.relivent evidence Includes geographical from Australia in which the fall in prostate Cancer mortality was much more substantial in the Tyrol, where screening was bothFree and encouraged and a policy of aggressive therapy was in place, compared with the rest of Austria. There is major variation in incidence rates between countries and ethnic groups, which are believed to indicate genuine difference in risk. The group with the highest record incidence rate the US black; high rates have also been observed for men in the Caribbean and those cannot be explained by disclosure bias since black are less Likely to avail themselves of screening than whites .The population with the lowest recorded incidence and mortality rates are Orientals such as Chinese and Japanese; whilst these incidence rates would be increased somewhat by more widespread application of the disclosure methodologies used in US and Western

Europe they would certainly remain the lowest rates by a substantial ratio (Bartsch et al, 2009) .

All cancer caused by combination in varying proportion of inherited factors with Exogenous exposures. The most exogenous in fluencies on cancer are probably Ionizing Radiation .smoking and diet, the evidence of ionizing radiation to prostate cancer is limited to ecological studies which have shown high correlation between average indoor household radon in regions in Europe and UK and incidence of prostate cancer to occupational cohorts of radiation workers in which standardized morbidity ratio for prostate cancer significantly exceed 100.these workers were exposed to other possible risk factors including several heavy metals .

These conclude that ionizing is not major influence on prostate cancer (Hilson et al, 1999). Epidemiomology data are consistent in their conclusions that smoking does not increase risk of incidence.Dietaryfactors appear as important but Poorly understood influences on prostate cancer (Lumeyet al, 1997).

Most of the suspected exogenous influence on its etiology are potentially interpretable as exposure to hormones (or their chemical equivalents) or influence On hormonal milieu. There is dearth of firm information regarding risk factors As cause of, even definitively, associated with prostate cancer. They only established Risk factors are age ethnic origin country of residence and family history of prostate Cancer (Mettlin C, 1999), this phenomenon, has the potential to artefactualy increase in the influence of family history of prostate cancer relatives of men with the disease Are more likely to be offered ,or seek, screening.There is very strong evidence of familial aggregation of the disease which is due to high pentrant gene(Eeles RA et al,1999).which have mendelian inheritance under an autosomal dominant model and Are associated with early onset of disease and risk of up to 89% in carriers by age 85.

Many environmental and life styles factors have been considered in literature in relation to risk of prostate cancer these include:

(i) Influence on prostate gland activity and proliferation.

(ii) Environmental estrogens and other agrichichemicals

(iii) Diet

(iv) Physicalactivities.(Emard et al,2001)(Nilsen et al,2000).

Abnormal versus normal PSA levels

Since PSA is enzyme found in men without disease .one difficulty using this marker comes in defining the normal range for PSA. An increased leakage of PSA into the circulation appears what causes most PSA elevations in prostatic disease. The PSA level in prostatic fluid is approximately one million-fold higher than that found in serum. An epithelial layer, basal layer, and abasement membrane separate in intraductal PSA form capillary and lymphatic drainage of the prostate .When disease such as prostitis or cancer interferes with this natural barrier; it is believed the leakage of PSA into the serum increases, causing and elevated PSA (Brawer et al, 1989). While prostate carcinoma is undoubtedly the most significant cause of raised of PSA level, it is not the only one, other conditions can increase PSA level in the serum include trauma and inflamition.Another lesion associated with an increase in PSA level is pre-malignant in human prostate known as prostatic intra epithelial neoplasia (PIN)(Brawer et al,1989).prostitis,prostatic massage and prostate needle biopsy has also identified as potentially resulting in increased elevations on serum PSA(Dalton,1989;Neal et al,1992,Amitage et al,1988).No effect on serum of PSA of standard digital rectal examination(Yuan et al,1992;Brawer et al,1988). Stamey et al

Reported serum PSA increased 1.5 to 2 times following prostate message, leading to conclusion that serum for PSA should be drown before prostatic message. Yuan et al

Similar elevation in serum PSA values in 100 men following prostate needle biopsy.

Recent data by Tchetgen et al has suggested an acute elevation in serum PSA levels Following ejaculation.

PSA distribution for men without disease was determined by using the Tandem- R assay suggested a reference range (mean+2s.d.)of less than 4.0ng/ml.in men over 40 years who are without disease, chan et al describe a reference range(mean**+3 s.d**) as being up to 2.8 ng/ml .for the men up to age 40 years, the reference range was up to 2.0ng/ml . further elevated men over 40 years and found the reference range(mean+2s.d)to be less than 4.0ng/ml. for normal males under age 40years ,all tested had PSA value under 4.0ng/ml (Ercole et al).

Prostate cancer are relatively grow slowly and will not become manifest during a man`s lifetime. Cancer present with symptoms from local obstruction ,from local invasion of surrounding organs and from metastatic disease .the detection could be by PSA testing, digital rectal examination (DRE) and trans-rectal ultrasound(TRUS) and as incidental finding after transurethral prostatectomy(TURP) for presumed benign disease (wolffJM,Eur Urol1998).

PSA elevation is the most predictive single test for the presence of prostate cancer (Catalona et al,1994).in addition it improves the diagnostic accuracy of DRE and and, unlike , both DRE and TRUS is not reliant upon the expertise of the examiner (Catalona et al ,1994; Ellis,1994; Cooner et al 1990; Hammer,1994).the chances of malignancy depending on abnormal DRE and or an elevated of PSA are 15% when DRE abnormal / and PSA<4.o ng/ml,56% when DRE abnormal /and PSA>4ng/ml,6% when

DRE normal / PSA <4.0 ng/ml,and 23% when DRE normal /PSA>4.0ng/ml.

Brawer et al demonstrated the value of PSA as predictor of prostate cancer .patients who were found to have a PSA of 4.0 ng/ml or greater were further evaluated with a digital rectal examination, transrectal ultra sonography and six systematic transrectal prostate needle biopsies. Prostate cancer detected in 27% of group whose PSA values were between 4.1 and 10.0ng/ml.for those PSA over 10.0ng/ml,50% were found to have carcinoma of prostate.PSA alone is not a good predictor of high risk of prostate cancer in patients. However, study conducted by Dameco et al ,2004,suggested that the rate of increase in PSA level in year before diagnosis may be important predictor of outcome in that study in 1095 men with localized prostate cancer ,patients with PSA velocity of >2ng/ml/year had significantly shorter time to death from prostate cancer(p=0.001) and death from any cause(p=0.01)compared with those patients who had PSA velocity of <2 ng/ml/year (Dameco,et al,2004).This study performed by Janane,AHajji and agree with me ,there was relationshipBetween bone metastasis and increase of PSA level. this study show that, the Patients were 46---85 with a mean age of 68 years. PSA levels ranged from 2- 998 ng/ml with a mean value of 86.63 ng/ml. The time interval between PSA determination and bone scan was within 27 days Bone metastases were identified in 102 out of 348 patients. The patients were stratified into 4 groups according to their PSA level: the first group of patients had a PSA level ranging from 0 to 10 ng/ml (n = 75), the second group had a PSA level ranging from 11 to 20 ng/ml (n = 63), the third group had a PSA ranging from 21 to 100 ng/ml (n = 159), and the fourth group was those having a serum PSA level higher than 100 ng/ml (n = 51). The prevalence of osseous metastases proven by bone scintigrams increased progressively with PSA level, rising from 0% (0 out of 75) for PSA level<11 ng/ml, to

100% (51 out of 51) for PSA level >100 ng/ml ($P < 0.001$). Bone scintigraphy results with respect to PSA levels are summarized in Table 1.

This study done by Miranda H.Y. Lai, F.R.C., and the study done for116 patients diagnosed to have CaP were reviewed retrospectively for bone scan results, PSA levels, and Gleason score. Thirty-four patients were proven to have bone metastases based on positive bone scintigraphy result. None of these patients had a PSA level of less than 10 ng/ml. Two patients had PSA level between 11 and 20, and 15 patients had PSA level between 21 and 200. For patients with PSA level over 201, 17 had bone metastases on bone scintigraphy.

Based on the PSA level, the likelihood of positive bone scintigraphy result can be postulated. According to PSA levels, staging investigations can be more selective for patients with confirmed CaP. The risk of having positive bone scan is so low that it is not required for patients with PSA level less than 10 ng/ml. On the other hand, on studying the correlation between Gleason score and PSA level or bone scan results, no statistically significant relationship was established.

Chapter Three

Methodology

3.1Materials and method

3.1.1Materials

Blood sample

3-5ml of venous blood sample was taken from each patient. Centrifugations were done for samples,and serum were obtained and used for PSA estimation.

Reagents:

The reagent used in this study include kits for PSA and Technetium 99m (^{99m}Tc),Methylene Diphosphate (MDP),Hydroxy Methylene Diphosphate (HMDP) for bone scan. This reagent include (anti-PSA coated beads,standards with different concentrations,I^{125}Anti PSA tracer,0.5 M phosphate buffer, 3m Nacl,10% triton x-100,Stock protein solution,Sodium Azide and Qualitycontrols).

3.2.1. Methods

Equipment Required:

- Manual pipette
- Repeating pipette
- Rotator and Vortex
- Gamma counterI^{125}.

Determination of serum total prostate specific Antigen

This was done by ImmunoRadiometric Assay(IRMA).

Principle of IRMA:

IRMA is one of immunoassay that are most widely used. They depend on the use of selected specific antibodies as reagents. IRMA was developed by

haberman,(1968)(Richwood&Hames,1996).IRMA uses two antibodies to two different epitopes on the same antigen(Ag),out of which antibody is presented asolid phase(Ab)1,and other labeled antibody is presented as tracer reagent $(Ab)^{*}2$. All antigen in sampleor standard react with the solid phaseantibody during incubation time ,after that un reacted antigen is removed by decanting the solution following washing with buffer ,then add radioiodinated I^{125}monoclonal antibody $(Ab)^{*}2$, after incubation ,unreacted label is removed by decanting the solution following washing ,at end of the solid phase is containing Ab1-Ag-$Ab^{*}2$ complex so it count for radioactivity ,which directly proportional to concentration of analyet, then standard curve can be drawn and sample concentration can be read from it.

Determination of bone scans

Bone scan was assessed by bone scintigraphy

Bone scintigraphy has formed and still does form the main method of staging for metastatic disease in prostate cancer.it is far superior to skeletal survey which it has replaced to all intents and purpose(Lentle et al,1974).the development of Tc^{99m}-labeled phosphate complexes for bone imaging was introduced by Subramanian in1971.Tc^{99m} has excellent physical properties for nuclear medicine imaging because of its ideal characteristics for use with the unger scintillation camera.the short half life of Tc^{99m} allows several millicuries (mCi) of activity to be injected; image with high information density can obtained.

The accumulation of radionuclides in bone is related to both vascularity and rate of bone production,the accumulation of labrled phosphate compounds is probably related to the exchange of phosphorus groups into calcium of hydroxyl apatite.

- Reagent required:
- Methylene Diphosphate (MDP).
- Hydroxy Methylene Diphosphate(HMDP).

- Equipments:
- Gamma camera(SPECT or Planar).
- Generator Mo^{99}/ Tc^{99m}(melopdenium99/ Technetium99m)

Dose calibrator

3.2.2. Area of Study

This study carried out at the department of Nuclear medicine and oncology at National Cancer Institute (NCI),where Radioimmunoassay (RIA) tests performed, the National Cancer Institute ,university of Gazira,Sudan which all patients in this study referred to it for diagnosis, treatment and follow up.

3.2.3. Study population

This study include 50 Sudanese patients with prostate cancer ,their ages between 42-93 years, all of them were diagnosed at urology Department in Wad madani teaching hospital and National Cancer Institute in period from February 2020 to March 2021.

Inclusion criteria

All patients diagnosed with prostate cancer and referred to NCI.

Exclusion criteria

Patient without histological evidence of prostate cancer.

The project ethically approved from the ethical committee of the National Cancer Institute

Study design:

Cross-sectional, patients based study.

3.2.4 Statistical Analysis:

Data introduced in an excel sheet and analyzed by Statistical Package for Social Science(SPSS) computer program .

3.2.5. EthicaIssue:

Permission of Nuclear Medicine Department has been granted

Chapter Four

Results

Table 4-1 a frequency table show the distribution of age groups

Age groups	Frequency	Percent
45-49	1	2.0
60-64	4	8.0
65-69	12	24.0
70-74	13	26.0
75-79	9	18.0
80-84	5	10.0
85-89	4	8.0
90-94	2	4.0
Total	50	100.0

Table 4.2 a frequency distribution table show the frequencies of metastasis.

Metastases	Frequency	Percent
Positive	27	54.0
Negative	23	46.0
Total	50	100.0

Table4.3 a frequency distribution table of the occupation in study object

Occupation	Frequency	Percent
Farmer	28	56.0
Police	2	4.0
Driver	6	12.0
Teacher	1	2.0
Others	13	26.0
Total	50	100.0

Table4.4 a frequency distribution table of prostate cancer in regions

Region	Frequency	Percent
Gezira	37	74
Gadaref	07	14
Darfur	02	04
Sennar	04	08

Table 4.5: show relation between PSA level before treatment and metastasis

Metastasis	N	Mean	Std. Deviation	Std. Error Mean
Positive	27	138.04	100.168	19.277
Negative	23	57.43	80.359	16.756

Independent Samples Test

	Levene's Test for Equality of Variances		t-test for Equality of Means						
								95% Confidence Interval of the Difference	
	F	Sig.	t	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
pasb	1.826	.183	3.100	48	.003	80.602	25.998	28.330	132.875
			3.156	47.849	.003	80.602	25.542	29.243	131.962

Table 4.6: show relation between PSA level after treatment and metastasis

Metastasis	N	Mean	Std. Deviation	Std. Error Mean
Positive	27	37.44	54.055	10.403
Negative	23	8.30	10.381	2.165

Independent Samples Test

		Levine's Test for Equality of Variances		t-test for Equality of Means						
									95% Confidence Interval of the Difference	
		F	Sig.	t	Df	Sig. (2-tailed)	Mean Difference	Std. Error Difference	Lower	Upper
Pasb	Equal variances assumed	12.783	.001	2.542	48	.014	29.140	11.463	6.091	52.189
	Equal variances not assumed			2.742	28.238	.010	29.140	10.626	7.383	50.898

Table 4.7: Show relation between PSA level and TYPES of treatment

Treatment	N	Mean	Std. Deviation	Std. Error Mean	Sig (2-tailed)
Medication	39	100.97	94.556	15.141	.999
Radiation	11	100.91	119.949	36.166	
Medication	39	27.92	46.922	7.514	0.054
Radiation	11	10.27	15.969	4.815	

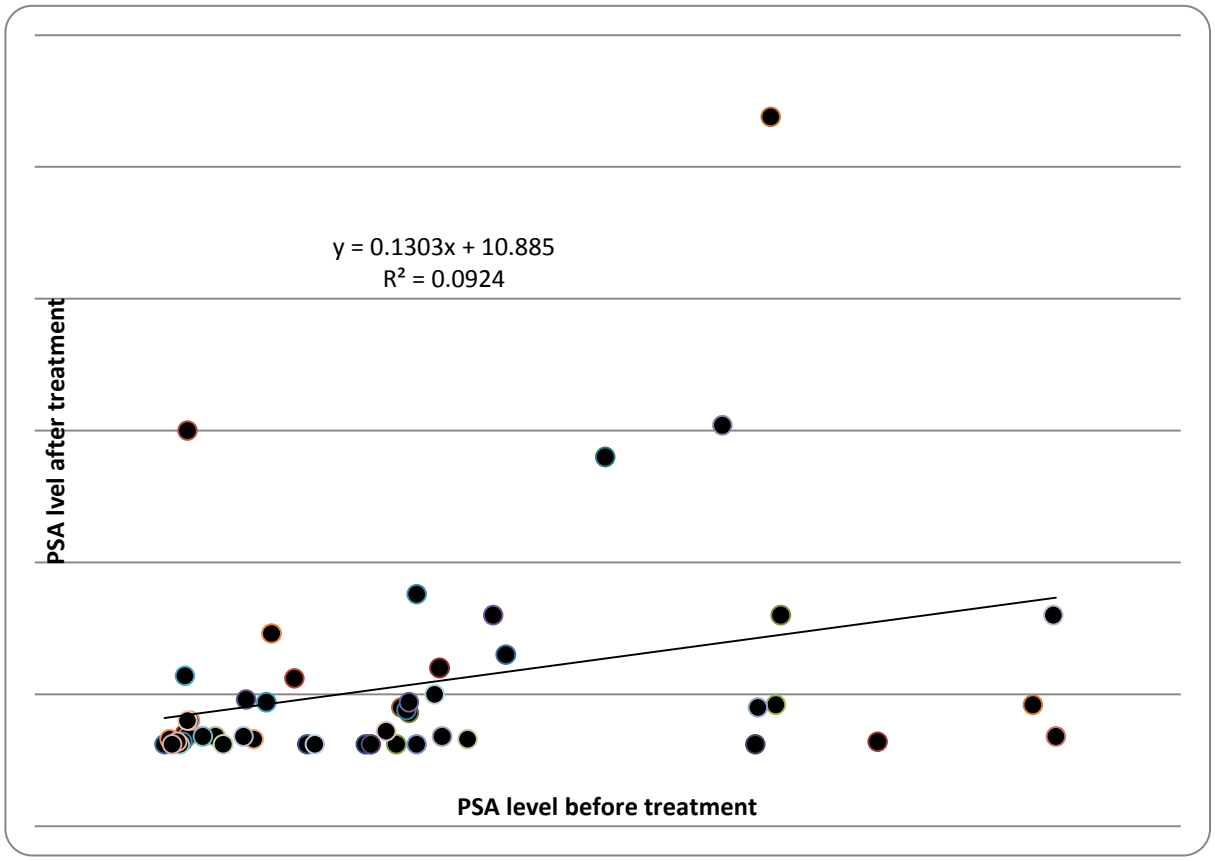

Figure 4.1 scatter plot of PSA level before treatment and after treatment with a trend line depict the relationship

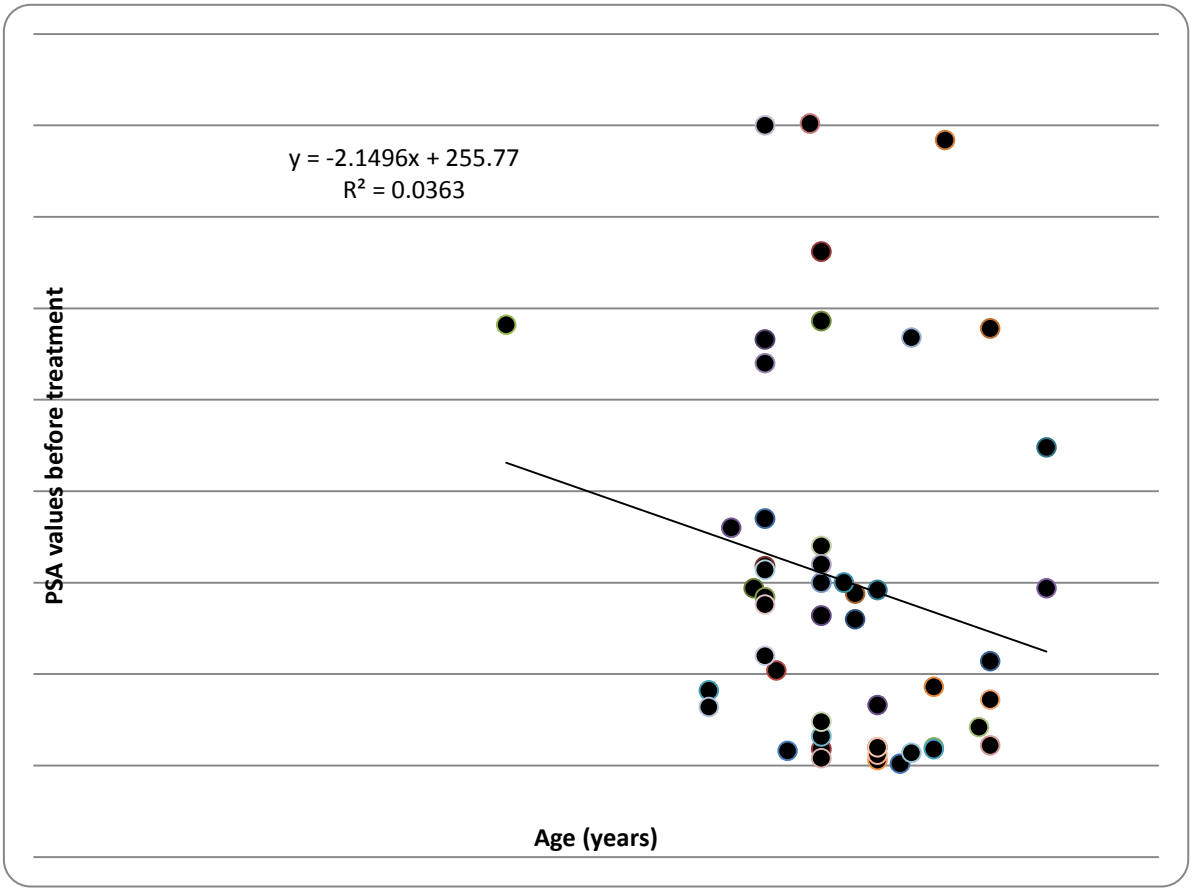

Figure 4.2 scatter plot of PSA level before treatment versus age with a trend line show the linear relationship

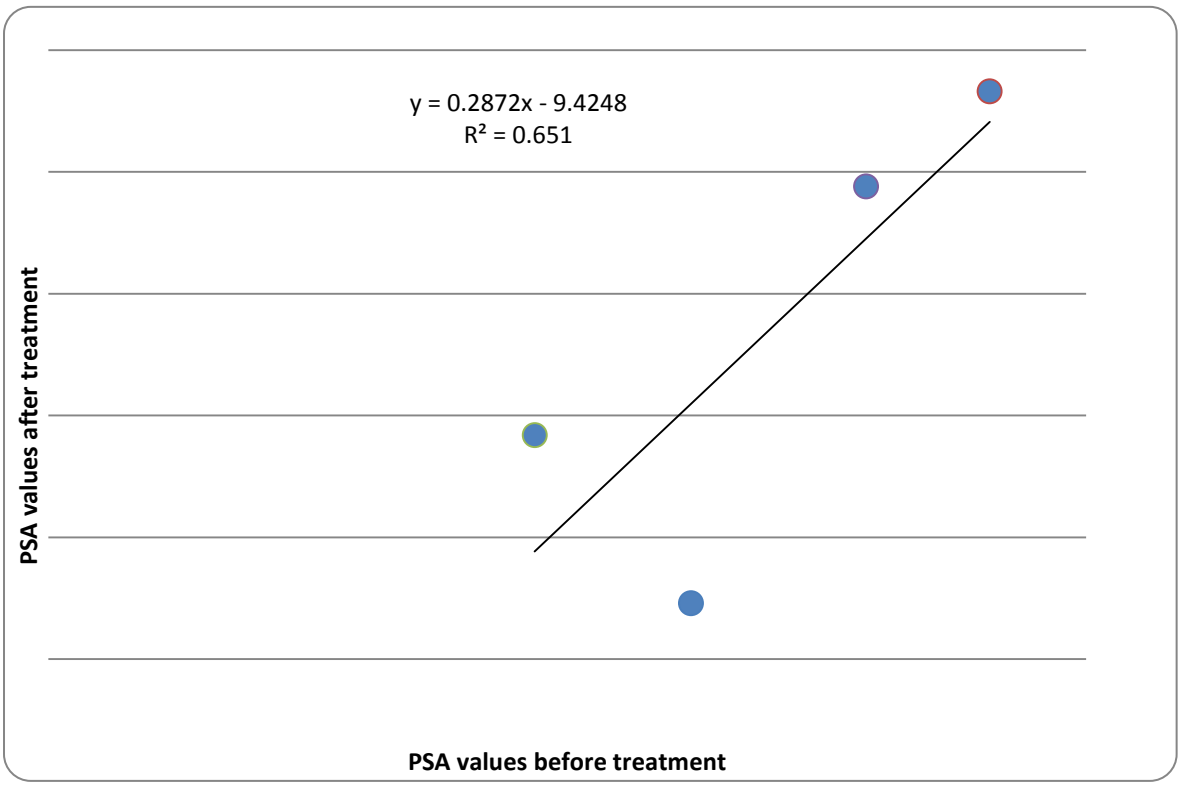

Figure 4.3 scatter plot of PSA level after treatment versus age a trend line show the linear relationship

Table4.8. cross tabulation table show the relationship between age group and average of PSA before and after treatment

PSA level	**Age Group (years)**			
	42-54	55-67	68-80	81-93
PSA Before	86.7	127	65.6	110.3
PSA After	7.3	28.3	14.2	24.4

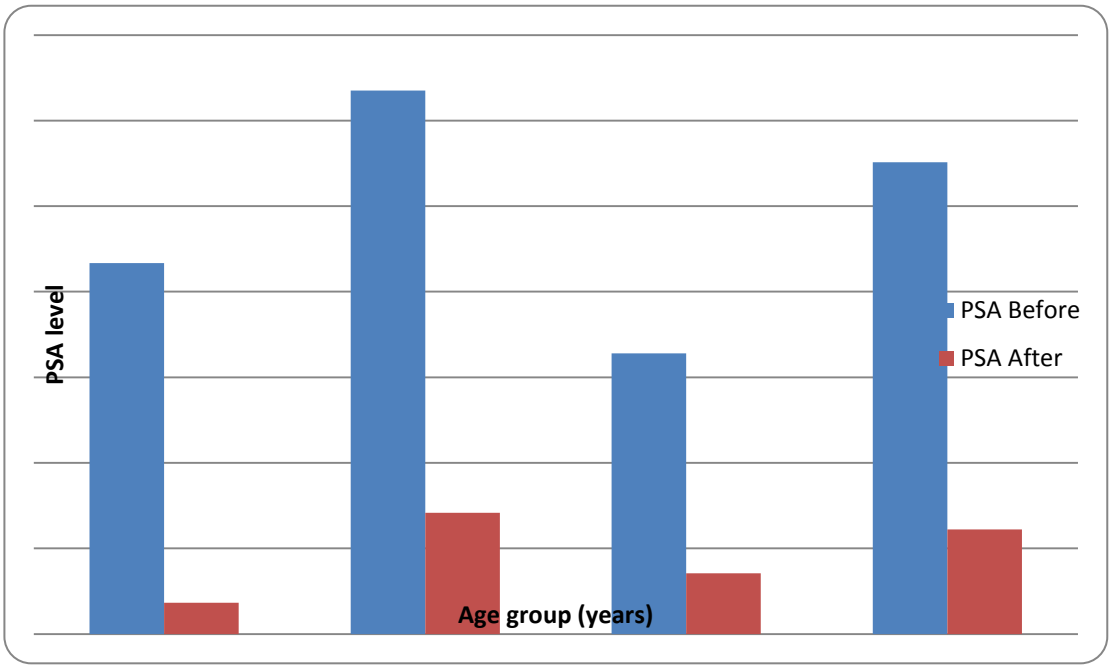

Figure 4.4 scatter plot of the average PSA before treatment versus average PSA after treatment

Table 4.9: Show the distribution of metastasis at regions of body

Metastasis	Frequency	Percent
Skull	6	23.1
Shoulder	4	15.4
thoracic spine	4	15.4
Lumbar spine	6	23.1
Pelvis	4	15.4
Others	2	7.7
Total	26	100.0

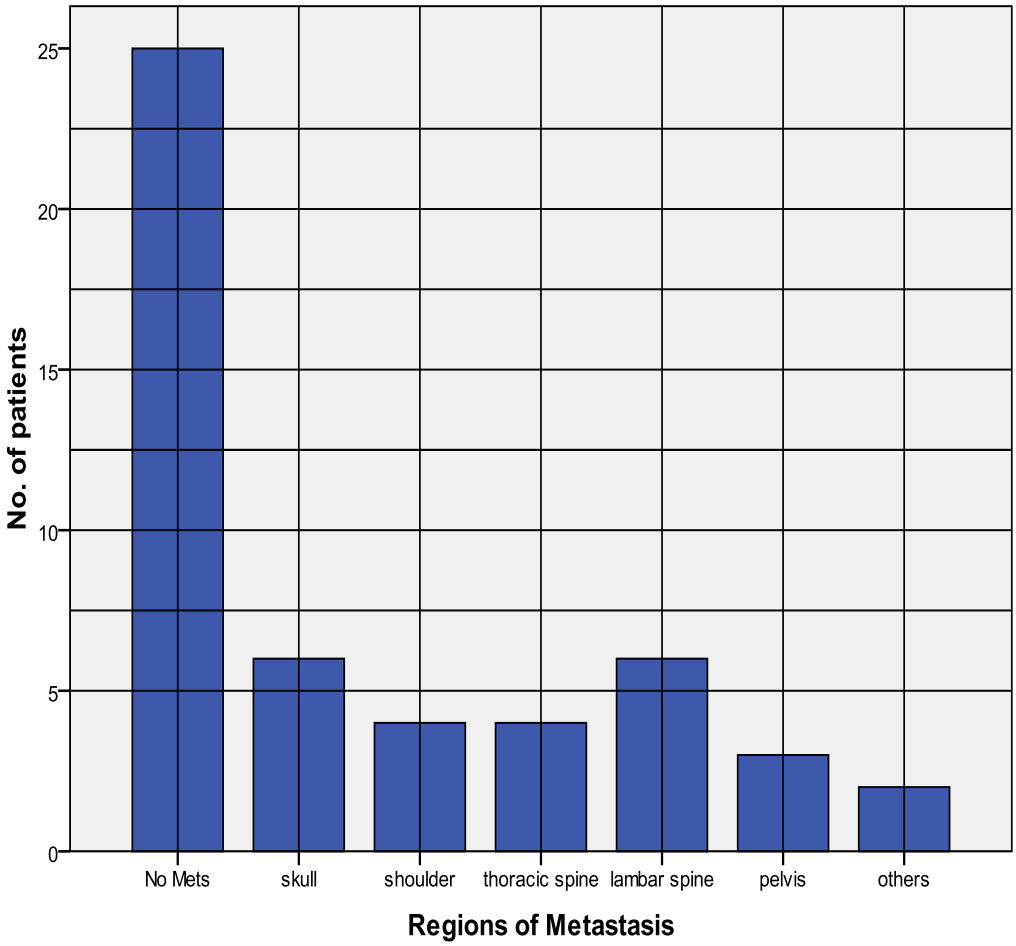

Figure 4.5 region of metastasis

Chapter Five

5.1 Discussion

Prostate cancer more commonly affects old men .biochemical investigations for screening and follow –up of prostate cancer included serum PSA and Bone Scan is used to assess metastasis of disease in bone. This study included 50 prostate cancer patients their age ranges between 42-93 years (the medium of age is 68 years).In this study there were 27 patients has bone metastasis (table1.1). According to the occupation, the farmers presented 56% of prostate cancer patients in this study (table1.2), and there was no correlation between occupation and metastasis (p=.492)(table3.3) , also most affected was present in al Gazera state which presented 74%. (table1.3)

According to t-test, the relation between PSA level before treatment and metastasis,the test was Found that there was different in mean between two group ,positive and negative group.the positive Group the mean was 138±100.2 ,t=3.2 and p-value =0.003 . and this presented asignificant correlation Between PSA level before treatment and metastasis.group negative their mean was 57.4±80.4 show Table 1. Also relation between PSA level after treatment and metastasis the result show there was different in mean between tow groups ,at positive group the mean was 37.4±54.1, t=2.4 p-value 0.013 And the mean at negative group was 8.3±10.4, and this show the significant correlation between PSA After treatment and metastasis.show table 2.Table 3. Show relation between two types of treatment Medication and radiation and it found that there was no significant different in two types p- value=0.054 .Figure 4.1,present the relation between PSA level before treatment and PSA level after treatment,it was found that the PSA level after treatmentdecreased by

y=0.13, and there was a significant correlation p-value =0.003 show table. figure 4.2 presents relation between PSA level before treatment and age ,it was found that by increasing of age the PSA level was decrease . Figure 4.3 show relation between PSA level after treatment and age,it was found that by increasing of age PSA level was dcreasd.

In this study there was correlation between PSA level before and after treatment with metastasis (p=003),(p=014)show (table 3.1) and (table3.2). and most region affected with bone Metastasis was the skull show (table4.2).

5.2 Conclusion:

- Most of prostate carcinoma patients were found in ages from 50-80 years in the study subjects.
- There was no correlation between occupation and bone metastasis in the study
- There was no relationship between age groups, locality and prostate specific antigen among the study group.
- There is significant relationship between PSA levels and bone scan results in the in study subject

5.3 Recommendations:

- Screening tests must be done to detect prostate cancer in Sudanese population above 40years old.
- Bone scan cannot be done unless PSA level more than50ng\ml.
- Further study with large sample size recommended for confirmation the relationship between PSA level and bone scan.
- Further study recommended screen patients from different areas in Sudan with same sample size to confirm the results of PSA level and locality.

References

- ArmitageTC,cooperEH,Newling WW et al.the value of the measurement of serum PSA in patient
- With BPH and un treated prostate cancer. Brit J Urol,1988;62:584 - 589.
- Bartech G,WolfgangH,etal.prostate cancer mortlity after introduction of proststae specific antigen
- Mass screening in the fedral state of Tyrol,A sutria.Uorology,2001; 58:471 – 421.
- BostwickDG,Dundor PA.(1997) Biopsy interpretation of the prostate.
- Brawley OW. Prostate carcinoma incidence and patient Mortility.AmercancerSoc 1997;1857.
- Brawley MK PSA ,SchifmanRB,Ahman FR et al.The effect of DRE on serum level of PSA.Arch Path lab
- Med ,1988;112(11):1110 -1112.
- Brawley MK,Relles MA ,Nagle RB et al.Serum PSA and prostate pathology in men having simple
- prostactomy.AmJClin path.1989;92(6):760-764.
- Brawley MK ,Chetner MP ,BeatieJ.Screening for prostate carcinoma with PSA .JUrol 1992;147:841- 845.
- BurtisC.A,Ashwood ER,AND Border BG.Tietz Fundamental of clincical chemistry.5 edition .(2001).W.B.
- Saunder Company; 391 -392,396,398,399.
- Catalona W J ,Smith DS ,Ratiff TL ,et al. Measurement of PSA in serum as a screening test for prostate
- Cancer Sem ,1991;324:1156 -1161.

- Catalona W J ,Richie JP,Ahmnn FR et al.comparison of DRE and serum PSA in early detection of prostate
- Cancer:Rwsults of amuti center trial of 6630 men .J Urol 1994;151:1283- 1290.
- Cooner WH Mosley BR Rutherford CL et al.Prostate cancer detection in a clinical uorogical practice by
- Ultrasonography,DREand PSA. J Urol 1990;143:1146-1154.
- Chybowski FM ,Larson Keller JJ.predecting radionuclide bone scan findings in patient with early
- diagnosed prostate cancer :PSA is superior to all other clinical parameters.JUrol(1991);145:313-318.
- Dalton DL .Elevated serum PSA due to acute bacterial prostatitis.Urology,1989;33:456.
- D AmicoAV,ChenMH,Roehl kA, CatalonaWJ.Preoperative PSA velocity and the risk of death from
- Prostate cancer.NEngl J Med2004;351:125-35.
- Eeles RA ,et al.Familial prostate cancer :the evidence and CRC British prostate group (CRC\BPG) UK
- Familial prostate cancer study .Br Urol 1997;791:8-14.
- Ellis and Calne .Lecture Note in general sergury .6 edition (1982).Black well,345,347,353- 366.
- Elis WJ,ChetnerMP,person SD, Brawer MK et al.Diagnosis of prostate carcinoma:Theyied of PSA ,DRE
- and TRUS .J Urol 1994;52:1520 – 1525.
- EmardJF.DrouinG.ThouezJP.Ghadirianp.Vasectomy and prostate cancer in Qubec.Canda.Health and
- Place 2001;7:131- 137.

- Epstien JI .partin AW ,SauvageotJ.WalshPC.Prediction of progression following prostatectomy .A
- multivariate analysis of 721 men with long –term follow-up. Am J SurgPathol 1996;20:280-92.
- FerlayJ,Autier P, BoniolM,HeanueM,BoyleP.Estimates of cancer incidence and Mortility in Eroup
- In 2006 .Ann O ncol 2007;18:581-92.
- FrizerHL.HumpheryPA,Buurchette JL. Immunoreactive prostate specific antigen in male priuretheral
- gland L Urol.(1992);147;246.
- Graves HCB,SenaubaughGF,and Black RT.Postcoital detection male specific semen protein.Aplication to
- investigation of rape. Engel JMed (1985);312:338.
- Hammerer p and HulandH.Systematic sextant biopsy in 651 patients referred for prostate evalution
- Urol 1994;151:99 – 102.
- Hilson. A. Prostate cancer and radionuclides BRMed J 1994;308:1994.
- HoedmaekerRF,VisAN,Van Der Kwast TH. Staging prostate cancer.Microse Res Tech 2000; 51:423 -9.
- Hudson MA,Bahnson RB ,Catalona .Clinical use of PSA in patients with prostate cancer . J Urol
- 1989;142;1011 – 1017.
- Kumar P, clark M. clinical medicine 6th edition (2007) Bailliere Trindall;522,486.
- Lumey LH, Pittman B ,Zang EA, WynderEL.Cigarettesomking and prostate cancer .prostate 1997;33:195 -200.

- Lentle BC ,McGowan DG,DierichH.Technetium -99^{m}polyphosphate bone scaning in carcinoma of
- Prostate .Br J Urol 1974 ;46:543 – 548.
- Lilja H.A kallikrein- like serine prostate in prostatic fluid is the predominant seminal vesicle protein
- J Clin invest (1985);76:1899 -1903.
- Mettlin C .Recent developments the epidemiology of prostate cancer .Eur J cancer 1997;33:340,347.
- Neal DE,ClejanS,Sarma D, Moon TD.PSA and prostatitis 1.prostate ,1992;20(2):105 -111.
- Nilsen TIL, Johnson R, Vatten L J. Socico- economic and life style factors associated with risk prostate
- cancer.British Journal of cancer2000;82:1358 – 1363.
- Oliver SE,MayMT,GunnellD.International trends in prostate cancer mortility in PSA .International Journal of cancer 2001 ;92:893 -898.
- Papsiderol LD ,kuriyamaM,WangM,etal.prostate marker for human prostate epithelial cell. J Nat／
- Cancer Inst ,(1981);66;37 – 42.
- Ries L A, MelbertD,Krapcho M et al eds SEER Cancer Statistics Review,1975 – 2004,National cancer
- Institute,Bethesda ,MD,USA, based on November 2006.
- Shibata A,MaJ,white more AS .prostate cancer and mortility in united States and united kingdom .J Natl
- cancer Inst 1998;90:1230 – 1231.
- SkarsgardD,TonitaJ,prostate cancer in Saskatchewan Canda,before and during the PSA era. Cancer
- causes and control 2000;11:79 – 88.
- Snell MD,Richard S .Clinical Anatomy .8th edition.2007.

- StameyTA,KabalinJN,Ferrari M. PSA in the diagnosis and treatment of adenocarcinoma of 111.Radiation
- treated patient Urol (1989);141:1083 – 7.
- Steven A, low JP Pathology .(1995).Mosby,585.
- Tanagho E,A, McaminchJ.W.Smiths. General Urology (1995).Asimon&Schuster company;392 – 424.
- TchetgenMB.Song J T,Strawderman Metal. Ejaculation increase the serum PSA concentration ,Urology,
- Terli S , England A, Haldorsen T, et al .prostate cancer – look to Denmark Natl cancer Inst 1996;88:128.
- Tewari A, Jobson C,Divine G et al ,long – term survival probability in men with clinically localized
- Prostate cancer case control ,propensity modeling study .J Urol2004;171:1513 – 9.
- Tominaga S ,Kurdish T .Aoki K. Cancer mortility Statistic in 33 countries;1953 - 1992;1998:UICC,Japan.
- Wang MC, Valenzuela LA , Chu TM. Purification of human PSA .InvetUrol (1979);17:17:159 – 163.
- Yong CY. F,Andrews PE .Montagomery,BT.Tissue specific and hormonal regulation of human prostate
- Glandular kallikrein biochemistry,(1992);31:818 – 824.