

# CHAPTER ONE

## **1.1 : Introduction:**

Prostate cancer is a form of cancer that develops in the prostate 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

Medication formation and research center, annual report it is the first male cancer in Sudan majority of patient present with bone metastasis.

### **1.3 Objectives**

The **main Objective** of this study to find out the relationship between PSA level and Bone metastasis in prostate cancer patients.

#### *Specific objectives*

- To estimate the PSA level in patients with prostate cancer.
- To determine the relation between PSA level and bone metastasis.
- To find the relationship between the age and PSA level.
- To find the common site of metastasis.
- To find if their relationship between residence and prostate cancer.

### **1.4 Significance of the study**

This study will provide information about the relation of PSA level in respect to metastasis and the most common side of metastases in bone scan result.

### **1.5 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

## Theoretical background and literature reviews

### 2.1: Anatomy o 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.

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 per urethral glands are embedded in the longitudinal smooth muscle of the proximal urethra (prostatic portion of the urethra). The elevator any 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 uricle.

#### 2-1-1: 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.

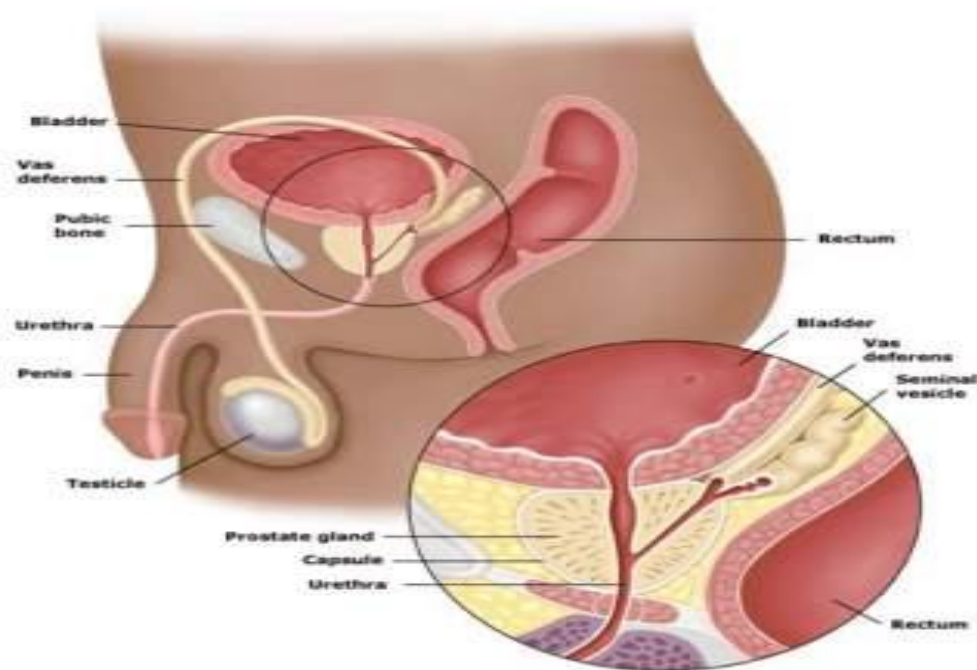
**Inferiorly:** The apex of the prostate lies on the upper surface of the urogenital diaphragm. The urethra leaves the prostate just above the apex on the anterior surface.

**Interiorly:** The prostate is related to the symphysis pubis, separated from it by the extra peritoneal fat in the retro pubic space (cave Retzius). The prostate is connected to the posterior aspect of the pubic bone by the facial pub prostatic ligament.

**Posterior:** 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 elevator an as they run posterior from the pubis.



**Male reproductive system (fig 2.1)**

### **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 interiorly. 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 verumontanum.

*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 vesicle and middle rectal arteries, branches of internal iliac artery.

#### **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 facial sheath, drains into internal iliac veins, but it communicate with vesicle venous plexus and the vertebral venous plexuses

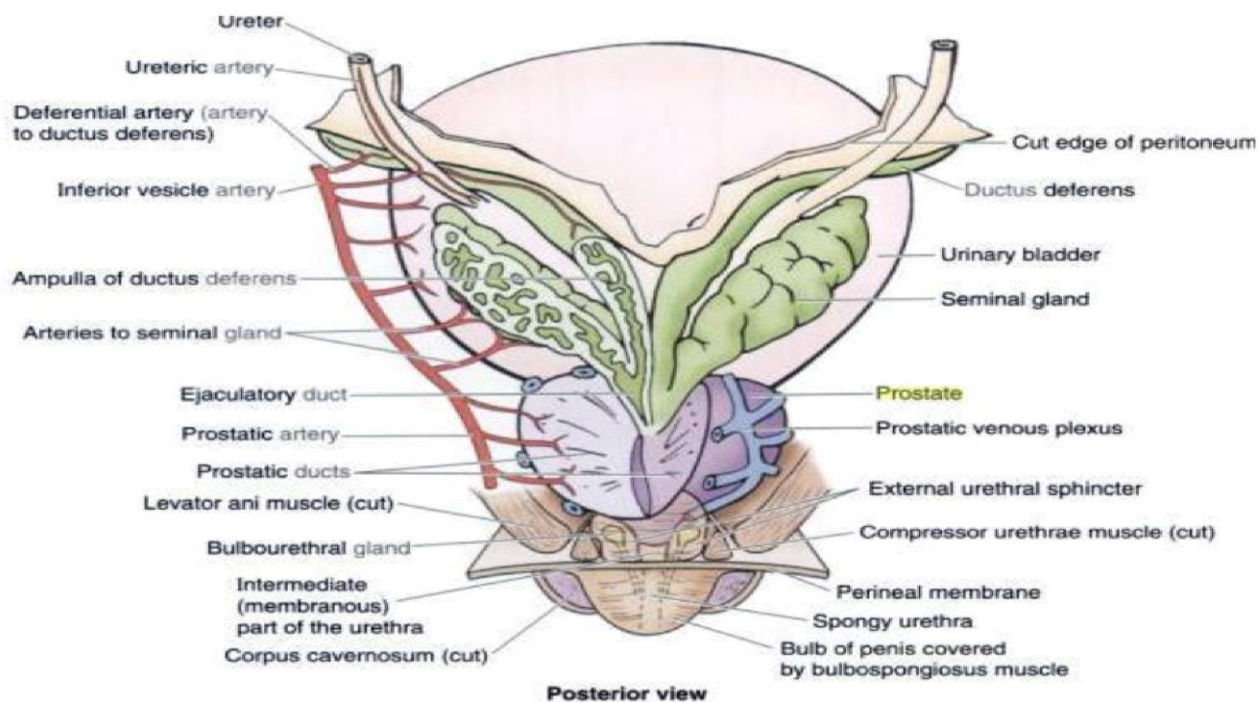
#### **Lymphatic Drainage of the Prostate:**

Parasympathetic fibers arise from the pelvis splanchnic nerves. The

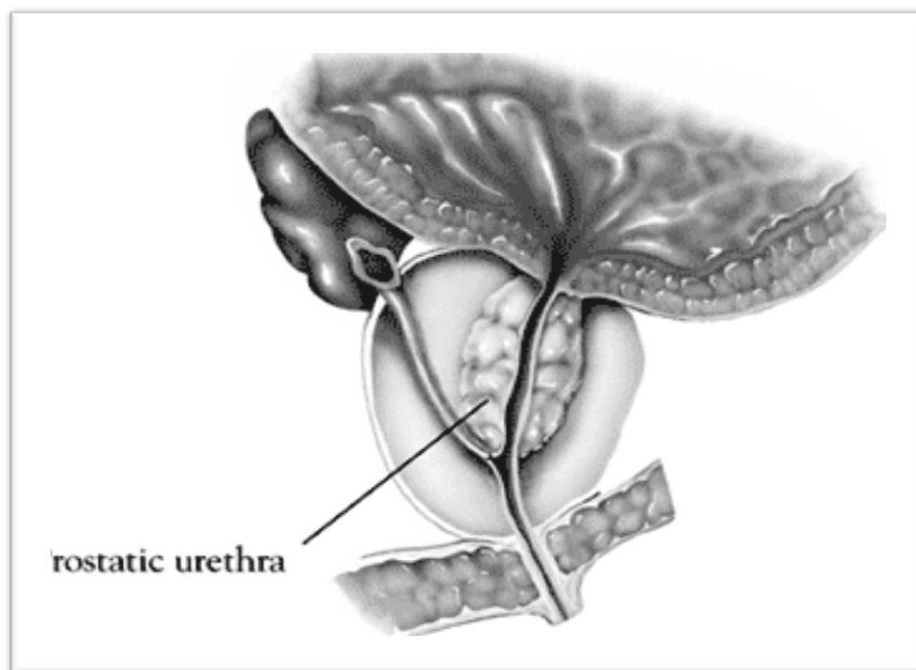
sympathetic fibers are derived from the inferior hypo gastric plexuses

#### **2.1.1d: 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- 2) shows: Arterial supply, venous drainage, and Lymphatic drainage of the prostate.**



**Figure (2- 3) 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 secrete 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 Struma 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 Struma. A marked degree of stromal edema and periodical 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 suppurative prostatitis**

Acute prostatitis usually results from spread of infection along the prostatic ducts secondary to urthritis 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 tuberculosis 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 Struma. 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 ischemic, 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.

### **2.1.2c: 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 arises in the inner transitional and zones of the prostate, while most carcinoma (70% to 80%) arises 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 or in men with genetic diseases that block androgen activity. Dihydrotestosterone (DHT), an androgen derived from testosterone through the action of  $5\alpha$ -reductase, and metabolite,  $3\alpha$ -androstane- $20\alpha$ -diol, seems to be major hormonal stimuli for stromal and glandular proliferation in men with nodular hyperplasia. DHT binds to nuclear androgen receptors and, in turn, stimulates synthesis of DNA, RNA, growth factors, and other cytoplasm proteins, leading to hyperplasia. This form the basis for the current use of  $5\alpha$ -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 parenchyma cells, thereby functioning in the pathogenesis of nodular hyperplasia.

#### **2.1.2d: 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 remains 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 diethylstilbestrol. 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 figures more importantly in the growth of established lesions than 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 over expression 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.

### **2.1.3: Bone scintigraphy:**

<sup>99m</sup>Tc bone scintigraphy is an effective method for screening the whole body for bone metastases.<sup>[51, 52]</sup> <sup>99m</sup>Tc diphosphonates, most commonly <sup>99m</sup>Tc methylene diphosphonate (MDP), is the most frequently used isotope. <sup>99m</sup>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 scanning 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.

#### **2.1.4: 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 becomes 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 the lymphatic and capillaries. Cause of elevated PSA includes 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 extra capsular and much less likely to be curable. Elevation of the PSA is a better indicator of clinically significant tumor with extra capsular spread than is provided by DRE. Elevated level of PSA is 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.

### **2.1.5. 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 2006.<sup>4</sup> This is nearly 3 times higher than the number of new cases that occurred in 1985. Mortality from prostate cancer increased by 20% between 1976 and 1994 and showed stabilization and then a downward trend since 2000. An estimated 27,350 deaths due to prostate cancer are expected in 2006. Many studies have shown the increased incidence of prostate cancer. 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.<sup>9,10</sup> 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.<sup>11,12</sup> 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.<sup>13,14</sup> 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.<sup>15,16</sup> In this trial, 38,350 men were randomly assigned to the screening arm from November 1993 through June 2001. 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 of 4 ng/mL. Of the men with positive screening tests, 74.2% underwent additional diagnostic testing; and 31.5% 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 2006 and 2010 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. In most industrial countries prostate cancer incidence rates are increasing, whereas mortality rates are declining. In 2004, Baade et al 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 of prostate cancer in 1991 was 26-fold lower than in the United States.<sup>20</sup> A retrospective analysis of 431 consecutive patients treated for prostate cancer at six Chinese institutions showed that median patient age at diagnosis was 72 years and the median PSA was 46.1 ng/mL. 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. 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. This evolution cannot simply be attributed to screening practices. Therefore, some authors have suggested

that environmental and/or genetic changes also may be responsible of the increasing incidence of prostate cancer. Cook et al analyzed the incidences of prostate cancer in Chinese, Japanese and Filipino immigrants and their descendants in 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 al and Tsugane et al, 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 studies:**

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 2008, Raghoebar *et al.* 2002, Steiner & Pound 2003, Smith *et al.* 2008). Human and rodent prostates express both estrogen receptor  $\alpha$

(ER $\alpha$ ) and ER $\beta$  during development and into adulthood with ER $\alpha$  primarily found in stromal cells (Schulze & Claus 1990, Prins & Birch 1997) and ER $\beta$  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.* 2007). 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.* 2002, Lakshman *et al.* 2008) and animal models (McCormick *et al.* 2007), 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 are responsive to environmentally relevant exposures.

One consequence of the steep rise of the incidence rate is that increase reported numbers of cases will arise in the absence of any other temporal trend in population with increasing proportion of older people. To monitor corresponding trends in age-adjusted mortality rate; the literature has two striking examples: mortality rate almost constant across the Nordic countries but incidence in Iceland exceeding that in Denmark by factor of all most

three (Trtli et al, 1996). In the incidence rate in US whites were 2.2-2.4 times 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 mortality 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, 1997). 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 cancer Mortality rates have risen quite consistently in most countries from the 1950 until the 1980 (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, 2000) and without and Australia (Oliver 2001). Several authors have interpreted recent descriptive data on prostate cancer mortality as evidence that PSA screening is effective in causing its reduction. Relient evidence Includes geographical from Australia in which the fall in prostate Cancer mortality was much more substantial in the Tyrol, where screening was both Free 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, 2001) .

All cancer caused by combination in varying proportion of inherited factors with exogenous exposures . The most exogenous influences 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, 1994). Epidemiology data are consistent in their conclusions that smoking does not increase risk of incidence. Dietary factors 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, 1997), this phenomenon, has the potential to artefactually 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 penetrant gene(Eeles RA et al,1997).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) Physical activities.(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 prostatitis 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 aReported 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 alSimilar elevation in serum PSA values in 100 men following

prostate needle biopsy, Recent data by Tchetchgen et al has suggested an acute elevation in serum PSA levels following ejaculations 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 40 years ,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( wolff JM, Eur Urol 1998).

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 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 <4.0 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 relationship Between bone metastasis and increase of PSA level. The 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 establish

# **CAPTER THREE**

## **MAERIALS AND METHODS**

### **3.1: materials:**

#### **3.1.1: Study population:**

This study include 50 Sudanese patients with prostate cancer ,their ages between60 -90 years, all of them were come to Alnelien Diagnostic Center for bone scan scintigraphy in period from January 2017to April 2017.

#### **3.1.2:Study area:**

This study carried out at the department of Nuclear medicine and in ALnelien Medical Diagnostic center Khartoum, Sudan which all patients in this study referred to it for diagnosis and follow up.

#### **3.1.3: Study period:**

From January 2017to April 2017.

#### **3.1.4. Inclusion criteria**

All patients diagnosed with prostate cancer and referred to Alnelein Diagnostic Center

#### **3.1.5. Exclusion criteria**

Patient without histological evidence of prostate cancer.

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

#### **3.1.6. Study design**

Experimental study.

#### **3.1.7.Ethical Issue:**

Permission of nuclear medicine Department has been granted.

- **3.1.8:Equipments:**

- **3.1.8.1:Tc99m generator:**

A technetium-99m generator, or colloquially a **technetium cow** or **moly cow**, is a device used to extract the metastable isotope  $^{99m}\text{Tc}$  of technetium from a source of decaying molybdenum-99.  $^{99}\text{Mo}$  has a half-life of 66 hours<sup>[1]</sup> and can be easily transported over long distances to hospitals where its decay product technetium-99m (with a half-life of only 6 hours, inconvenient for transport) is extracted and used for a variety of nuclear medicine diagnostic procedures, where its short half-life is very useful..

- **3.1.8.2:Dosecalibrator:**

an ionization chamber used in nuclear medicine to measure the amount of radioactivity of a radionuclide before injection into a patient.

- **Gamma camera (spect):**

also called a **scintillation camera** or **Anger camera**, is a device used to image gamma radiation emitting radioisotopes, a technique known as scintigraphy. The applications of scintigraphy include early drug development and nuclear medical imaging to view and analyse images of the human body or the distribution of medically injected, inhaled, or ingested radionuclide emitting gamma rays.

- **Reagent (mdp)for bone scan:**

The methylene di phosphonate is reagent used for bone scan scintigraphy it is powder form mixed with Tc99m and injected after 20min .

- **5ml injections**

## **3.2 Methods:**

### **3.2.1 method of data collection:**

From data patient records and files.

### **3.2.2: Method of data Analysis**

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

### **3.2.3: technique 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<sup>99m</sup>-labeled phosphate complexes for bone imaging was introduced by Subramanian in1971.Tc<sup>99m</sup> 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<sup>99m</sup> 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.

We inject the patient 20mci of mdp/Tc99m, waiting for (2-3) hours before screening

# CHAPTER FOUR

## RESULTS

(Table 4.1) shows the relationship between PSA level and bone metastases

PSA level (ng/ml)	frequency	Bone scan findings(mets)
15-35	6	Solitary
36-56	12	Multiple
57-77	1	Wide spread
78-100	2	Wide spread
>100	3	Super scan

(Table 4-2) : shows age groups of the study sample:

Age groups	Frequency	Percent
60-65	6	12
66-70	4	8
71-75	6	12
76-80	10	20
81-85	16	32
86-90	8	16
Total	50	100

**(Table 4-3): shows the frequency of metastases**

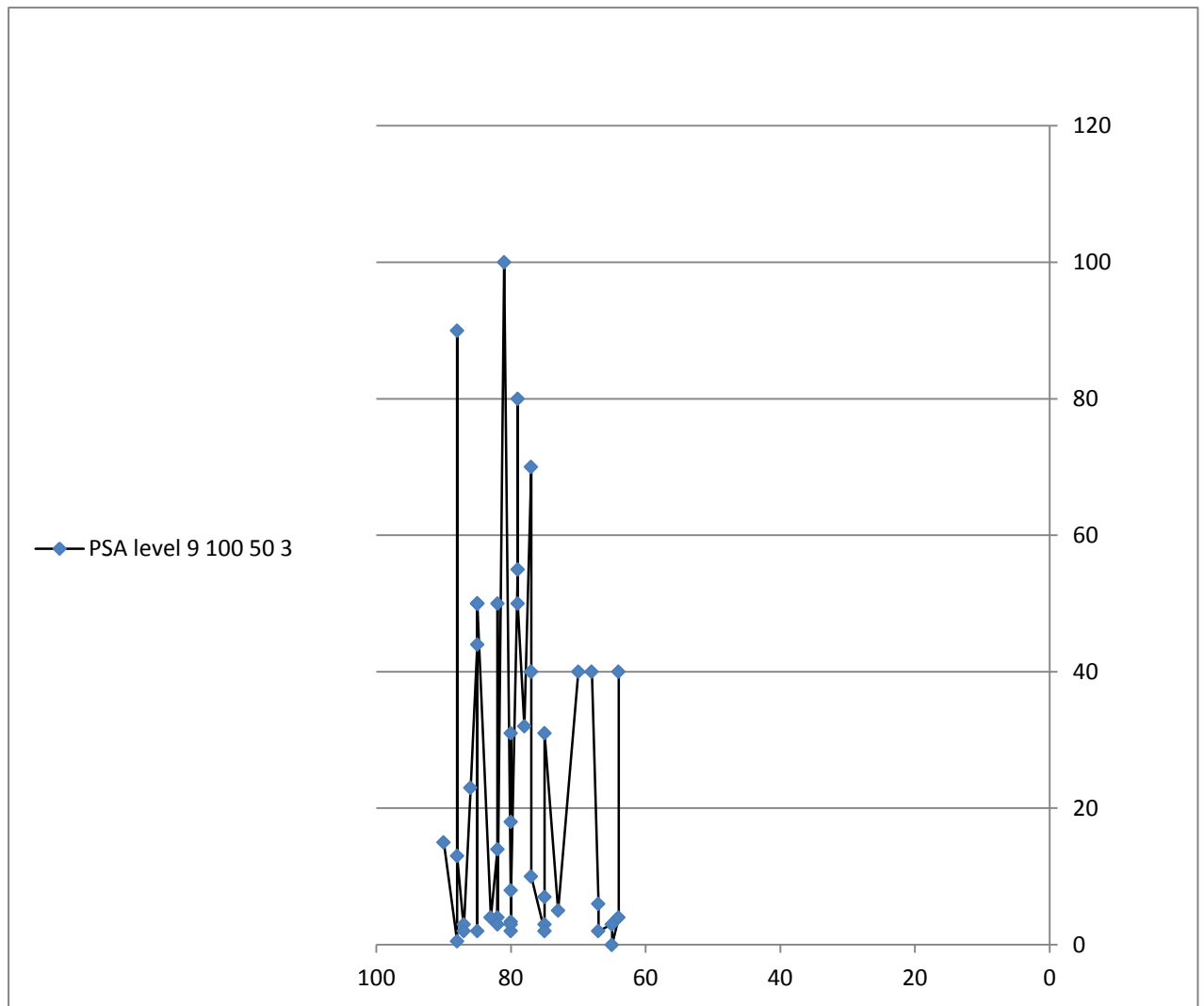
<b>Metastases</b>	<b>Feruecy</b>	<b>Percent</b>
Positive	24	48%
Negative	26	52%
Total	50	100%

**(Table 4-4) shows geographical distribution of prostate cancer for the study sample:**

<b>Geo .Region</b>	<b>Feruency</b>	<b>Percent%</b>
<b>Alkhrطوم</b>	14	28
<b>Algazira</b>	13	26
<b>North Sudan</b>	9	18
<b>North kordofan</b>	4	8
<b>West kordufan</b>	2	4
<b>South Sudan</b>	2	4
<b>White Nile</b>	3	6
<b>Ethiobia</b>	1	2
<b>Nahr Alneel</b>	2	4

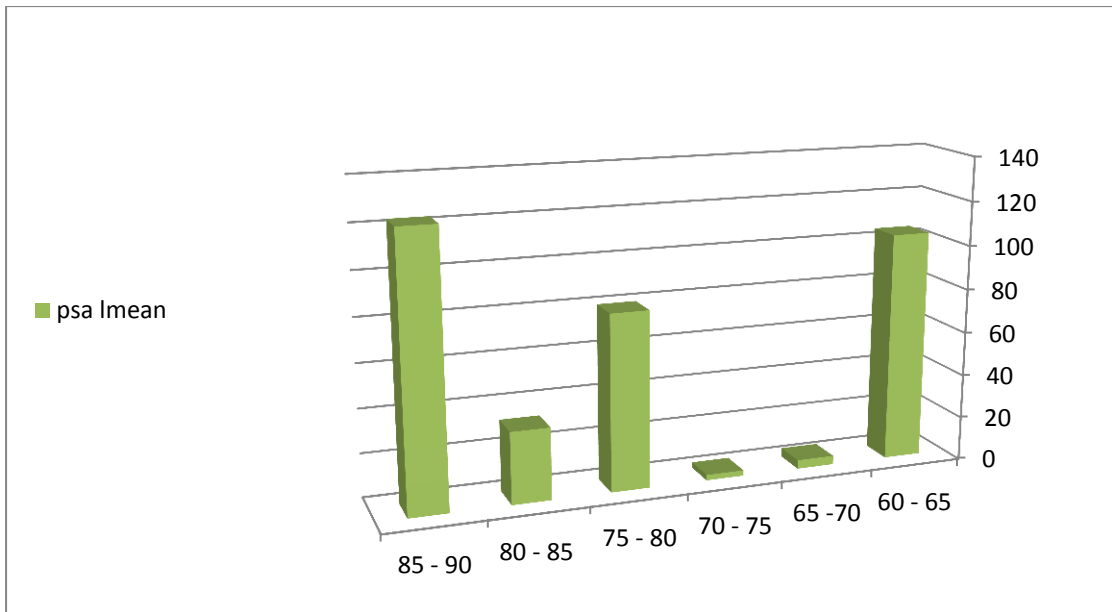
**(Table:4.5) shows the regions of metasises:**

Ribs	1	2%
Skull	1	2%
Shoulder	4	9%
Thoracic spine	4	9%
Lumber spine	3	6%
Pelvis	7	15%
Other	3	2%

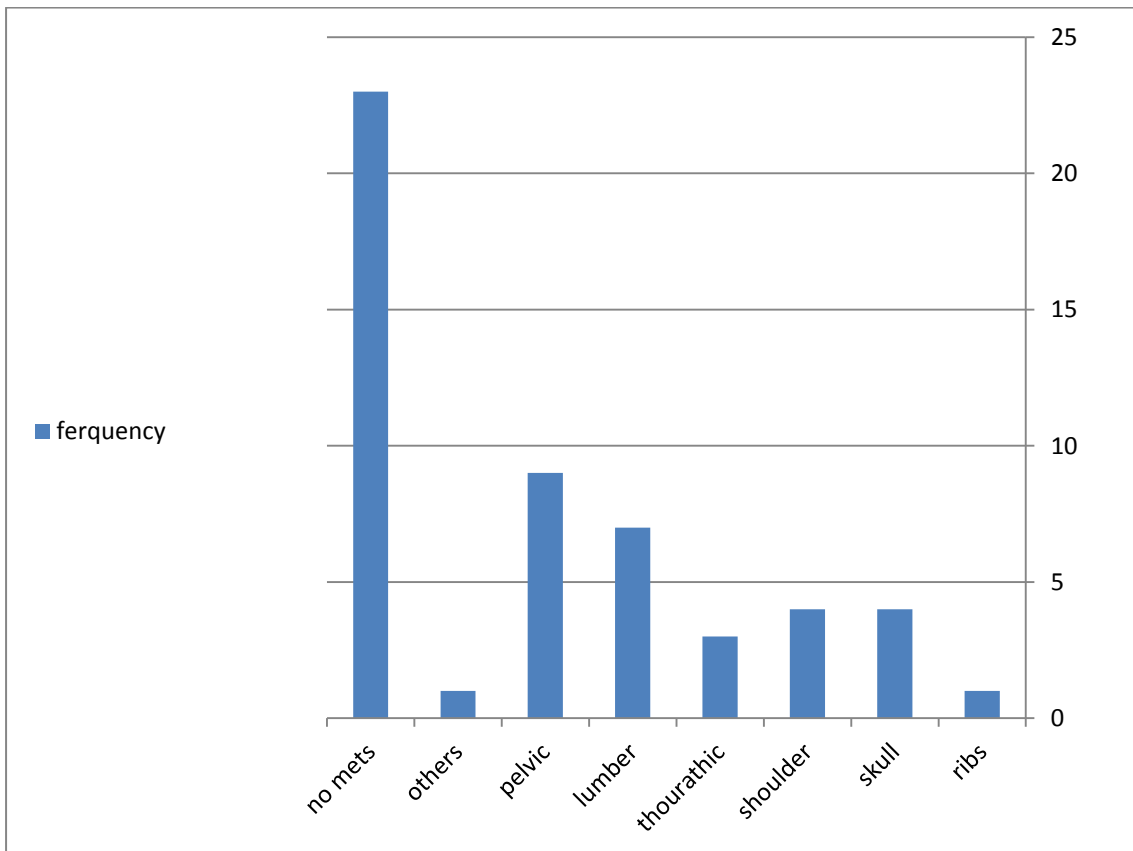


**(Figure 4.1) shows the relation between PSA level in ng/ml and age**

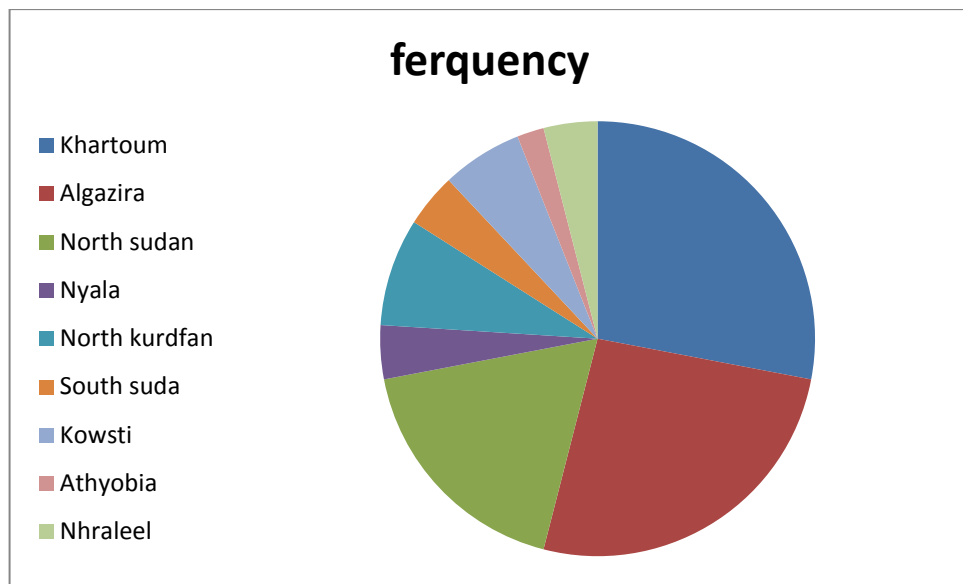




(Figure 4.2) shows the relation between PSA mean and age groups



(Figure 4.3) shows distribution of regional metastases, and patients with no mets



**(Figure 4.4) shows the geographical distribution of prostate cancer for the study sample**

# CHAPTER FIVE

## DISCUSSION, CONCLUSION AND RECOMMENDATIONS

### 5.1 Discussion

The study consist of 50 patients, their ages between 60-90. The study showed that 24 patients (48%) have bone metastases, PSA level range from 15ng/ml -100ng/ml . According to the study ,the risk of prostate cancer above 60 years is 50% and it reached 89% by the age 85 years.

The mean of PSA for the study sample was 30.3ng/ml, whereas the mean of PSA level for patients who had bone metastases was 46.1ng/ml.

There was relationship between the PSA level and bone metastases in the study, the patient with PSA 15g/ml have solitary or limited metastases and with increased PSA level the patients showed multiple metastases (table 4-1).

All patients with PSA level over 100ng/ml have bone metasises.

Patients with PSA level less that 15 ng/ml have normal bone scan.

In this study there was no relationship between PSA level and age (table4.2)

In this study there was no relationship between PSA level and geographical region (table 4.4).

The recherché found that the most common site of metasises is the pelvic bones, but in the previous study the most common site of metastases was the skull(table 4.5)

The most cases which showed metastases were from Khartoum . (figure4.7).

## **Conclusion:**

This study included 50 prostate cancer patients their age ranges between 60-90 years were diagnosed with prostate cancer and send to Alnelen Diagnostic Center for bone scan, the data concerned the PSA level, bone scan result age of patients and the geographical rgiions. Excel sheet and (SPSS) program was used to analysis the date.

From the result the rechercher found that there was relationship between PSA level and bone metastases, the study contain 24 patient with bone metastases the PSA level of the patients ranged from 15-100ng/ml. Although the PSA level increases the bone metastases side increase in bone scan result. In this study all the patients with PSA less than 15 ng/ml had normal bone scan, and all patients with PSA level more than 100ng/ml had bone metastases.

There was no relationship between the age and PSA level. There was no relationship between geographic region and PSA level in this study.

The most common site of metastases in this study was pelvic bone.

Most prostate cancer patients were found in Khartoum state with 28% of population.

## **Recommendations:**

- The researcher recommend that Bone scan must be done if the PSA level was more than 15 ng/ml.
- Further study with large sample size is recommended for confirmation of the relationship between PSA Level and bone metastases.
- Any male over 60years should have routine test for PSA levels.
- Further study is recommended for screening patients from different regions of Sudan with same sample size to confirm the result of PSA level and locality.
- Khartoum city have the major population in this study, so additional researches are advisable.
- The researcher advice is to conductor more studies to find the relationship between prostate cancer and the family history for this type of cancer .
- The researcher recommended that more studies should be done to find the relation between diet, life style and prostate cancer.

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