Chapter one

1.1 Introduction

The ca breast is commonly affecting female with a percentage rate equal to 34.5% in Sudan (Samira and Magda.2006) and scarcely among males 0.1%. However, some women are susceptible to breast cancer than others in a condition of the followings: relative involvement with breast cancer, historical relation with breast cancer or benign tumor disease, early menstrual period or younger, late menopause, infertility, radiation exposure at chest wall, administration of estrogen in high doses after menopause and obesity (Lehman et al, 2007). Some studies suggested that the more alcohol intake the greater the risk of breast cancer (Saslow et al, 2007).

The most common symptom of breast cancer is a painless lump in the breast. The lump is often difficult to feel. Most women find the lump themselves during a breast self-exam. Sometimes the skin over the lump may be dimpled or wrinkled. There may be a discharge from the nipple or the nipple may be pulled inward.

After the cancer spreads, it can form new tumors in other parts of the body. These tumors are called metastases. The secondary tumors commonly originated in the bones of the pelvis, spine, legs, ribs, and skull (Clines et al 2008). The metastases may also be found in the lungs, liver, and brain.

Also the cancer secondaries might develop in part of the brain leading to headaches and nausea. The headaches are often at the back of the head. They are often worsened by coughing and sneezing. Sometimes the first sign of a spread of the cancer to the brain may be a seizure. Secondary cancer may affect an area of the brain which controls a certain part of the body. This can occasionally cause an arm or a leg to become weaker than usual, or there may be a feeling of numbness. Sometimes, secondary cancer in the brain may cause a change in personality (Chang et al, 2003).

The spread signs appear as palpable lymph adenopathy at axilla or in the neck, but can affect lymph nodes in other parts of the body, such as internal mammary chain (IMC) behind the sternum. The symptoms of metastases depend on the area of the body in which they are found. Bone metastases are usually accompanied by pain in

that area and fractures from minimal trauma, loss of function or sensation in limbs, spinal cord compression and hypercalcaemia (Mundy et al, 1984).

An enlarged liver found during a physical exam may indicate liver metastases and may feel generally unwell and tired, with a loss of energy, weight and lack of appetite. It may feel uncomfortable in the area of the liver. Lung metastases may be found if a cough or shortness of breath develops. If cancer cells settled on the outside of the lungs, they irritate the pleural membrane, leading to a formation of fluid which in turn presses on the lungs (Solomayer et al, 2000).

NM technology could detect the cancer during the stage of carcinoma, one of the studies carried out at NM section to reveal and assess the metastatic cases of breast cancer is bone scintigraphy. (Sharp et al, 1998)

The effort to diagnose and to evaluate breast cancer metastasis has been carried out by a set of modalities. In this realm CT can visualize the pathological evidence depending on the CT number (the number that characterize the radiation absorption at a given point of an object and are referred to as the attenuation value or CT density which measured in Hounsfield unit HU,while MRI depends on proton resonance accumulation within the tumor bulk detection of cancer metastasis has been well established, as NM technology could detect the cancer during the stage of carcinoma in-situ (Sharp et al, 1998). One of the studies carried out at NM section to reveal and assess the metastatic cases of breast cancer is bone scintigraphy. (Hans et al, 1989).

The use of bone scintigraphy dated back to the early days in the 1950s and early 1960s. The development of the $^{99}Mo/^{99m}Tc$ generator in 1958 at Brookhaven Laboratories by Tucker and Greene, and further refined with the collaboration of Powell Richards, opened the door to bone imaging. (Hans et al, 1989).

The wide spread use of ^{99m}Tc as the radionuclide of choice for variety of nuclear medicine imaging procedures has been based mainly on its physical properties like short half life of (6 Hrs), 140 KeV photon energy and ready available than the other generators like ^{68}Ge- ^{68}Ga generator. The later system has the advantage that the parent has along half life but the physical characteristic of gallium are not well

matched to modern imaging system except those specially designed for usage with positrons (Fred et al, 2006).

A bone scan is a nuclear scanning test that identifies new areas of bone growth or breakdown. It can be done to evaluate damage to the bones, find metastasized cases to the bones, and monitor conditions that can affect the bones (including infection and trauma). The bone scan can often detect the pathological problem in days to months earlier than a regular X-ray test (Galasko et al, 1972).

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The indications of bone scintigraphy are to find bone cancer or determine whether a cancer from another area, such as the breast, lung, kidney, thyroid gland, or prostate gland, has spread (metastasized) to the bone, help diagnose the cause or location of unexplained bone pain, such as ongoing low back pain , help diagnose broken bones, such as a hip fracture or a stress fracture, not clearly seen on X-ray, find damage to the bones caused by infection or other conditions, such as Paget's disease, Detection and follow up of metastatic disease, and to differentiate between osteomyelitis and cellulitis. (Galasko et al, 1972).

The researchers have an intension to characterize findings for the patients whom known case of Ca Brest being treated by radiation and referral to nuclear medicine department in Khartoum state for bone scintigraphy.

1.2 Problem statement:

Despite the growing burden of cancer worldwide, it continues to receive low priority in Africa, across the continent and specifically in Sudan, the real scope of cancer in Sudan is not known, the reported cases have increased from 303 in 1967–6303 in 2010, according to global estimates, the top most common cancers in both sexes are breast so the researcher scope in the real character of bone metastasis from female breast cancer patients by using bone Scintagraphy to describe the tumor pathological behavior in sundaes population.

1.3 General objective of the study:

The general objective of this study is to characterize bone metastasis from female breast cancer patients by using bone Scintagraphy.

1.4 Specific Objectives of the study:

- To determine the distribution and common involvement areas for secondary bone metastasis in breast cancer patients.
- To estimate the metastasis percent from both breasts.
- To identify the rick age group of Ca breast

1.5 Thesis out line:

The following research will be consists of five chapters.

- Chapter one will deal with introduction, problem of the study, objectives and thesis out line.
- Chapter two will highlights the literature review related to the current study and the theoretical view for the study.
- Chapter three will shows the methodology
- Chapter four will shows the results and discussion
- Chapter five will shows the, conclusion, and recommendation, references and appendix.

Chapter two

Literature review

2.1 Anatomy of the breast:

The female breast overlies the 2nd to the 6th rib; two-thirds of it rests on pectoralis major, one-third on serratus anterior, while its lower medial edge, the breast is made up of 15–20 lobules of glandular tissue embedded in fat; the latter accounts for its smooth contour and most of its bulk. These lobules are separated by fibrous septa running from the subcutaneous tissues to the fascia of the chest wall (the ligaments of Cooper), each lobule drains by its lactiferous duct on to the nipple, which is surrounded by the pigmented areola. This area is lubricated by the areolar glands of Montgomery; these are large, modified sebaceous glands which may form sebaceous cysts which may, in turn, become infected, the male breast is rudimentary, comprising small ducts without alveoli and supported by fibrous tissue and fat. Insignificant it may be, but it is still prone to the major diseases that affect the female organ just overlaps the upper part of the rectus sheath as shown in figure 2.1 (Harold Ellis.2006)

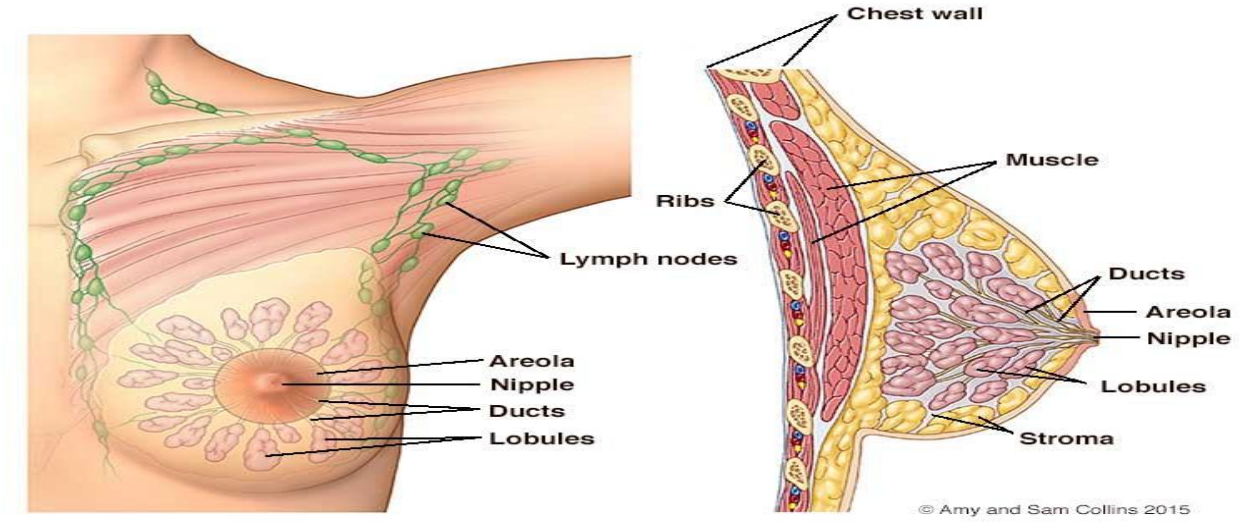

Fig 2.1 The anatomical structures of the breast (Amy etal.2015)

While in children and men they are rudimentary. In the female after puberty they enlarge and assume their hemispherical shape under the influence of the ovarian hormones. The ducts elongate, but the increased size of the gland is mainly from the deposition of the fate. In the young adult female the breast overlies the second to this sixth ribs and their costal cartilages and extend from the lateral margin of the sternum to the mid axillary line. (Maloney.2004)

The greater part of the gland lies below superficial fascia. Its upper lateral edge, (called the axillary tail) extends around the lower border of the pectoralis major and enters the axilla. In the middle aged multifarious women the breast may be large and pendulous, and they reach their maximum size during lactation. (Maloney.2004)

Each breast consist of 15-20 lobes which radiate out from the nipple, the main duct from each lobe opens separately on the summit of the nipple .The nipple is small projection and surrounded by a colored area of the skin called the areola .

The lobes of the glands are separated by fibrous septa that serve as suspensory ligaments. The breast are separated from the deep fascia which covering the underlying muscles by a retromammary space. (Maloney.2004)

2.1.2 Arterial and venous supply:

The breast is supplied from the axillary artery via its lateral thoracic and acromiothoracic branches, and from the internal thoracic (internal mammary) artery via its perforating branches; these pierce the first to the fourth intercostal spaces, then traverse pectoralis major to reach the breast along its medial edge the first and second perforators are the largest of these branches, from the intercostal arteries via their lateral perforating branches; a relatively unimportant source and the venous drainage is to the corresponding veins.(Harold Ellis.2006)

2.1.3 Lymph drainage:

The lymph drainage of the mammary gland is importance because of the frequent development of cancer in the gland and the subsequent dissemination of the malignant cells along the lymphatic vessels to the lymph nodes. (Maloney.2004)

The breast is divided to four quadrants' when considering the lymph drainage, the lateral quadrants' drain in to the axillary or pectoral group of nodes, which subdivided

as follows: the highest lymph nodes including the subclavicular group from beneath the clavicle to the lower boarder of the pectoralis minor muscles, and the interpectoral nodes lying between the pectoralis major and pectoralis minor muscles, the lower axillary vein group from the lower boarder of the pectoralis muscles to the lateral limits of dissection and the central group including external mammary ,paramammary and scapular nodes.(Maloney.2004)

The medials quadrants drain by means of vessels that pierce the intercostals spaces and enter the interthoracic group of nodes. The internal mammary lymph nodes accompany the internal mammary artery and vein. They are found in the intercostals spaces at the sternal border deep to the intercostals muscles.(Maloney.2004)

A few lymphatic vessels follow the posterior intercostals arteries and drain posteriorly in to the posterior intercostals nodes, some vessels communicate with the lymphatic vessels of the opposite breast and with those of the anterior abdominal wall. (Maloney.2004)

2.4 Physiology of the breast:

The primary function of mammary glands is to nurture young by producing breast milk. The production of milk is called lactation, lactation is used for the breast milk production or formation in mothers after the birth of baby. Lactation starts following delivery or birth of baby, the preparation of effective lactation starts during pregnancy. (Maloney.2004)

The lactation can be divided into four stages to understand its proper physiology: (preparation of breasts or mammogenesis, synthesis and secretion of milk from breast alveoli or lactogenesis, ejection of milk outside the breast or galactokinesis, maintenance of lactation or galactopoiesis. (Maloney.2004)

2.5 Pathology of the breast:

2.5.1 Tumors of the breast:

Tumors are the most importance lesions of the female breast they arise from either connective tissue or epithelial structures.

2.5.1.1 Benign tumors of the breast:

2.5.1.1.1 Fibro adenoma:

The fibro adenoma is the most common benign tumor of the female breast. Increase in estrogen play role in the development .It appears in young women, usually in third decade of life.(Kumar.2003)

2.5.1.1.2 Phylloides tumors:

This tumor is less common than fibro adenomas and arises from the interlobular stroma. They may by small (3 to 4 cm in diameters) but most grow to large, possibly massive size destining the breast. Some become lobulated and cystic; they have been designated Phylloides tumors.(Kumar.2003)

2.5.1.1.3 Intraductal papilloma:

This is a neoplastic papillary growth within the duct. Most of them are solitary, less than 1cm in diameters, always benign and they are due to Blood nipple discharge, Small subareolar tumor and rarely nipple retraction. In some cases there is multiple papilloma in several ducts or intraductal papillomastasis which may become malignant. (Kumar.2003)

2.5.1.2 Carcinoma of the breast:

It's the more feared cancer by the women because unknown reason, there has been an increase in the incidence of the breast cancer through the word and are divided in to:

2.5.1.2.1 Non invasive breast cancer:

Breast cancer refers to cancer in which the cells have remained within their place of origin; they haven't spread to breast tissue around the duct or lobule. The most common type of noninvasive breast cancer is: (Kumar.2003)

2.5.1.2.1 a. Ductal carcinoma in situ (DCIS):

Ductal carcinoma in situ refers to the most common type of noninvasive breast cancer in women. In situ, or "in place," describes a cancer that has not moved out of the area of the body where it originally developed, with DCIS, the cancer cells are confined to milk ducts in the breast and have not spread into the fatty breast tissue or to any other part of the body (such as the lymph nodes). DCIS is often first detected by a mammogram (an x-ray examination of soft breast tissues used to identify lumps,

cysts, tumors, and other abnormalities). DCIS may appear on a mammogram as tiny specks of calcium (called micro calcifications), generally too small to notice by physical examination. (Kumar.2003)

2.5.1.2.1 b. Lobular carcinoma in situ (LCIS)

Lobular carcinoma in situ (LCIS) is actually indicators that have a higher chance of developing breast cancer in the future. LCIS is an area of abnormal tissue growth that occurs within and stays within the lobules or milk glands located at the end of the breast ducts.(Kumar.2003)

LCIS usually doesn't show up on mammograms. The condition is most often discovered as a result of a biopsy done for another reason, such as a suspicious breast lump or an abnormal mammogram.(Kumar.2003)

Women with LCIS have a 10 to 20 percent lifetime risk of developing invasive breast cancer in either breast. Fortunately, effective screening and treatment options are available to reduce the risk of invasive breast cancer in women with LCIS. (Kumar.2003)

2.5.1.2.2 Invasive breast cancer:

Invasive breast cancers spread outside the membrane that lines a duct or lobule, invading the surrounding tissue, the cancer cells can then travel to other parts of the body, such as the lymph nodes. (Kumar.2003)

2.5.1.2.2 a. Invasive ductal carcinoma

(Not otherwise specified NOS) and it's by far the most common, the IDC (Invasive ductal carcinoma) accounts for about 70 percent of all breast cancers, the cancer cells form in the lining of the milk duct, then break through the ductal wall and invade nearby breast tissue, the cancer cells may remain localized staying near the site of origin or spread (metastasize) throughout the body, carried by the bloodstream or lymphatic system. (Kumar.2003)

2.5.1.2.2 b. Invasive lobular carcinoma

Although less common than invasive ductal carcinoma, this type of breast cancer invades in a similar way, starting in the milk-producing lobules and then breaking into the surrounding breast tissue. ILC can also spread to more distant parts of the

body, with this type of cancer typically feel a distinct, firm lump but rather a fullness or area of thickening. (Kumar.2003)

2.5.1.2.2 c. Medullary carcinoma:

This type of breast cancer is found in only 3 to 5% of all breast cancers diagnosed. It is quite difficult to distinguish from invasive ductal carcinoma and is usually treated the same as invasive ductal carcinoma. Medullary carcinoma has been found in about 5% of breast cancer diagnoses. (Kumar.2003)

Medullary cancer is more common in women who have genetic susceptibility to breast cancer. The boundaries between this type of cancer cells and the normal cells are well defined and its prognosis is better than that of other types of invasive carcinoma. However, it should still be treated as the usual invasive ductal breast cancer.(Kumar.2003)

2.5.1.2.2 d.Colloid carcinoma (mucious carcinoma):

Mucinous (colloid) carcinoma is a rare type of invasive breast cancer that is formed when cancer cells within the breast produce mucous. This mucous contains breast cancer cells that are easily distinguished from normal cells under a microscope; this type of breast cancer rarely spreads to the lymph nodes. (Kumar.2003)

2.5.1.2.2 e.Tubular carcinoma:

Tubular carcinomas account for 2% of all breast cancer diagnoses. Patients who develop tubular carcinoma are usually 50 years of age or older.

Tubular breasts, or tuberous breasts, are a congenital breast condition in which the breasts don't develop as much glandular tissue as a normal mature breast. Tubular breasts may have large areolas, are very narrow at the chest wall, and grow in a drooping fashion. Plastic surgery can be done to reshape tubular breasts into a more normal shape. (Kumar.2003)

2.5.1.2.2 f.Paget's disease:

Paget's disease of the breast is a rare form of breast cancer, accounting for less than 5 percent of all breast cancers. Paget's disease of the breast starts in the breast ducts and extends to the skin of the nipple and to the dark circle of skin (areola) around the

nipple. Paget's disease of the breast isn't related to Paget's disease of the bone, a metabolic bone disease. (Kumar.2003)

Paget's disease of the breast occurs most often in women over age 50, most women with Paget's disease of the breast have underlying infiltrating ductal breast cancer. Only in rare cases is the cancer confined to the nipple itself. (Kumar.2003)

2.6 Metastatic cancer:

Metastatic cancer is cancer that has spread from the body where it started (called its primary site) to other part of the body (Stoll BA et al 1983). When cells break away from cancerous tumor, they can travel to other area of the body through either bloodstream or lymphatic channels. (Kumar.2003)

When the cell travel through lymphatic channels they can become trapped in lymph nodes, often those closest to the cancers primary site and when the cell travel through the blood stream they can go to any part of the body .Most of these cells die, but occasionally they don't. They settle in a new location, begin to grow, and form new tumors, when cancer comes back in patient who appeared to be free of cancer after treatment it's called a recurrence. (Kumar.2003)

2.6.1 Cancer recurs

Categorized as local recurrence (in or near the same organ it develop in) for example a recurrence of breast cancer in the skin of the chest near where the original cancer was removed, regional recurrence (in nearby lymph nodes or in the area those lymph nodes had been removed from), and distant recurrence (involving any other part of the body not included in local or regional recurrence). Distant recurrence is also called metastatic recurrence. (Kumar.2003)

2.7 Spread of breast cancer:

Spread occurs through lymphatic and hematogenous channels, nodal metastasis are present in about 40% of cancer presenting as palpable masses but less than 15% of cases found by mammography. (Kumar.2003)

Outer quadrants are centrally located lesions typically spread first to axillary nodes. Those in the inner quadrants often involve the lymph node along the internal mammary arteries, the supraclavicular nodes are the primary site of spread but they

may involve after only the axillary and internal mammary nodes, more distant dissemination with metastatic involvement as favored location is the liver, skeletal, brain and the lungs, metastasis may appear many years after therapeutic control of the primary lesions, sometimes 15 years later. (Kumar.2003)

2.8 Risk factors for breast cancer and metastatic breast cancer:

A risk factor is factor that increases a person's chance of getting a disease such as cancer; a risk factor however is neither a necessary cause nor a sufficient cause of the disease (James et al 1996).

Breast cancer is amultifactorial disease both endogenous (including genetic) and exogenous factors are involved in breast carcinogenesis and increase breast cancer risk, during the risk counseling, the woman's status regarding a number of risk factors should be determined. the available risk assessment technique are based on factors that have been shown to correlate with development of breast cancer as well as epidemiological principles that allow quantitative estimation of risk (Georage et al 2003).

Although the causes and natural history of breast cancer remain unclear. Epidemiology research has uncovered genetic, biological, environmental, and lifestyle risk factors for the disease most of this research has been conducted in Europe and North America. But studies conducted in other countries generally confirm those patterns (UNFPA, 2002).

2.8.1 Gender:

Simply being a woman is the main risk for breast cancer, while men also get the disease, it is about 100 times more common in women than in men women are at higher risk of breast cancer because they have much more breast tissue than men do. In addition, the female hormone estrogen promotes the development of breast cancer (Kathleen et al, 2000).

2.8.2 Age:

Age is the single most important risk factor for breast cancer. The chance of getting breast cancer goes up as a woman gets older. About 2 out of 3 women with invasive breast cancer are age 55 or older when the cancer is found. Women are 10 times as

likely to develop breast cancer in their thirties, 40 times as likely in their forties, 60 times as likely in their fifties and 90 times as likely after age 60 years old. So breast cancer is higher in middle aged and elderly women than younger women (Kathleen et al, 2000).

2.8.3 Family history:

Women who have a family history of breast cancer are at a higher risk for breast cancer than those who lack such a history, women who have an especially strong family history (e.g., two or more first-degree relatives [a mother, daughter, or sister] with breast cancer, particularly before menopause) have a greater than 50 percent chance of developing breast cancer. This represents an approximately 5 to 10 fold increase in a woman's baseline risk of developing breast cancer. (Kathleen et al, 2000).

2.8.4 Alcohol consumption:

Women who consume alcohol have an increased risk of breast cancer, perhaps due to elevated levels of estrogen in the body. The more alcohol a woman drinks, the greater her risk. However, moderate alcohol intake may protect against other diseases, there is evidence that women can protect themselves against the alcohol breast cancer link by consuming an adequate amount of folic acid with a daily multivitamin and by eating leafy green vegetables. (Kathleen et al, 2000).

2.8.5 Reproductive risk factors:

Hormones, especially estrogens play important in the development and growth of breast cancer, and may be the common factor behind the many reproductive variables associated with breast cancer (Kathleen et al, 2000).

2.8.5.1 Pregnancy and breastfeeding:

Women who have never given birth are more likely to develop breast cancer after menopause than women who have given birth multiple times, the timing of a first pregnancy also appears to play a role, women who have their first full term pregnancy at the age of 30 years or older have an increased risk of breast cancer as compared to women who give birth before age 30.

2.8.5.2 Hormone replacement therapy (HRT):

As a woman ages, the breast's glandular tissue, the tissue in which breast cancer arises, is gradually replaced by fat. HRT includes estrogen, which slows or reverses this process. A large clinical trial has found that long-term use of combined estrogen-progestin (approximately five years) in women ages 50 to 79 increases a woman's risk of breast cancer, as well as heart disease, stroke, and clots in the legs .The risk of breast cancer when estrogen is used alone does not appear to be increased, especially when used for a short time. (Kathleen et al, 2000).

2.8.5.3 Oral contraceptive hormone use:

It is still not certain what part oral contraceptives might play in breast cancer risk studies have suggested that women using oral contraceptives have a slightly greater risk of breast cancer than women who have never used them, women who stopped using oral contraceptives more than 10 years ago do not appear to have any increased breast cancer risk. (Kathleen et al, 2000).

2.8.5.4 Postmenopausal hormone therapy (PHT):

Postmenopausal hormone therapy (also known as hormone replacement therapy or HRT), has been used for many years to help relieve symptoms of menopause and to help prevent thinning of the bones (osteoporosis). There are 2 main types of PHT. For women who still have a womb (uterus), doctors generally prescribe estrogen and progesterone (known as combined PHT). Estrogen alone can increase the risk of cancer of the uterus, so progesterone is added to help prevent this. For women who no longer have a uterus (those who've had a hysterectomy), estrogen alone can be prescribed. This is commonly known as estrogen replacement therapy (ERT) (Lori et al 2002).

2.8.5.5 Menstrual periods:

Women who began having periods early (before age 12) or who went through the change of life (menopause) after the age of 55 have a slightly increased risk of breast cancer. They have had more menstrual periods and as a result have been exposed to more of the hormones estrogen and progesterone. (Kathleen et al, 2000).

2.8.6 Genetic risk factors:

About 5% to 10% of breast cancers are thought to be linked to inherited changes (mutations) in certain genes, the most common gene changes are those of the BRCA1 and BRCA2 genes. Women with these gene changes have up to an 80% chance of getting breast cancer during their lifetimes. (Vogel et al, 2000)

2.8.7 Earlier breast radiation:

Women who have had radiation treatment to the chest area (as treatment for another cancer) earlier in life have a greatly increased risk of breast cancer. (Vogel et al, 2000)

2.8.8 Height and weight:

Tall women are more likely than short women to develop breast cancer. Weight also plays a role, possibly because body fat alters a woman's estrogen metabolism. Obese women are more likely than thin women to develop breast cancer after menopause (George et al, 2003).

2.9 Cancer staging:

The stage of a cancer is a descriptor of how much the cancer has spread. The stage often takes into account the size of a tumor, deep it has penetrated, whether it has invaded adjacent organs, how many lymph nodes has been metastasized to, and whether it has spread to distant organs. Staging of cancer is important because the stage at diagnosis is the most powerful predictor of survival and treatments are often changed based on the stage (Robert et al, 2007).

2.9.1 Consideration of staging

Correct staging is critical because treatment is directly related to disease stage, thus incorrect staging would lead to improper treatment, and material diminution of patient survivability. Correct staging, however, can be difficult to achieve pathologic staging, where a pathologist examines sections of tissue, can be particularly problematic for two specific reasons: visual discretion and random sampling of tissue. "Visual discretion" means being able to identify single cancerous cells intermixed with healthy cells on a slide. Oversight of one cell can mean miss-staging and lead to serious unexpected spread of cancer. "Random sampling" refers to the

fact that lymph nodes are cherry-picked from patients and random samples are examined. If cancerous cells present in the lymph node happen not to be present in the slices of tissue viewed, incorrect staging and improper treatment can result. (Robert et al, 2007).

2.9.2 Overall stage grouping:

Overall Stage Grouping is also referred to as Roman Numeral Staging. This system uses numerals I, II, III, and IV (plus the 0) to describe the progression of cancer.

Stage 0 Carcinoma in situ, **Stage I** Cancers are localized to one part of the body, **Stage II** Cancers are locally advanced, **Stage III** Cancers are also locally advanced. Whether a cancer is designated as Stage II or Stage III can depend on the specific type of cancer; **Stage IV** Cancers have often metastasized, or spread to other organs or throughout the body. (Robert et al, 2007).

2.9.3 The TNM staging system:

Cancer staging can be divided into a clinical stage and a pathologic stage. In the TNM (Tumor, Node, and Metastasis) system, clinical stage and pathologic stage are denoted by a small 'c' or 'p' before the stage (e.g., cT3N1M0 or pT2N0).

Clinical stage is based on all of the available information obtained before a surgery to remove the tumor. Thus, it may include information about the tumor obtained by physical examination, radiologic examination, and endoscopy.

Pathologic stage adds additional information gained by examination of the tumor microscopically by a pathologist. (Robert et al, 2007).

Because they use different information, clinical stage and pathologic stage are often different. Pathologic staging is usually considered the "better" or "truer" stage because it allows direct examination of the tumor and its spread, contrasted with clinical staging which is limited by the fact that the information is obtained by making indirect observations at a tumor which is still in the body. However, clinical staging and pathologic staging should complement each other. Not every tumor is treated surgically, so sometimes pathologic staging is not available. Also, sometimes surgery is preceded by other treatments such as chemotherapy and radiation therapy which shrink the tumor, so the pathologic stage may underestimate the true stage.

TNM Staging is used for solid tumors, and is an acronym for the words "Tumor", "Nodes", and "Metastases". Each of these criteria is separately listed and paired with a number to indicate the TNM stage. For example, a T1N2M0 cancer would be a cancer with a T1 tumor, N2 involvement of the lymph nodes, and no metastases (no spreading through the body), Tumor (T) refers to the primary tumor and carries a number of 0 to 4, N represents regional lymph node involvement its can also be ranked from 0 to 4, Metastasis is represented by the letter M, and is 0 if no metastasis has occurred, or else 1 if metastases are present. (Sobin and Wittekind et al, 2002).

2.9.4 Cancer grading:

The grading is a sorting of cancer depending on the degree of cancer cell malignancy. In pathology, grading is a measure of the progress of tumors and other neoplasm. Some pathology grading systems apply only to malignant neoplasm (cancer), others apply also to benign neoplasm. Pathology grading systems are used to classify neoplasm in terms of how abnormal the cells appear microscopically and what may be the outcome in terms of rate of growth, invasiveness, and dissemination. Cancer is a disorder of excessive cell growth; hence cancer cells often are poorly differentiated. The grade reflects the degree of cellular differentiation and refers to how much the tumor cells resemble or differ from the normal cells of the same tissue type. An important part of evaluating a cancer is to determine its histological grade. Grade is a marker of how differentiated a cell is. Grade is rated numerically (Grade 1-4) or descriptively (e.g., "low grade" or "high grade"). The higher the numeric grade, the more "poorly differentiated" is the cell, and it is called "high grade". A low grade cancer has a low number and is "well-differentiated." A cancer that is very poorly differentiated is called anaplastic. Tumors may be graded on four-tier, three-tier, or two-tier scales, depending on the institution and the tumor type (Gleason et al 2002). The tumor grade, along with the staging, is used to develop an individual treatment plan and to predict the patient's prognosis.

2.9.4.1 Categories:

The most commonly used system of grading is as per the guidelines of the American Joint Commission on Cancer as per their standards, the following are the grading categories.

GX Grade cannot be assessed, **G1** well differentiated (Low grade), **G2** moderately differentiated (Intermediate grade), **G3** poorly differentiated (High grade), **G4** undifferentiated (High grade).

2.9.5 Breast cancer staging:

Cancer stage is based on the size of the tumor, whether the cancer is invasive or non-invasive, whether lymph nodes are involved, and whether the cancer has spread beyond the breast (Maloney et al, 2004).

The purpose of the staging system is to help and organize the different factors and some of the personality features of the cancer into categories, in order to have the following knowledge, best understand of prognosis (the most likely outcome of the disease), guide treatment decisions (together with other parts of pathology report), since clinical studies of breast cancer treatments the doctor will consider are partly organized by the staging system, provide a common way to describe the extent of breast cancer for doctors and nurses all over the world, so that results of treatment can be compared and understood (White D.R et al, 2005)

Breast cancer staging described as:

2.9.5.1 Stage 0

Stage 0 is used to describe non-invasive breast cancers, such as DCIS and LCIS. In stage 0, there is no evidence of cancer cells or non-cancerous abnormal cells breaking out of the part of the breast in which they started, or of getting through to or invading neighboring normal tissue. (White D.R et al, 2005)

2.9.5.2 Stage I

Stage I describes invasive breast cancer (cancer cells are breaking through to or invading neighboring normal tissue) in which:

The tumor measures up to 2 centimeters and No lymph nodes are involved

2.9.5.3 Stage II

Stage II is divided into subcategories known as IIA and IIB. (White D.R et al, 2005)

2.9.5.3 a. Stage IIA

Describes invasive breast cancer in which: no tumor can be found in the breast, but cancer cells are found in the axillary lymph nodes (the lymph nodes under the arm), the tumor measures 2 centimeters or less and has spread to the axillary lymph nodes, the tumor is larger than 2 centimeters but not larger than 5 centimeters and has not spread to the axillary lymph nodes(White D.R et al, 2005)

2.9.5.3 b. Stage IIB

describes invasive breast cancer in which: the tumor is larger than 2 but no larger than 5 centimeters and has spread to the axillary lymph nodes, the tumor is larger than 5 centimeters but has not spread to the axillary lymph nodes (White D.R et al, 2005)

2.9.5.4 Stage III

Stage III is divided into subcategories known as IIIA, IIIB, and IIIC. (White D.R et al, 2005)

2.9.5.4 a. Stage IIIA

No tumor is found in the breast. Cancer is found in axillary lymph nodes that are clumped together or sticking to other structures or cancer may have spread to lymph nodes near the breastbone, the tumor is 5 centimeters or smaller and has spread to axillary lymph nodes that are clumped together or sticking to other structures, the tumor is larger than 5 centimeters and has spread to axillary lymph nodes that are clumped together or sticking to other structures. (White D.R et al, 2005)

2.9.5.4 b. Stage IIIB

The tumor may be any size and has spread to the chest wall or skin of the breast, also may have spread to axillary lymph nodes that are clumped together or sticking to other structures, or cancer may have spread to lymph nodes or could have inflammatory breast cancer is considered at least stage IIIB. (White D.R et al, 2005)

2.9.5.4 c. Stage IIIC

There may be no sign of cancer in the breast or, if there is a tumor, it may be any size and may have spread to the chest wall and the skin of the breast, the cancer has spread to lymph nodes above or below the collarbone, the cancer may have spread to axillary lymph nodes or to lymph nodes near the breast bone. (White D.R et al, 2005)

2.9.5.5 Stage IV

Stage IV describes invasive breast cancer in which the cancer has spread to other organs of the body usually the lungs, liver, bone, or brain. (White D.R et al, 2005)

"Metastatic at presentation" means that the breast cancer has spread beyond the breast and nearby lymph nodes, even though this is the first diagnosis of breast cancer. The reason for this is that the primary breast cancer was not found when it was only inside the breast. Metastatic cancer is considered stage IV. (White D.R et al, 2005)

2.9.6TNM system in breast cancer staging:

Doctors use a staging system to determine how far a cancer has spread, the most common system is the TNM staging system which described by three characteristics size (T stands for tumor), lymph node involvement (N stands for node), whether it has metastasized (M stands for metastasis) and the T (size) category describes the original (primary) tumor:(TX means the tumor can't be measured or found, T0 means there isn't any evidence of the primary tumor, T is means the cancer is "in situ" (the tumor has not started growing into the breast tissue), the numbers T1-T4 describe the size and how much the cancer has grown into the breast tissue the higher T number, the larger the tumor and it may have grown into the breast tissue, the N (node involvement) category describes whether or not the cancer has reached nearby lymph nodes:(NX means the nearby lymph nodes can't be measured or found, N0 means nearby lymph nodes do not contain cancer, the numbers N1-N3 describe the size, location, and the number of lymph nodes involved. The higher the N number, the more the lymph nodes are involved). (White D.R et al, 2005)

The M (metastasis) category tells whether there are distant metastases (whether the cancer has spread to other parts of body):(MX means metastasis can't be measured or

found, M0 means there are no distant metastases, M1 means that distant metastases were found). (White D.R et al, 2005)

Once the pathologist knows T, N, and M characteristics, they are combined in a process called stage grouping, and an overall stage is assigned.(Sobin and Wittekind, 2002).

2.10 Bone metastasis mechanism:

The vast majority of bone metastases originate from cancers of the breast, lung, and prostate, followed by the thyroid and kidney. The most common sites of spread in the skeleton include the spine, pelvis, ribs, skull, upper arm, and leg long bones. Interestingly, these sites correspond to areas of bone marrow that demonstrate high levels of red blood cell production, the cells responsible for carrying oxygen to tissues in the body.

Several factors account for the frequency of bone metastasis, (Blood flow is high in areas of red marrow, accounting for the predilection of metastases for those sites. Furthermore, tumor cells produce adhesive molecules that bind them to marrow stromal cells and bone matrix. These adhesive interactions cause the tumor cells to increase the production of angiogenic factors and bone resorbing factors that further enhance tumor growth in bone). Bone is also a large repository for immobilized growth factors, including transforming growth factor, insulin-like growth factors I and II, fibroblast growth factors, platelet-derived growth factors, bone morphogenetic proteins, and calcium. These growth factors, which are released and activated during bone resorption, provide fertile ground in which tumor cells can grow. This "seeds-and-soil hypothesis" of the mechanism of bone metastasis was first advanced by Stephan Paget in 1889 and is supported by findings in animal models of bone metastasis (Coleman et al, 1987).

Two main theories are still entertained. In 1889, Sir James Paget, an English surgeon, developed his "seed and soil" theory by studying the medical records of 735 patients with breast cancer. The majority of metastases were noted to occur in the liver and brain. Dr. Paget realized there was a discrepancy between the blood supply and the frequency of metastasis in various organs. He then determined that local organ

factors must favor implantation in specific sites. He did not feel that metastasis was related to the blood supply to a particular organ, as skeletal muscle and the spleen have a rich blood supply but are not frequent targets for metastasis. Dr. Paget felt that it was not simply that the cancer cells had the ability to survive and spread to a new site (the seed), but that the local environment had to be nurturing of further tumor growth (the soil). Only with both factors could successful metastatic spread occur (Paget et al, 1889).

2.11 Bone metastasis complication and treatment:

Patients with advanced breast cancer who develop bone metastases suffer from long-term skeletal morbidity. Complications of bone metastases include pain, pathologic fractures, and spinal cord compression, hypercalcaemia and bone marrow infiltration which have a significant impact on the quality of life of patients (Rubens et al, 1998).

The primary treatment for metastasis is systemic therapy directed at the underlying neoplasm recent advances in therapy have led to the development of agents tailored to the treatment of bone metastasis including radiopharmaceuticals (e.g. strontium-89 chloride and bisphosphonates). (Rubens et al, 1998).

Bisphosphonates reduce bone resorption, pain and may directly disrupt the metabolism and adhesive abilities of tumor cells. The administration of bone-targeted radiopharmaceuticals has been associated with painful flare responses and myelosuppression, whereas bisphosphonates may lead to nephrotoxicity and osteonecrosis of the jaw. Identify patients with high risks of bone metastasis will assist the treatment plan of breast cancer patients most likely to benefit from these therapies to avoid the consequences of over- and under treatment. In addition, the possibility of prevention of bone metastases in early breast cancer patients is under investigation (Pavlakis et al, 2005).

2.12 Previous studies:

Other studies by Coleman et al (1988), Kunkler et al, (1985) and Koizumi et al (2001) suggested that the bone metastasis detection rates by bone scan are 0.82% for patients with stage I disease, 2.555% in stage II, 16.75% in stage III and 40.52 % with stage IV. However, results from a large randomize study of patients with breast

cancer immediately after initial treatment showed that semiannual screening by bone scan detected more metastasis than did clinical follow up alone.

In 1999 a retrospective study done by Gonial et al, (1999) to determine the incidence of bilateral breast cancer in female patients during period 1994-1999 among 521 patients. The data was analyzed focusing on the demographic information, family history, menstrual status, surgical therapy, chemotherapy, radiation therapy, staging and histopathological characteristics. They concluded that the incidence of bilateral breast cancer with percentage of 1.3% in 521 female patients.

In the realm of evaluating the breast cancer metastasis to skeletal system, considerable numbers of researchers have studied the behavior, manner and relative stage. For instance, a retrospective study done by Seliuman gaffer and Ahmed M. conducted on 509 female breast cancer patients, referred from central Sudan (Gezira State and surrounding area) during the period of 2001-2005. A number of 151 patients had bone metastasis, which had been detected by bone scan using gamma cameras single head and dual heads version nucline and mediso manufacture. Bone metastasis distribution on the skeleton had been evaluated versus age, menopausal status, histopathology type, tumor stage and lymph node involvement. Binary logistic regression model was established for predicting bone metastasis occurrence. The data were collected using questionnaire and analyzed using SPSS and Microsoft excels software. They found that from the total number of the study population 509 females with breast cancer. Their age ranged between 22-99-years. There was 42% of bone metastasis found in premenopausal women (age < 45years), 30% in premenopausal women (age 45-50 years) and 27% in postmenopausal women (age >50yrs). 68% of bone metastasis occurred in patients from rural area and 32% from urban area. There were 66% of bone metastasis occurred from left side breast carcinoma , 31% from right side breast carcinoma and 3% bilateral sides.

With regarded to distribution of bone metastasis according to histopathology type, there were 71% had invasive ductal. There was 78% of bone metastasis had more than for lymph node involvement and 22% less than four lymph nodes involvement.

According to TNM stages there were 4% occurred in stage 1, 11% in stage 11, 40% in stage 111 and 45% in stage IV (Maloney et al.2004, White et al 2005)

The patterns of bone metastasis were multiple in 76% patients and single in 24% of them. The percentage distribution of bone metastasis in the skeleton segments was 48% in axial skeleton, 10% the skull and 6% in the extremities.

The association between breast cancer bone metastasis and each of the variables (age, menopausal status, TNM stage, lymph node involvement and liver metastasis) showed that the TNM tumor staging, lymph node involvement and liver metastasis were found to have a significant association. While other factors such as age, menopausal status and histopathology types showed insignificant association. Their study demonstrates high prevalence of bone metastasis in young and premenopausal breast cancer patients in central Sudan. Multiple bone metastases have been shown in the majority of bone scintigraphy as the characteristic pattern. The axial skeleton was the common site of bone metastasis. The TNM tumor staging, lymph node involvement and existence of liver metastasis had a significant association with bone metastasis.

Anderson et al, (2008) have quantified the incidence of breast cancer in black and white women, and concluded that the breast cancer incidence is higher in black women with percentage of 15.5% than in white women with percentage of 13.1% among women younger than 40 years. On the other hand, Hickey et al, (2008) estimated that 12% of breast cancer incidence occurs in women with age ranged between 20-34 years and survival from breast cancer has significantly improved, and the potential late effects of treatment and the impact on quality of life have become increasingly important. Young women constitute a minority of breast cancer patients, but commonly have distinct concerns and issues compared with older women, including queries regarding fertility, contraception and pregnancy.

Study on the prediction of the progression of bone metastasis in the breast cancer patients was carried out by Elyass et al, 2009. It was retrospective review of medical records of 50 females with breast cancer with only bone metastases evaluated at Magee Women's Hospital in Pennsylvania, between June 1998 and September 2007.

Patients' progression of their bone disease was followed based on serial bone scans and they concluded that breast cancer is mostly diagnosed in elderly women aged 65 years and they constitute about 41% of all newly diagnosed cases. Bone metastases was a very common event in these patients especially those with estrogen receptor positive subtypes.

Similar retrospective study conducted by Salim and Elhaj, (2008) to determine the prevalence of bone metastasis from breast cancer in central Sudan was a retrospective Review of 500 patients with breast cancer showed that out of the total 500 female breast patients 58% were diagnosed as having bone metastasis and the age of 30% of bone metastatic patients ranged from 30-40 years which was very high in young age, premenopausal of onset with the mean age of 46.8 84% were married women and 16% were unmarried women. The results indicated the highest prevalence of bone metastasis in female breast cancer patient in central Sudan especially in young women and premenopausal women. Likewise Koizumi et al, (2003) estimated the skeletal metastasis from breast cancer and compared between solitary metastasis and multiple metastases according to anatomical distribution. Study covered 703 patients who developed metastatic lesions up to September 2002 after beginning treatment for breast cancer from 1988-1998. Skeletal metastasis was surveyed by bone scintigraphy and the results showed that 99% of all patients have bone metastasis, 41% (289) have solitary metastasis and 59% (414) showed multiple skeletal metastasis.

The diagnostic base for the above mentioned studies was the comparison between the normal appearance and abnormal one in the NM image. Usually in such cases the normal scan varies significantly in appearance between children and adults (Fred et al 2006). In children, the area of growth in the region of the epiphyses showed intense radionuclide accumulation while in adults the quality of bone scan can be related to age, in general the older the patient the higher proportion of poor quality scans. There is usually good visualization of the skull with relatively increased accumulation of activity in the region of Nasopharynx which may be secondary to the high proportional blood flow in this region. Activity in the skull is often patchy, even in

the normal patients so care must be taken in assessing skull lesions without an accompanying radiograph. Often there is focal maxillary or mandibular alveolar ridge activity in adults owing to dental disease. There is activity throughout the spine and it is common to see focal areas of increased activity in the lower cervical spine even on anterior images. On the anterior view there is prominent visualization of the sternum, sternoclavicular joints, acromioclavicular joints, shoulders, iliac crests and hips. Increase activity in the knees in older patients is relatively common because of the propensity for arthritic changes. On the posterior view, the thoracic spine is well seen, as are tips of the scapulae. The spine often demonstrates increase activity in the area of hypertrophic degenerative change, and the sacroiliac joints are usually pronounced. Because the human skeleton is symmetric any asymmetric osseous activity should be viewed with suspicion. In addition, it is important on the posterior view to examine the scan for the presence and location renal activity. The kidney and bladder should be routinely scrutinized for focal space occupying lesions producing photogenic defect in the renal cortex or displacement of the kidneys or bladder. Asymmetric renal activity is not uncommon, because the scans are usually obtained in the supine position, activity may accumulate in external pelvis. If urinary tract obstruction is suspected, kidneys views should be repeated after the patient has ambulated to distinguish obstruction from position related collecting system activity. While the abnormal appearance would show asymmetric focal areas of increased or decreased activity which super scan with bone uptake showing brightly, no kidney, bladder, distal extremities, facial bones, or soft tissue uptake apparent on the film at normal intensities caused by intense or widespread metastatic involvement. Tumors causing this type of osseous metastases are breast, prostate, lung, renal and bladder

Chapter Three

Material and Method

Nuclear medicine imaging is an effective diagnostic tool because it shows not only the anatomy structure of an organ or body part but the function of the organ as well. This additional "functional information" allows nuclear medicine to diagnose certain diseases and various medical conditions much sooner than other medical imaging examinations which provide mainly anatomic (structural) information about an organ or body part. Nuclear medicine can be valuable in the early diagnosis, treatment, and prevention of numerous medical conditions and continues to grow as a powerful medical tool. Nuclear medicine imaging scans are performed for a number of diagnostic purposes among which are the evaluation of bones for fractures, infection, arthritis and tumors and determine the presence or spread of cancer in various parts of the body. (Fred et al, 2006).

In this study the whole body scan was performed using ^{99m}Tc-MDP. Bone seeking radiopharmaceuticals are analogs of calcium, hydroxyl groups, or phosphates. By far the most widely used radiopharmaceuticals for skeletal imaging are technetium labeled with diphosphonates and polyphosphates (Subramanian et al, 1971).

Diphosphonates contains organic P-C-P bonds which are more stable in vivo than are in organic bonds (pyrophosphates), primarily because of their resistance to enzymatic hydrolysis. Because the diphosphonates have rapid renal excretion, they provide high target to non target ratio in 2 to 3 hours after injection with 50% to 60% of the activity localizing in the bone and the remainder being cleared by the kidneys (Metteler et al, 2006).

3.1 Material:

3.1.1 Study subject:

The study was included 150 female patients whom have Ca breast with age ranged between 25-90 years, all patients were known breast cancer and were received different types of treatment.

3.2 Machine specifications:

The machine was used in this study is Mediso Gamma camera-SEMENS, Digital, Model: Digital Nuclei, software: Acquisition console, Processing: DIAG.

3.2.1 Gamma Camera devices:

Schematic diagram of conventional planner gamma camera that predominantly used in Nuclear Medicine as imaging device is shown in Fig.3.1

Once a radiopharmaceutical has been administered, it is necessary to detect the gamma ray emissions in order to attain the functional information. The components making up the gamma camera are the collimator, detector crystal, photomultiplier tube array, position logic circuits, and the data analysis computer.

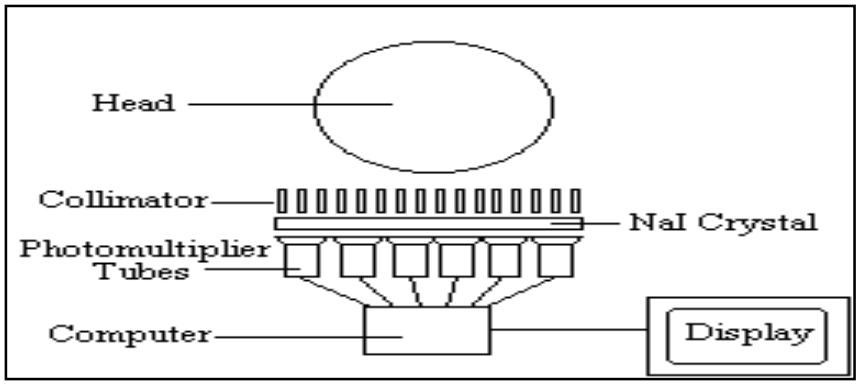

Fig 3.1 The components of the gamma camera of nuclear medicine instruments

(Anderson WF.2008)

3.2.1.1Camera collimator:

The first object that an emitted gamma photon encounters after exiting from the body is the collimator. The collimator is a pattern of holes through gamma ray absorbing material, usually lead or tungsten that allows the projection of the gamma ray image onto the detector crystal, the collimator achieves this by only allowing those gamma rays traveling along certain directions to reach the detector; this ensures that the position on the detector accurately depicts the originating location of gamma ray.

3.2.1.2 Scintillation detector:

A scintillation detector is used to detect the gamma photon. A Thallium-activated Sodium Iodide [NaI (Tl)] detector crystal is generally used in Gamma cameras. This is due to the crystal's optimal detection efficiency for the gamma ray energies of radionuclide emission. A detector crystal may be circular or rectangular. It is typically 3/8" thick and has dimensions of 30-50 cm; the gamma ray photon interacts with the detector by means of the Photoelectric Effect or Compton Scattering with the iodide ions of the crystal. This interaction causes the release of electrons which in turn interact with the crystal lattice to produce light, in a process known as scintillation.

3.2.1.3 Photomultiplier tubes:

Only a very small amount of light is given off from the scintillation detector. Therefore, photomultiplier tubes are attached to the back of the crystal.

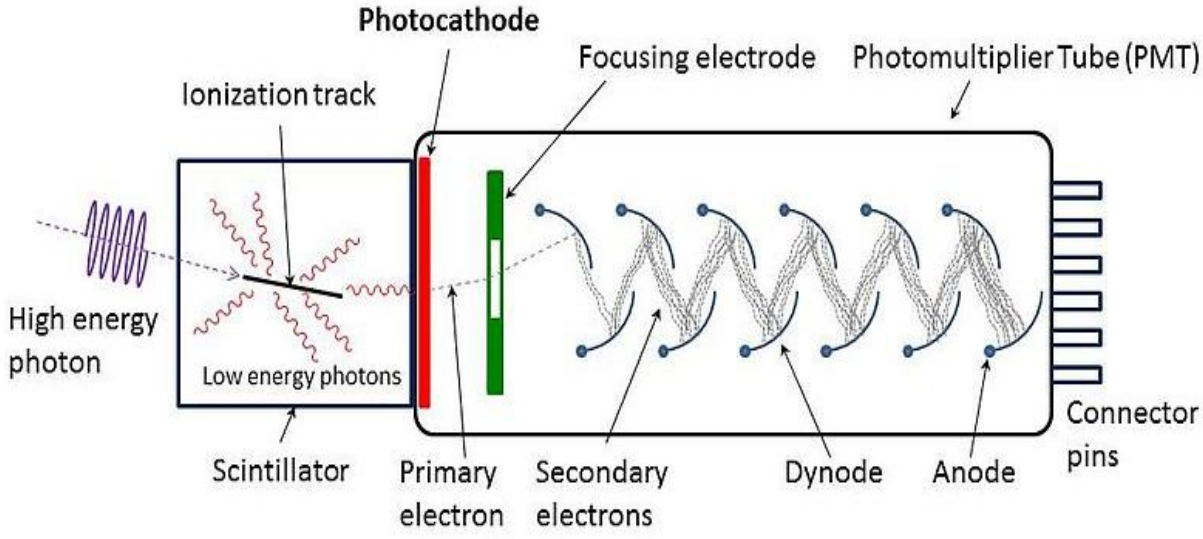

Fig 3.2 The structure of the PMT and the amplification process of the electrons (Anderson WF.2008)

At the face of a photomultiplier tube (PMT) is a photocathode which, when stimulated by light photons, ejects electrons. The PMT Figure (3.2) is an instrument that detects and amplifies the electrons that are produced by the photocathode. For every 7 to 10 photons incident on the photocathode, only one electron is generated. This electron from the cathode is focused on a dynode which absorbs this electron

and re-emits many more electrons (usually 6 to 10). These new electrons are focused on the next dynode and the process is repeated, at the base of the photomultiplier tube is an anode which attracts the final large cluster of electrons and converts them into an electrical pulse, each gamma camera has several photomultiplier tubes arranged in a geometrical array; the typical camera has 37 to 91 PMTs.

3.2.1.4 Position circuitry:

The position logic circuits immediately follow the photomultiplier tube array and they receive the electrical impulses from the tubes in the summing matrix circuit (SMC). This allows the position circuits to determine where each scintillation event occurred in the detector crystal.

3.2.1.5 Data analysis computer:

Finally, in order to deal with the incoming projection data and to process it into a readable image of the distribution of activity within the patient, a processing computer is used. The computer may use various different methods to reconstruct an image, such as filtered back projection or iterative reconstruction.

3.2.2 Molybdenum-99-Technetium99m Generators:

System used to generate a radionuclide for routine clinical practice. The most widely used generator system is the molybdenum-99/technetium-99m generator on which much of current routine nuclear imaging relies because of the half live 6 hours and optimum energy of 140keV. In this generator, the mother nuclide ^{99} Mo decays into the daughter nuclide ^{99m}Tc with a half life of 6 hours, in this a generator the half-life of the mother nuclide is much longer than that of the daughter nuclide, 50% of equilibrium activity is reached within one daughter half-life, 75% within two daughter half-lives. Hence, removing the daughter nuclide from the generator (milking the generator) is reasonably done every 6 hours or, at most, twice daily in a ^{99}Mo/^{99m}Tc generator. Most commercial ^{99}Mo/^{99m}Tc generators use column chromatography, in which Mo-99 is adsorbed onto alumina. Passing normal saline through the column of immobilized Mo-99 elutes the soluble Tc-99m, resulting in a saline solution containing the Tc-99m which is then added in an appropriate

Concentration to the kits to be used, the useful life of a $^{99}Mo/^{99m}Tc$ generator is about 3 half life's or approximately one week. Hence, any clinical nuclear medicine units purchase at least one such generator per week or order several in a staggered fashion.

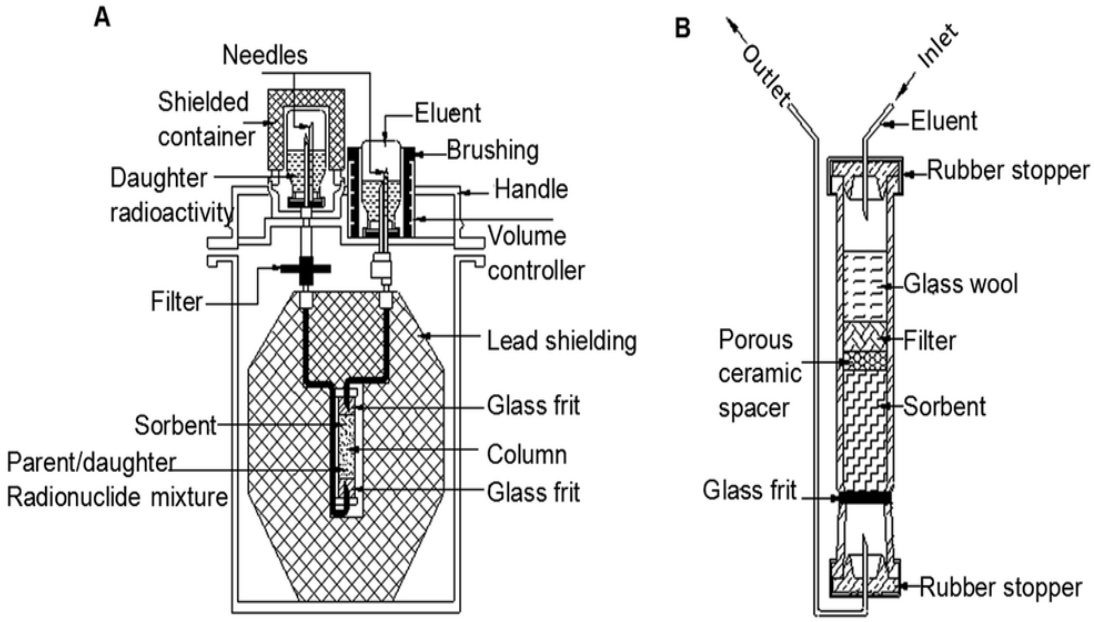

Fig 3.3 Schematic drawing of a Molybdenum-99/Technetium-99m generator system (Anderson WF.2008)

3.2Method of the study:

This data was collected retrospectively from bone Scintagraphy images for known case of breast cancer's patients who have bone Scintagraphy by gamma camera dual heads

3.2.1 Sample size:

150 females pts whom known case of breast cancer patients

3.2.2 Study area:

The nuclear medicine departments in Khartoum state hospitals and nuclear medicine departments

3.2.3 Study duration:

The study was conducted during the period from January 2017 to May 2017,

3.2.4 Data interpretation:

The data was interpreted by nuclear medicine specialists and collected from reports

3.2.5 Data analyses

The data was analyzed by Microsoft office (EXCELL)

3.3 Bone Scintagraphy procedure:

From the reception hall of patient, the patient was called to hot lab for recording the name, age, weight and height upon which the dose was determined and injected intravenously (^{99m}Tc-MDP) using syringe shield and butter fly for protection purposes.

3.3.1 Preparation of 99mTc-MDP injection:

The MDP kits contains sterile component in lyophilized form which after reconstitution with pertechnetate solution a complex of methylenediphosphate ((MDP) with technetium^{99m}TC formed, which show an affinity to hydroxyapatite of the bone tissue.

Under sterile condition 5ml of sodium pertechnetate solution with maximum activity of 100-500mCi was added to the MDP vial content through the stopper. The vial Content was mixed for a period of 20 minute, the pH value of the prepared Radiopharmaceutical has 5-7. The 99mTc-MDP preparation is administered within 6 hours from the preparation time.

3.3.1.2 Patient preparations:

Patient was instructed to be well hydrated by drinking water. Prior to the imaging, the patient has to drink at least one liter of fluid between injection and imaging.

The patient was encouraged to avoid immediately prior to imaging, if the catheter is present the back should be emptied before imaging.

Breast feeding patient should stopped breast feeding 24 hours after injection of radiopharmaceuticals.

3.3.1.3 Patient positioning

Patient was laid in supine position, a pillow was placed under the patients knees for comfort if necessary as shown in Fig 4.2. Metal objects were removed (e.g. coin and keys) prior imaging.

3.3.1.4 Mode of administration of ^{99m}Tc-MDP:

From the reception hall of patient, the patient was called to hot lab for recording the name, age, weight and height upon which the dose was determined and injected intravenously (^{99m}Tc-MDP) using syringe shield and butter fly for protection purposes. Then the patient was left to stay for 2 hrs at specially waiting room. During this period the patient was allowed to have water as well as voiding.

After the intravenous administration the TC99m-MDP complex is taken up by soft tissues and accumulated in the kidneys then redistribution starts and accumulation in the skeleton increases. The maximum accumulation in the bones is reached 1 hour after administration.

3.3.1.5 Imaging Procedure:

Image was obtained after 2 to 4 hours following administration. A longer delay image is helpful in elderly patients with slower bone uptake. SPECT image technique includes anterior and posterior views of axial skeleton.

If anterior and posterior are equivocal spot views were helpful (e.g. pelvic, lateral skull views) where bladder activity obscures pelvic structures lateral or squat views were obtained or a further post void image undertaken. If the patient was unable to empty the bladder masking the retained urinary activity with lead shielding will allow improved detail in the rest of the pelvis.

Chapter Four

Results

In this chapter the researcher will present the general results dealing with the bone metastasis of breast cancer evaluated by bone scintigraphy.

The parameters will be considered are percentage of breast involvement (i.e. right or left), age, cancer secondaries from right breast, cancer secondaries from left breast and lung secondaries from both breast to complete the characterization .

Table 4.1: The percentage distribution of cancer for women breast

Breast	No.	Frequency%
Right breast cancer	74	49.3
Left breast cancer	76	50.7
Bilateral	0	0

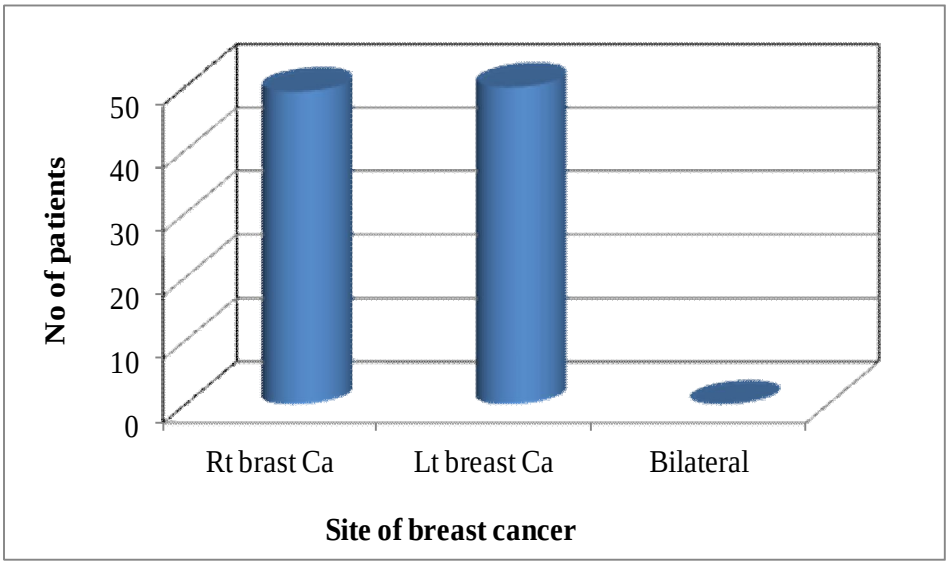

Fig 4.1: show percentage Site of breast cancer

The distribution of breast cancer among the women based on their ages is shown in Table 5.2. It is apparent that 33.3% of the sample was found to be in women with age group 40-55 years and 24% in women with age 25-40 years old.

Table 4.2: The distribution of cancer involvement based on women age

Age	No.	Frequency %
25 – 40	36	24
40 – 55	50	33.3
55 – 70	39	26
70 – 85	20	13.3
85 – 100	5	3.3
Total	150	99.9

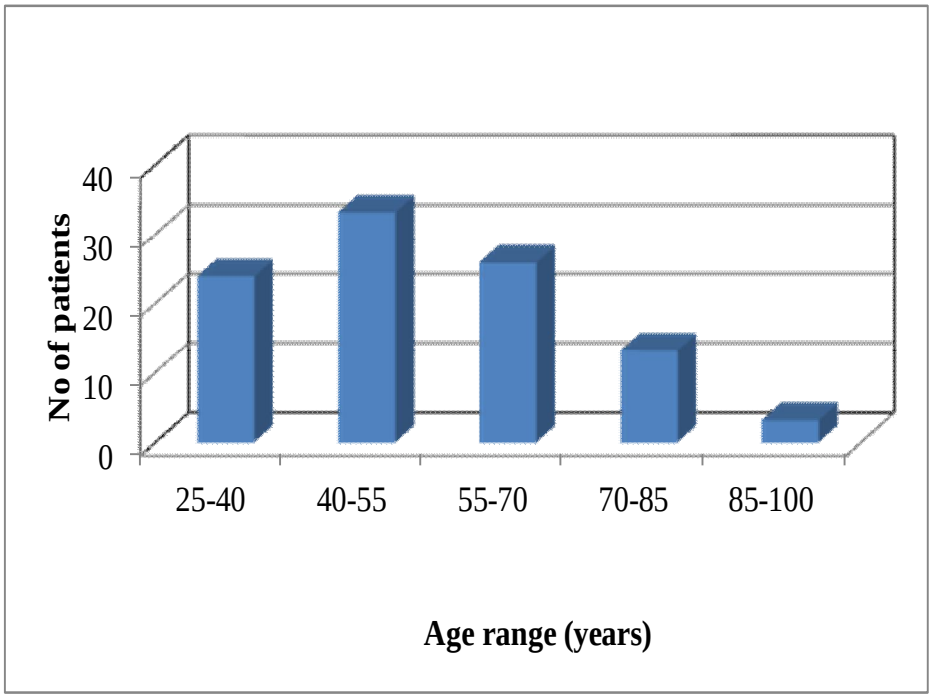

Fig 4.2: The percentage of distribution of cancer involvement based on women age.

In Table 4.3 the data shows the common regions of skeletal system where the cancer cells could be seeded to establish secondary tumors from the right breast cancer. The carcinoma of the right breast is commonly gives some considerable metastasis to the Lumber vertebrae with a percentage of 26.7%, the dorsal vertebrae with a percentage of 14%, the pelvic bone with a percentage of 10%, the cervical vertebrae with a

percentage of 8.7%, the skull with a percentage of 7.3% and femur bone with percentage of 6.7%. The results have been plotted in Fig 4.3 to enhance the easy reading and study.

Table 4.3: The common regions of cancer secondaries among women for right breast

Region of cancer secondaries	Frequency %
Skull (Sk)	7.3
Ribs (Rib)	5.3
Clavicle (clavic)	1.3
Humorous(Humrs)	1.3
Hand	1.3
Cervical vertebrae (CV)	8.7
Dorsal vertebrae (DV)	14
Lumbar vertebrae (LV)	26.7
Sacral vertebrae (SV)	6.7
Pelvic bone(Pelvic B)	10
Shoulder joint(ShJ)	1.3
Sacroiliac joint (SIJ)	2.7
Hip joint (HJ)	3.3
Knee joint (KnJ)	2.7
Femur	6.7
Tibia	3.3
Foot	1.3

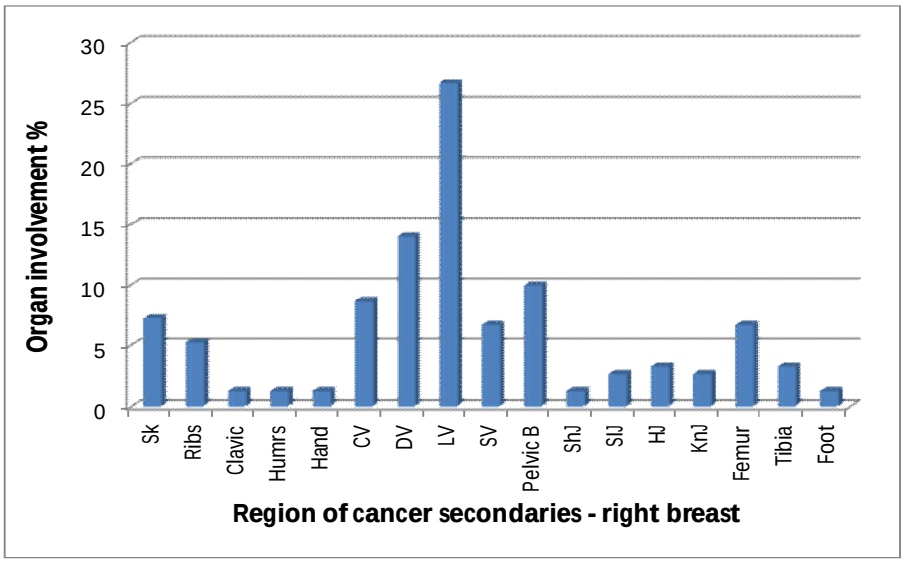

Fig 4.3: The percentage of common regions of cancer secondaries among women for right breast:

Table 4.4 presents the common regions of cancer secondaries among women for the left breast. The carcinoma of the left breast is commonly gives some considerable metastasis to the Lumber vertebrae with a percentage of 22%, the dorsal vertebrae with a percentage of 19.3%, the pelvic bone with a percentage of 12.7%, the ribs with percentage of 11.3%, the cervical vertebrae with a percentage of 10.7% and the femur bone with a percentage of 10%.

Table 4.4: The common regions of cancer secondaries among women for left breast

Region of cancer secondaries	Frequency %
Skull (Sk)	9.3
Ribs (Rib)	11.3
Clavicle (clavic)	2.7
Humorous(Humrs)	2.7
Cervical vertebrae (CV)	10.7
Dorsal vertebrae(DV)	19.3

Lumbar vertebrae (LV)	22
Sacral vertebrae (SV)	2
Pelvic bone(Pelvic B)	12.7
Shoulder joint(ShJ)	3.3
Sacroiliac joint (SIJ)	2.7
Hip joint (HJ)	1.3
Knee joint (KnJ)	2
Femur	10
Tibia	1.3

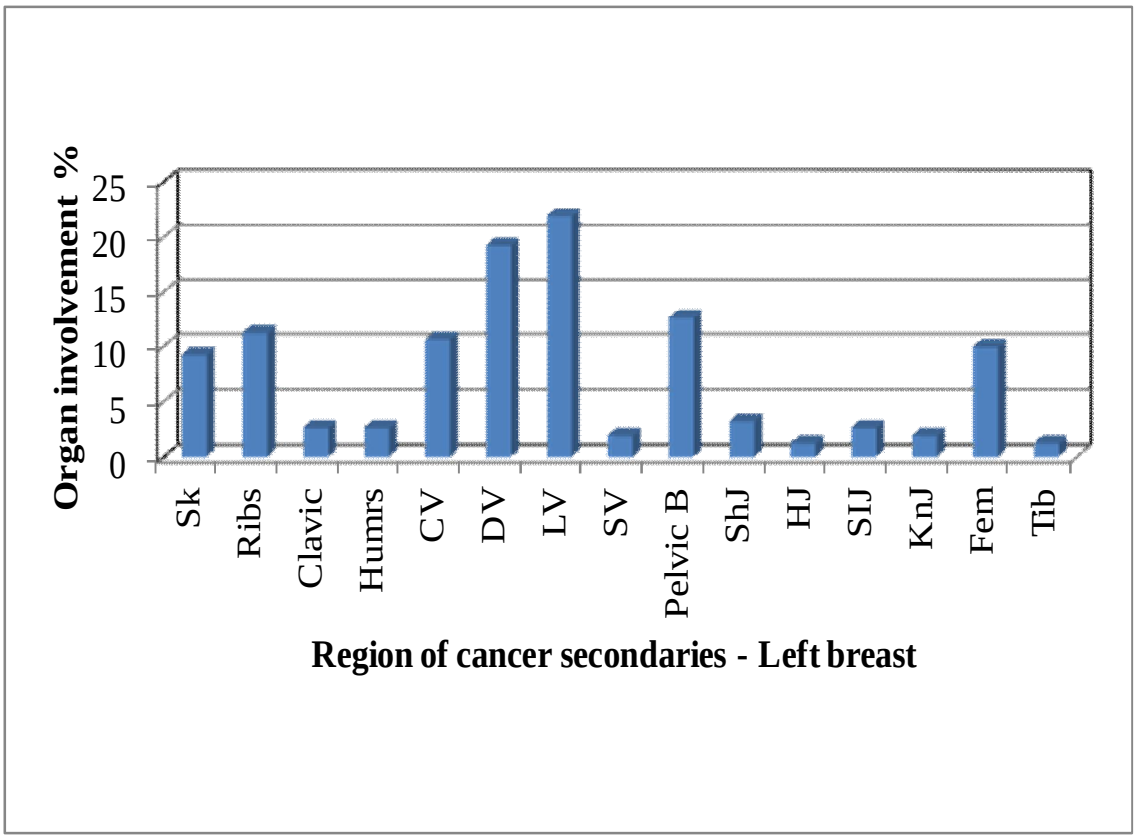

Fig 4.4: The percentage of common regions of cancer secondaries among women for left breast:

Figure 4.5 shows the metastasis percentage in organs from right and left breast cancer, In general, the metastasis from both breasts to human system have shown

same preferences; as to metastasize to certain organs higher than others i.e. the left and right breast cancer give metastasis to LV, DV and the pelvic bone as most higher than other parts of skeletal system. They also show the same phase of metastasis to other skeletal system segments, this could be due to symmetrical net of lymphatic drainage as well as the blood supply arteries and the drainage veins. The identity of both breasts cancer metastasis to general skeletal system has been shown in Fig 4.5

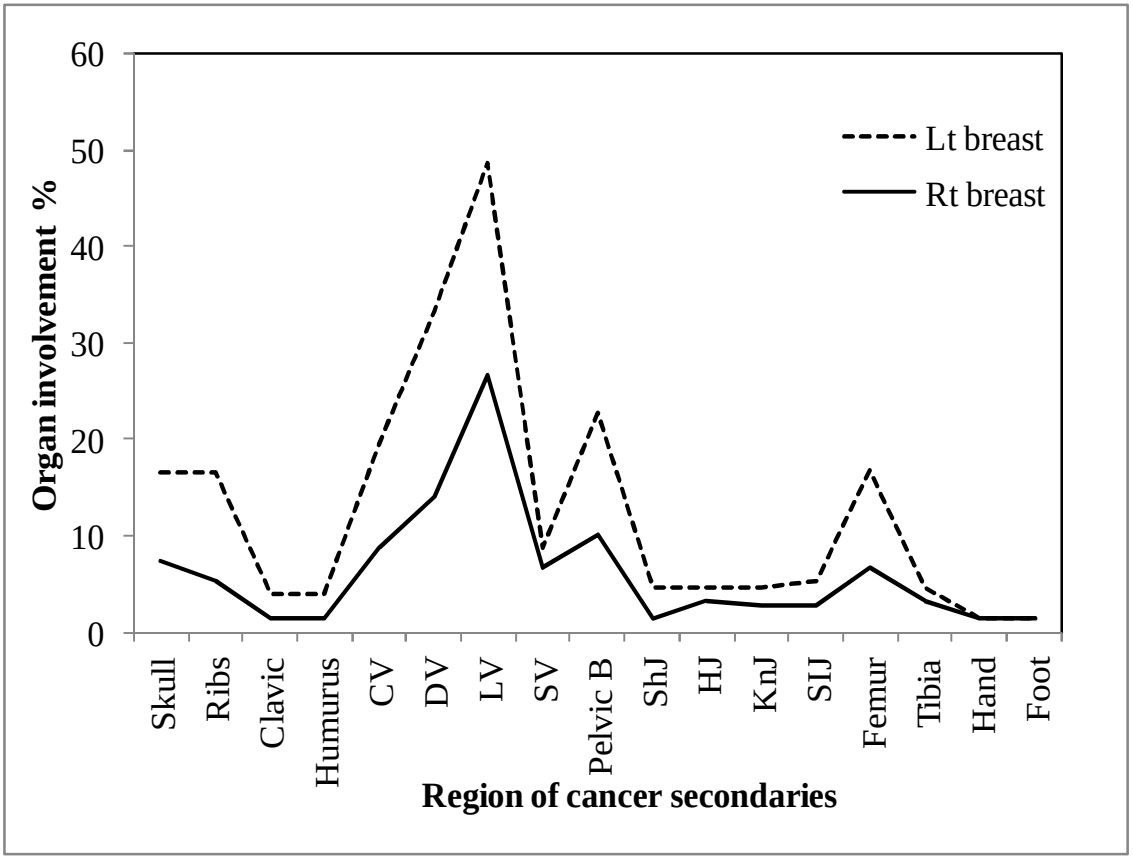

Fig 4.5: The metastasis percent on organs from right and left breast cancer

Chapter five

Discussion conclusion and recommendation

5.1 Discussion:

The results indicated that the left breast is so more susceptible to breast cancer than the right one, such evidence clearly shown in Fig 4.1 with a percentage of 50.7% greater than the right one which is 49.6% and bilateral breast cancer has zero percentage, and the result is in agreement with the document of Suliman and Ahmed (2009) which indicated that the carcinoma of the breast affects the left breast with percentage of 66% greater than the right breast which has 31% and bilateral breast cancer 3%, this result indicate that bilateral breast cancer incidence represent very small proportion of all breast carcinoma cases.

And this result have a great agreement with the study of Roida Bushra (2010) which reveal that indicated that the left breast is percentage 51.4% so more susceptible to breast cancer than the right one greater than the right one which is 48.6% and bilateral breast cancer has zero percentage from 150 patients.

On the other hand, Gonial et al (1999), reported that the incidence of bilateral breast cancer with percentage of 1.3% from 521 patients.

In developed country it was found that the breast cancer is predominant among the age group of 20-43 years old i.e. 12 % (Hicky et al, 2008).

The prevalence of breast Ca. among age group of 40-55 years old is clearly demonstrated in Fig 4.2 with a percentage of 33.3% from the general sample. This finding is in agreement with Anderson et al, (2008); they found that the breast cancer is so predominant among black women and commonly above the age of 40 years old.

The common metastatic properties from breast cancer is due to estrogen receptor positive subtypes (El Ayass et al, 2009) This finding is an agreement with the literature review which stated that the breast cancer commonly gives metastasis to bone (Salim and Alhaj, 2008), however there are some organs more susceptible to metastasis than other parts as our study shows that within the skeletal system there is most common region for secondaries such as LV, DV and Pelvic bone. The

researchers assume that the success of secondary growth is due to opportunity of the cell impaction, good climate and blood supply. Bacac and Ivan, (2008) stated that growth of secondaries is mortgaged to factors of cell growth. The routes of skeletal metastasis are direct extension or invasion, lymphatic spread, hematogenous dissemination and intraspinal spread. Skeletal metastases of breast cancer will mainly occur from lymphatic spread and hematogenous dissemination.

As its demonstrated in Fig 4.4. similar results obtained by Koizumi et al (2003) which concluded that bone is the most common sites of breast cancer secondaries. Within the skeletal system the most common region for secondaries are pelvic, upper leg bone (femur) and ribs but the spine is the most common site of bone metastasis (LV and DV). This finding is in agreement with the Gray et al, (2006) which found that the breast cancer is the most common site of origin of metastatic deposits in the skeleton and most commonly affects the spine, ribs, pelvis, and proximal long bones.

5.2 conclusions:

This study was done to characterize the secondary metastasis in a known case of female ca breast by used ^{99m} Tc-MDP bone scintigraphy, and the researcher concluding that:

The breast cancer is commonly affecting the female with age group greater than 40 and less than 60 years old and the age between 55-70 years old is considered as the second age group, ca breast able to attack the left breast more than the right one in the percentage of 50.7% to 49.3% respectively.

The carcinoma of the left breast is commonly gives some considerable metastasis to the Lumber vertebrae, dorsal vertebrae, pelvic bone, ribs, cervical vertebrae and the femur bone respectively.

The carcinoma of the right breast is commonly gives some considerable metastasis to the Lumber vertebrae, dorsal vertebrae, pelvic bone, cervical vertebrae, the skull and femur bone, the metastasis in the left and right ca breast following the same behavior in popular anatomical region in spiriting but a different percentage of anatomical region invading and the bilateral breast cancer has zero percentage from the total sample size.

5.3 Recommendations:

- A large sample size is needed for further characterization of ca breast metastasis.
- Encouraging the annual screening for women breast with low cost or free of charge.
- Bone scintigraphy should be done for women who are accused of breast cancer as well as pre/after radiation therapy cycles.
- By increasing of Ca breast in the sundaes population the nuclear medicine departments must be reducing the cost of bone scintigraphy examination.
- Using another radiological modality is useful in grading and staging of the tumor (CT scan) to represent other organs involvement.
- Using a modified technique in bone scintigraphy TC^{99m} with (MIBI) is use full in detection of other soft tissue high uptake.

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Appendix (1) represents the design of Data collection sheet

Data collection sheet

1. Patient no: ……
2. Age…..
3. Gender:

Male ☐ Female ☐

4. **The breast involvement:**

Right ☐ Left ☐ bilateral ☐

5. **Cancer secondaries from:**

Right breast ☐ Left breast ☐ bilateral ☐

6. **The common regions of cancer secondaries among women for right breast:**

Skull ☐ Shoulder.j ☐ Ribs ☐ Clavicle ☐ Humerus ☐ and ☐

C.vertebra ☐ D.vertebrae ☐ L.vertebrae ☐ S. vertebrae ☐ Pelvic ☐

Sacroiliac.j ☐ Hip j ☐ Femur ☐ Knee.j ☐ Tibia ☐ Foot ☐

7. **The common regions of cancer secondaries among women for left breast:**

Skull ☐ Shoulder.j ☐ Ribs ☐ Clavicle ☐ Humerus ☐ and ☐

C.vertebra ☐ D.vertebrae ☐ L.vertebrae ☐ S. vertebrae ☐ Pelvic ☐

Sacroiliac.j ☐ Hip j ☐ Femur ☐ Knee.j ☐ Tibia ☐ Foot ☐

Image (1): Represents normal bone scan (symmetrical uptake within skeleton)

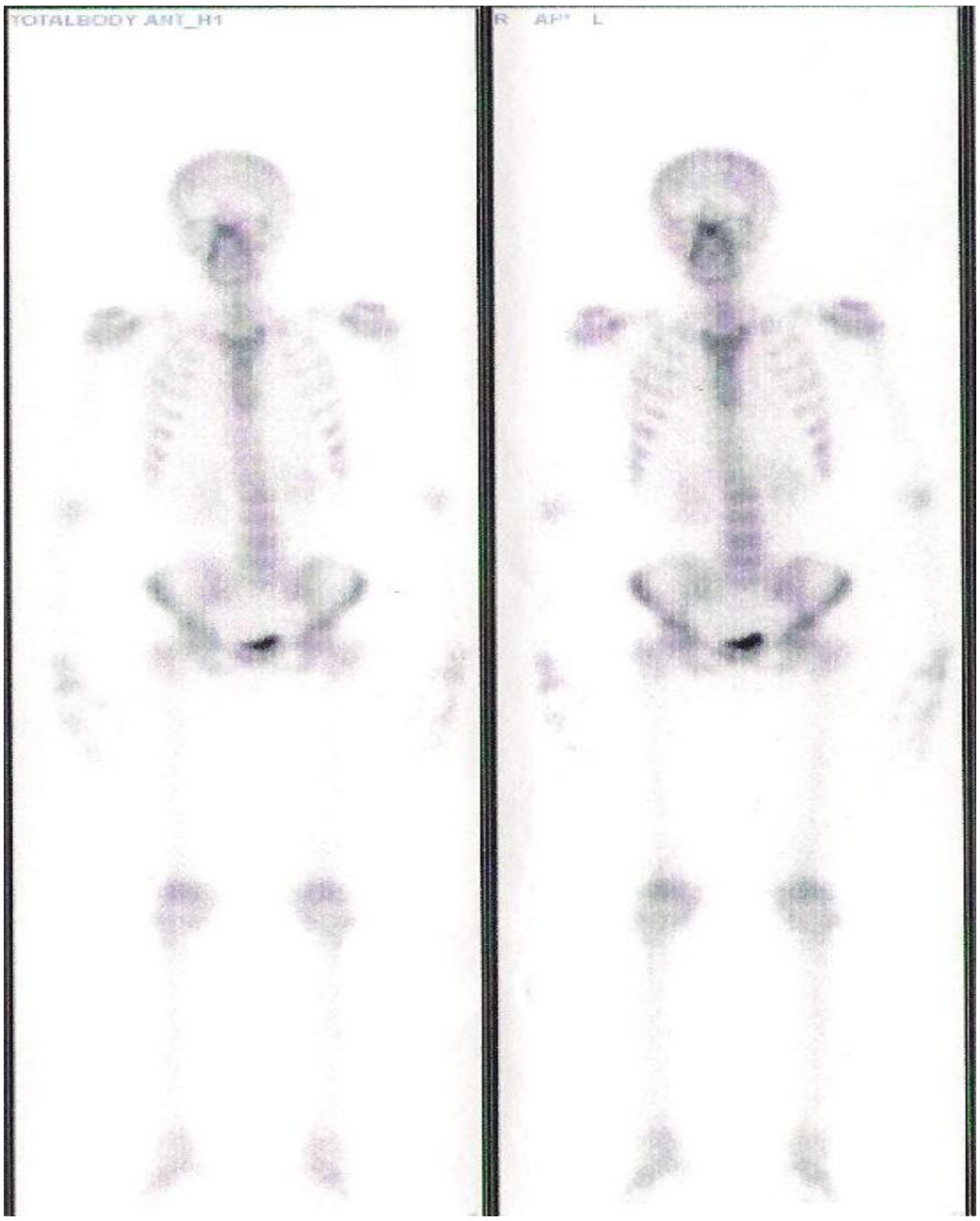

Image (2): Represents abnormal bone scan diffusely increased uptake in the skull, shoulder joint, Ribs, vertebrae, Rt knee and Rt pelvic bone. (Multiple bone metastasis)

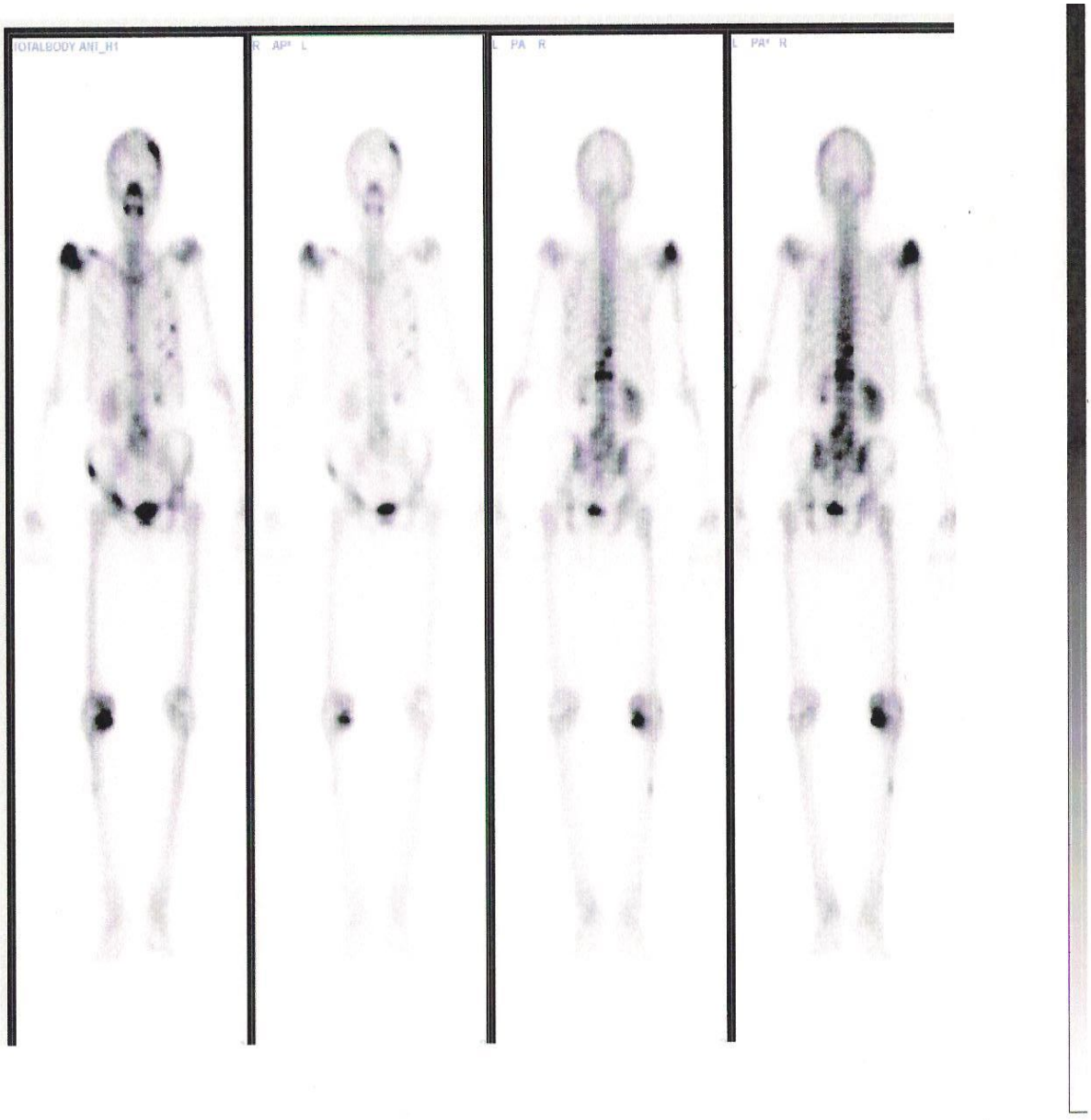

Image (3): Represent high uptake in the vertebrae, ribs, clavicle, and shoulder joint, elbow joint and iliac bone.

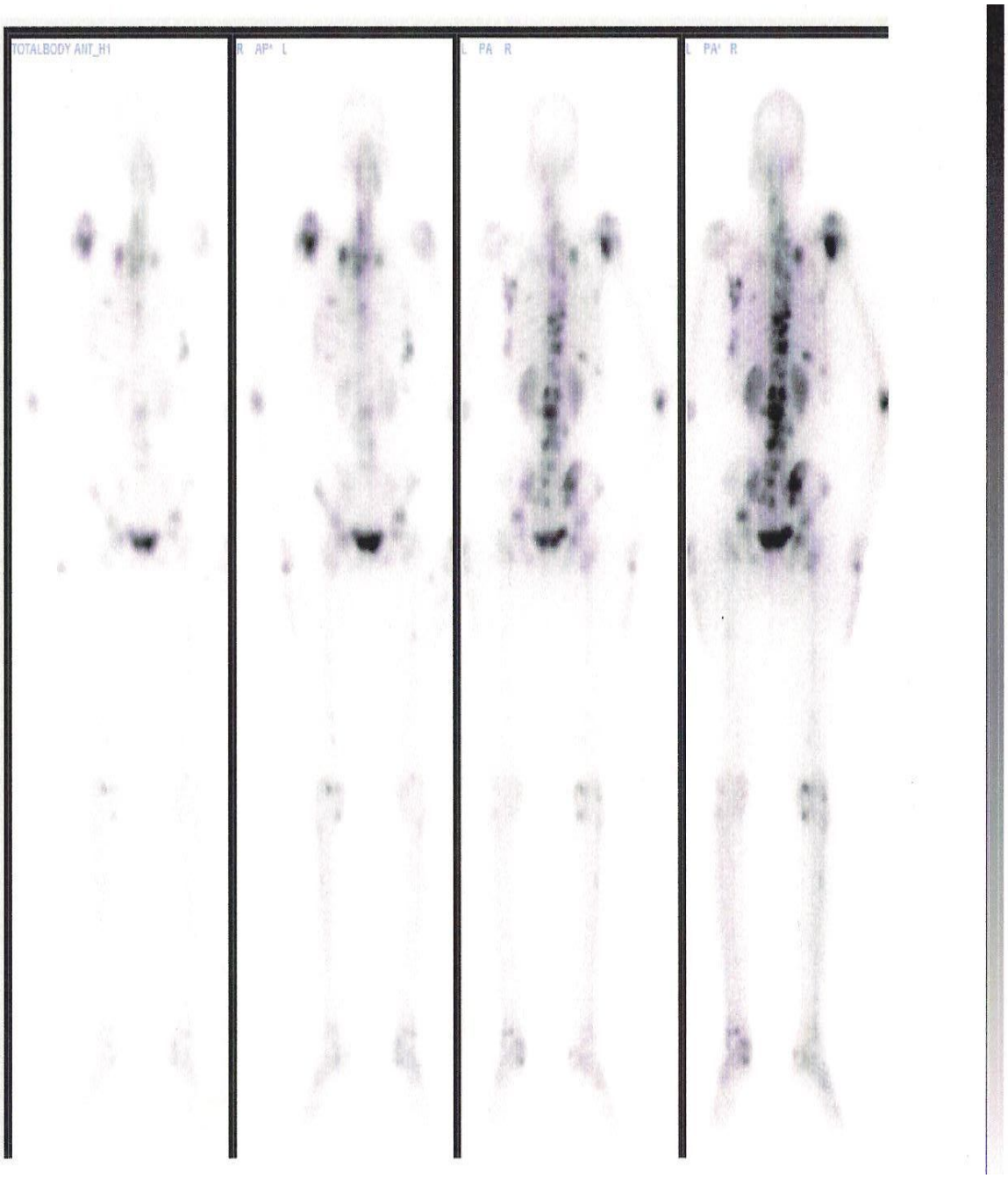

Image (4): Represent an increase in uptake skull, vertebrae, foots and pelvic bone.

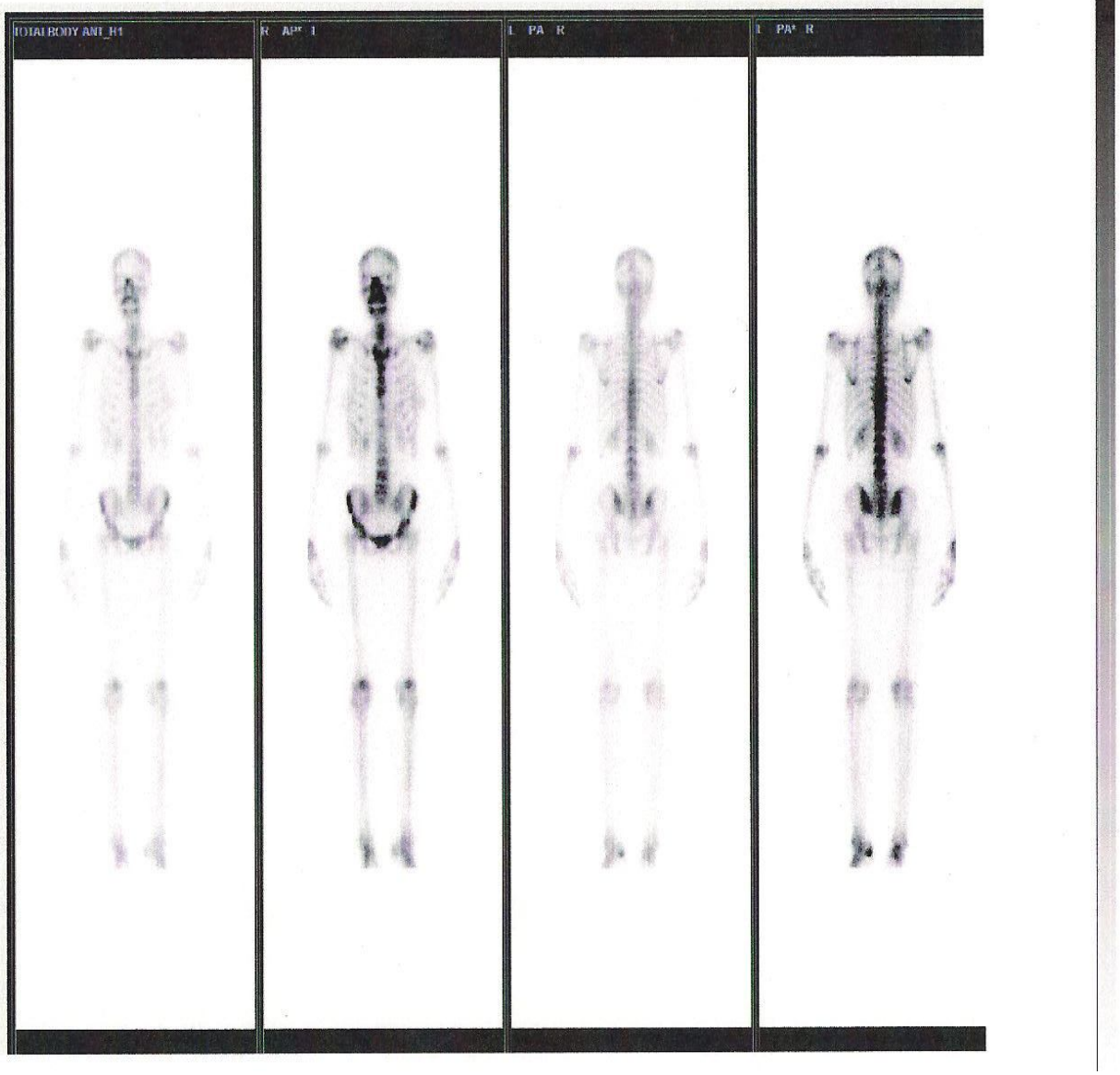

Image (5) shows the patient position for bone scintigraphy (Anderson WF.2008)