Chapter One

1.1 Introduction

Imaging of the skeleton using radioactive substances has been possible for over 40 years. Improvements in radiopharmaceuticals and instrumentation have taken place over this time, most notably the introduction of technetium-labeled phosphates in the 1970s and the development of the dual-headed gamma camera in the 1990s. However, the basic technique of the radionuclide bone scan has changed very little. Despite advances in other forms of imaging,

Bone scintigraphy is a test done in nuclear medicine department to investigate the bones for possible abnormalities in the skeletal system (***show in figure 1***).

It is primarily used to help to diagnose a number of conditions relating to bones, including: cancer of the bone or cancers that have spread (metastasized) to the bone, locating some sources of bone inflammation (e.g. bone pain such as lower back pain due to a fracture), the diagnosis of fractures that may not be visualize well in traditional X-ray images, and the detection of damage to bones due to certain infections and other problems. The indications of bone scintigraphy are to achieve the following the bone scan remains an extremely valuable diagnostic tool and is still one of the most common procedures performed in nuclear medicine departments. It has sustained its position because of several noteworthy qualities. It is exquisitely sensitive and demonstrates abnormality early in the disease process, often at a stage where no lesion is evident on plain radiographs. The whole skeleton can be imaged in a single examination which most patients can tolerate. It is widely available and comparatively inexpensive, with relatively low radiation dose compared to computed tomography (CT). There are no known contraindications. The bone scan has an oft-quoted lack of specificity, but this is

less of a problem if scan interpretation takes account of the clinical context, including the patient's age, and other available imaging. Indeed, part of its utility stems from this non-specificity, making its application appropriate and helpful in the wide variety of clinical settings.(*Mccarthy, EF, et al. 1997*).

Bone is the most common site to which breast cancer metastasizes. Between 30% and 85% of patients with metastatic breast cancer will develop bone metastases during the disease (*Solomayer et al. 2000*) Bone also represents the first site of metastasis for 26% to 50% of patients with metastatic breast cancer. Complications of bone metastasis include bone pain, pathologic fractures (the incidence of which ranges from 16% to 60%), hypocalcemia, and spinal cord compression, any of which can profoundly impair quality of life. (*Theriault RL,& Lipton A, 1998).*

Technetium-99m methylenediphosphonate (Tc-99m MDP) is one of the preferred bone-seeking agents used for the diagnosis of various malignant and benign bone diseases. It is preferentially adsorbed in immature amorphous calcium phosphate and mature hydroxyapatite crystal.(*Vinholes J et, al1996*)

Breast cancer is an abnormal cell growth, the growth of which is uncoordinated with the normal one and persists with excessive manner after the cessation of the stimuli that evoke it (*Robert J.et, al 2005*), with a tendency to metastasize to other vital organs via the circulatory system, lymphatic system, and direct invasion. The phenomena of cancer metastasize due to some properties of the cancer cell, as cancer cells show uncontrolled mitotic divisions causing unorganized growth, amebic movement, and cancer cells do not undergo differentiation. The breast cancer is commonly affecting female with a percentage rate equal to 34.5% in Sudan (*Samira A &.Magda Al 2006*), and scarcely among males 0.1%. Such high incidence of breast cancer among female also confirmed by Kathleen et al., (*Kathleen M. and Morgen M 2000*) in which they ascribed the high incidence of

female breast cancer to estrogen hormone that promotes the development of breast cancer.

Chemotherapy Treatment uses medicine to weaken and destroy cancer cells in the body, including cells at the original cancer site and any cancer cells that may have spread to another part of the body .Chemotherapy, often shortened to just "chemo, " is a systemic therapy, which means it affects the whole body by going through the bloodstream.

In this research the case under study selected by barest cancer. Chemotherapy was used to treat the early stage, invasive breast to get rid of any cancer cells that may be left behind after surgery and to reduce the risk of the recurrence, advanced stage cancer to destroy or damage the cancer cells as much as possible and in some cases, chemotherapy is given before surgery to shrink the tumor size. (*Petrie K. et Weinman J.1997)*.

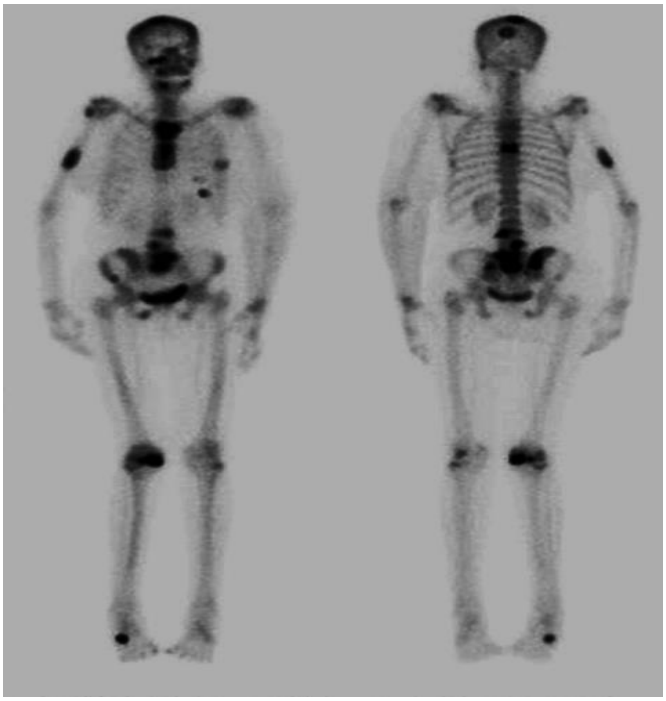

Figure 1-1: Whole-body bone scintigraphy of a patient showing multiple hot spots

1.2 Problem of the study

There are a great percentage of patients who referred to nuclear medicine department for whole body bone scan after they treated with chemotherapy, by in direct effaced of renal function there images results are not clear due to bad or poor distribution of the radiotracer on the images, this became very difficult in the interpretation of the image as well as medical decision making.

1.3 Objectives of the study

1.3.1 General objective

The general objective of this study was to evaluate the effects of chemotherapy on bone scintigraphy to enhance the reliability of the acquired image and hence the diagnostic quality.

1.3.2 Specific objective

- To determine the appropriate time for the bone scan after chemotherapy.
- To correlate between GFR and bone count and background count ratio, And how far the chemotherapy degrades this concept.
- To find the relationship between the three should limit and the elapse days after chemotherapy
- To determine the effect of chemotherapy in GFR
- To determine image quality and degree of enhancement by three should.
- To correlate between the optimum count ratio of bone scintigraphy with and without chemotherapy.

1.4 Significance of the study

This study will provide a Sudanese index (Brest under the chemotherapy treatment)

1.5 Overview of the study

The skeleton of the thesis is built upon five chapters. Chapter one is consist of the introduction, the problem of the study, general, specific objectives and significant of the study. Chapter two concerns with Literature review. Chapter three is about the methodology which includes material and method, chapter four about the result presentation, chapter five about the discussion, conclusion, recommendation, and limitations including the references and appendixes.

Chapter Two

Literature review

2.1 Anatomy of the bone

Bone is living tissue that makes up the body‘skeleton; Bones are classified by their shape aslong, short, flat, and irregular .Primarily, they are referred to as long or short. There are 206 bones in the human skeleton show in (*fig 2-1*), not including teeth and sesamoid bones 80 axial bones, which include :The head, facial, hyoid, auditory, trunk, ribs, and sternum., 126 appendicle bones, which include :arms, shoulders, wrists, hands, legs, hips, ankles, and feet.Bone is a strong and durable type of connective tissue it consists of Water (25%) Organic constituents including osteoid and bone cells 25%Inorganic constituents mainly calcium phosphate 50 (*Berkovitz A &Moxhamt. C,1988*)

The axial skeleton includes the bones of the spine, ribs and sternum, skull and facial bones, while the pelvis, scapulae and limb bones comprise the appendicular skeleton. Microscopically bone consists of a fibrous matrix, composed mainly of collagen, and a mineral matrix of inorganic salts, including calcium, phosphate, and carbonate, with the principal component being crystals of hydroxyapatite. Bone is a highly vascular, living tissue with remarkable resilience and capacity for regeneration and remodeling. Two cell types in bone perform this remodeling process: the osteoclasts, which are large phagocytes responsible for bone resorption and removal, and the osteoblasts, which form new bone. It is the synthesis of bone by osteoblasts that accounts for the accumulation of radiolabeled phosphate on a bone scan, with the radiopharmaceutical being incorporated into newly formed crystals of hydroxyapatite. This system of bone

resorption and synthesis is finely balanced and continues throughout life, with complete skeletal turnover approximately every 20 years. In normality, the process occurs diffusely in the skeleton and uptake of radionuclide is uniform and of low intensity. In disease states causing increased bone turnover, there is a greater accumulation of radionuclide concerning normal(*Semin N, 1997*)

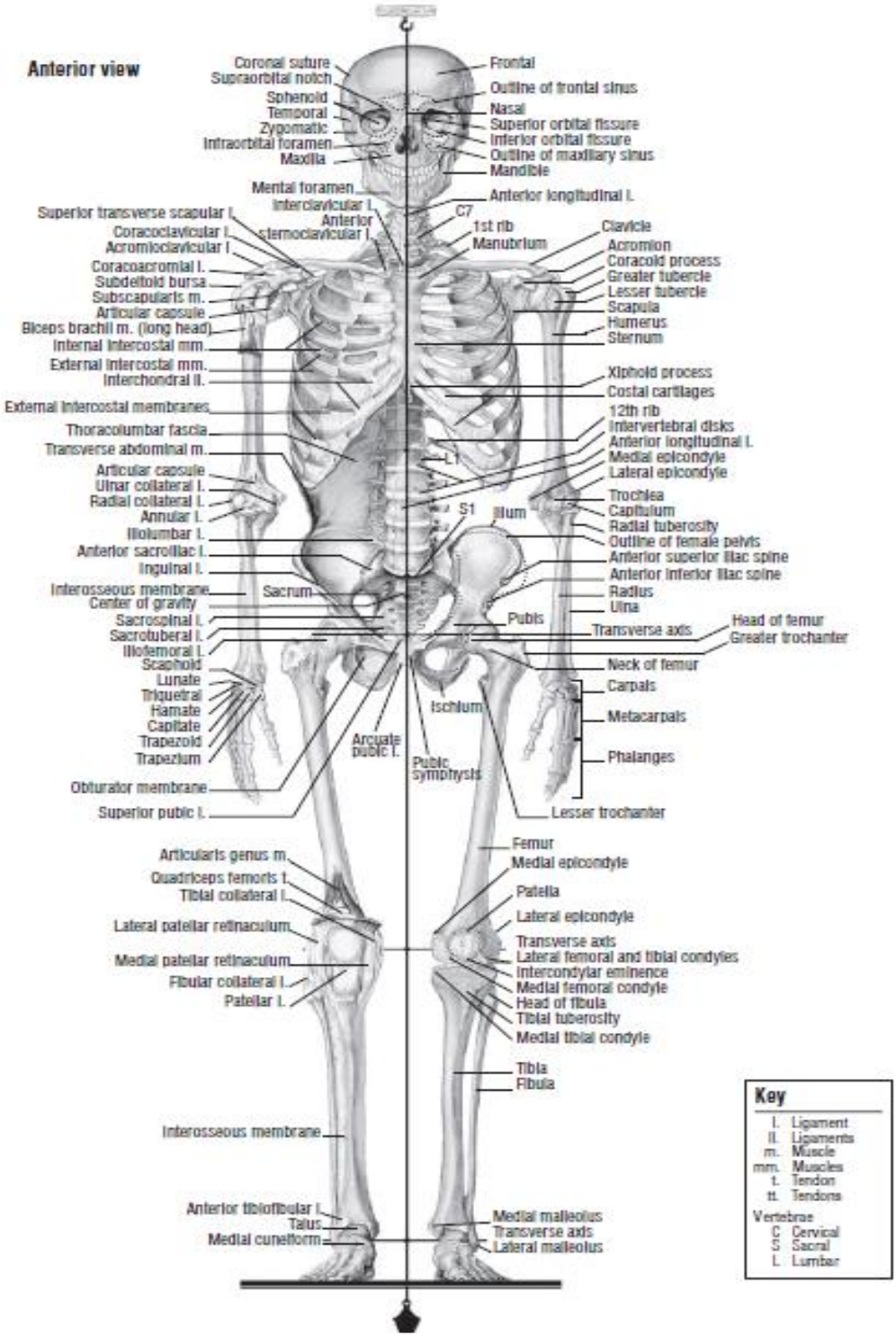

Figure 2.1Showing the skeletal system.

2.2 Physiology of the Bone

The cells responsible for bone formation are the osteopath .Osteopath and chondrocyte cartilage-forming cells develop from the same parent fibrous tissue cells .Differentiation into osteogenic cells, rather than chondroblasts, is believed to depend upon an adequate oxygen supply .This may be a factor affecting healing of fractures. These are the bone forming cells that secrete collagen and other constituents of bone tissue . Hormones that regulate the growth and consistency of size and shape of bones include the following Growth hormone and the thyroid hormones (thyroxin and triiodothyronine)are especially important during infancy and childhood Testosterone, and estrogens influence the physical changes that occur at puberty. Calcitonin from the thyroid gland and parathyroid hormone from the parathyroid glands are involved in homeostasis of blood and bone calcium levels required for bone development*(berkovitz BK and moxham BJ.1988).*

2.3. blood supply of the bone

Bones require their blood supply which travels through the periosteum to the inner bone marrow(*berkovitz BK and moxham BJ.1988).*

A dense vascular network delivers oxygen and nutrients to all 206 bones in the human body. In general, this requires a substantial portion of the total cardiac output. Experimental work in various animal species has demonstrated that a significant portion of the resting cardiac output is directed to the skeleton, likely between 10% and 15%.

For some time, the blood flow pattern in bones has been described as primarily centrifugal: blood is supplied to the cortical bone through the nutrient arteries in the marrow cavity (*Figure 2.2*) and returned by the periosteal veins. Particularly in long bones, the vascular anatomy is well characterized, with specific arterial inlets

(the main nutrient artery, periosteal arteries, metaphyseal arteries, and epiphyseal arteries) and veinous outlets, However, the structure of the vascular network can vary greatly depending on the skeletal site. For example, arteries in the greater trochanter enter from the medial, lateral, and superior surfaces to supply a vascular network within the trochanter that is functionally separated from the blood supply for the femoral neck and shaft (*Churchill MA&brookes M 1992*).

Blood Supply to the Bone Mature bones have an elaborate vascular system that supplies the cells of the marrow, bone tissue, and periosteum. Even within the dense cortical bone tissue, the organization of vascular canals ensures that no cell lies more than 300 micrometers from a blood vessel Disruptions of the blood supply to the bone due to disease, injury, or operative procedures can cause necrosis and impair healing. Thus, effective treatment of musculoskeletal injuries and good operative planning require an understanding of the blood supply to the involved bones.This is particularly important in such regions as the talus, scaphoid, tibia diaphysis. femoral head, and other epiphyses. Where trauma on an operation can easily disrupt the blood supply. The rate of blood flow varies among bones'.3, and the anatomy of the blood supply for each bone has some unique characteristics. Despite these differences. All long bones have the same general pattern of blood vessels, consisting of two circulatory systems: the pemiostealdiaphyseal-metaphyseal system and the epiphysealphyseal system. These two systems form anastomoses of variable extent on and within the periosteum and across the physes. (*Whiteside, L,1983*)

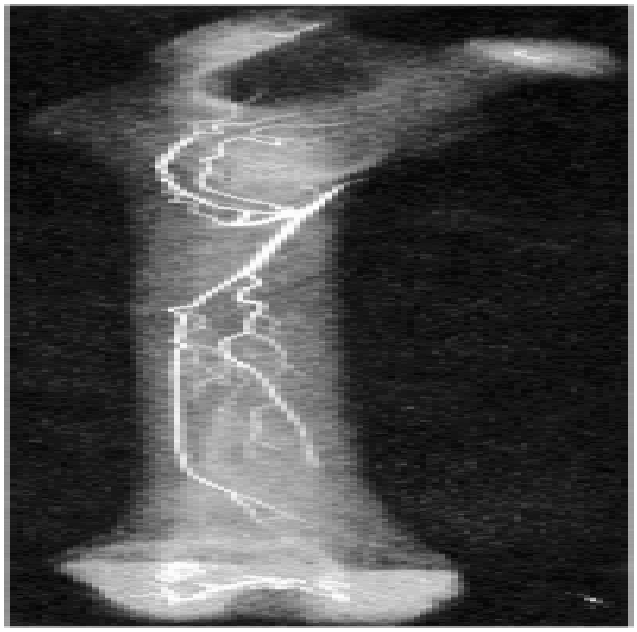

Figure 2-2Femoral blood supply. The principal nutrient artery and its main medullary branches are shown in this angiograph of a rabbit femur.

2.4. Function of bones

Provide the framework of the body, Give attachment to muscles and tendons, Permit movement of the body as a whole and of parts of the body, by forming joints that are moved by muscles, Form the boundaries of the cranial, thoracic and pelvic cavities, protecting the organs, Contain red bone marrow in which blood cells develop :haematopoiesis and Provide a reservoir of minerals, especially calcium phosphate (*Katja A and Hoehnet AS, 2007*).

2.5.Blood disorders caused by chemotherapy.

Bone marrow is the spongy tissue inside your bones. It makes new blood cells. Chemotherapy affects this process, so you might have side effects from having too few blood cells. Usually, the number of blood cells return to normal after chemotherapy is complete. But during treatment, low numbers of blood cells can cause problems and must be monitored closely.

2.6.Bone pathology

2. 6.1 Etiology of bone disease

2.6.2.Kidney Malfunction

Kidneys are largely responsible for balancing various chemicals, vitamins, and minerals in the human body; when they aren't working properly, the bones are affected .For example, vitamin D --often consumed in food or developed via sunlight exposure --balances calcium levels in the body .The kidneys then allow the vitamin D to create strong and healthy bone mass .Also, if the kidneys are malfunctioning, then the body cannot properly absorb other minerals and vitamins, such as phosphorous and aluminum, as they should .This leads to various bone diseases.(*Schwartz GJ& Furth SL 2007*).

2.6.2.Overactive Parathyroid glands

If the parathyroid glands are overactive, then they begin to create a hormone that drains calcium from bones throughout the body .Calcium is a vital element for bones and the body in general .When calcium is removed from the bones via the chemical process that occurs with overactive parathyroid glands, bones begin to weaken .This can be a very painful experienc.(Schwartz GJ& Furth SL 2007).

2.6.3Poor Bone Metabolism

Healthy bones in the human body are always breaking down and then being rebuilt to create stronger, newer bones .When your body has a healthy bone metabolism, this process goes smoothly and your bones essentially are always being recycled and turned into new bones .However, poor bone metabolism --often a result of Paget's disease --results in fragile bones that are also deformed and distorted.(*AhdjoudjS et , al,2002*)

2.6.4.Decrease in Sex Hormones

As noted before, women who are postmenopausal are especially at risk of developing a bone disease .This is because a decrease in the sexual hormone estrogen can lead to fragile bones and even bone loss .When enough estrogen isn't created or consumed via dietary supplements, then bone diseases such as osteoporosis are likely to occur.Women should consult with their doctors if they notice bone pain and should supplement their bodies with more estrogen if enough isn't being created.(*AhdjoudjS et , al,2002*) .

2.6.5.Genetics

Sometimes there's simply nothing you can do to prevent a disease, and bone diseases aren't excluded. Genetics play a major role in the development of bone disease, yet, it's possible to take preventative measures and treatment is always available .Be aware of your family history and, if the bone disease is a common ailment throughout your genial line, work closely with your physician to make sure your body is balanced and your bones are strong .

2.6.6.Osteomyelitis

Osteomyelitis is an infection of bone or bone marrow with a propensity for progression, usually caused by pyogenic bacteria or mycobacterium .It can be usefully sub classified by the causative organism, the route, duration and anatomic location of the infection .By definition, osteomyelitis is inflammation of the bone and marrow, but since it is always caused by an infection, it indirectly implies an infection (*Kumara al 2007*)

2.6.7 Osteosarcoma

Osteosarcoma is the most common type of malignant bone cancer, accounting for 35 %of primary bone malignancies .There is a preference for the metaphyseal region of long tubular bones .50 %of cases occur around the knee .It is a malignant

connective soft tissue tumor whose neoplastic cells present osteoplastic differentiation and form tumoral bone (*Osuna.A& Alava.AC 2009*)

2.7 Bone metastasis

Bone metastases, or cancer metastasis to the bone, is a major clinical concern that can cause severe pain, bone fractures, spinal cord compression, hypercalcemia, and rapid degradation in the quality of life for patients .The bone microenvironment, and the ECM in particular play a major role in the preferential metastasis by certain cancers, mainly prostate and breast cancer(*Chambers, AM . 2006*)

One metastasis are a frequent complication of cancer, occurring in up to 70 percent of patients with advanced breast or prostate cancer and in approximately 15 to 30 percent of patients with carcinoma of the lung, colon, stomach, bladder, uterus, rectum, thyroid, or kidney. The exact incidence of bone metastasis is unknown, but it is estimated that 350,000 people die with bone metastases annually in the United States.2 Furthermore, once tumors metastasize to bone, they are usually incurable: only 20 percent of patients with breast cancer are still alive five years after the discovery of bone metastasis.3 The consequences of bone metastasis are often devastating. Osteolytic metastases can cause severe pain, pathologic fractures, life-threatening hypercalcemia, spinal cord compression, and other nerve-compression syndromes. Patients with osteoblastic metastases have bone pain and pathologic fractures because of the poor quality of bone produced by the osteoblasts. For all these reasons, bone metastasis is a serious and costly complication of cancer.

2.7.1 Type of bone metastases

Metastases have been characterized as osteolytic or osteoblastic (Fig. 2.3). This classification represents two extremes of a continuum in which dysregulation of the normal bone remodeling process occurs (Fig. 2.5). Patients can have both

osteolytic and osteoblastic metastasis or mixed lesions containing both elements. Most patients with breast cancer have predominantly osteolytic lesions, although at least 15 to 20 percent of them have predominantly osteoblastic lesions.4 Also, the secondary formation of bone occurs in response to bone destruction. This reactive process makes it possible to detect osteolytic lesions using bone scanning, which identifies sites of active bone formation. Only in multiple myeloma do purely lytic bone lesions develop. In contrast, the lesions in prostate cancer are predominantly osteoblastic. However, there is also increased bone resorption in the osteoblastic lesions of prostate cancer, and agents that block bone resorption can decrease bone pain and the risk of pathologic fractures.

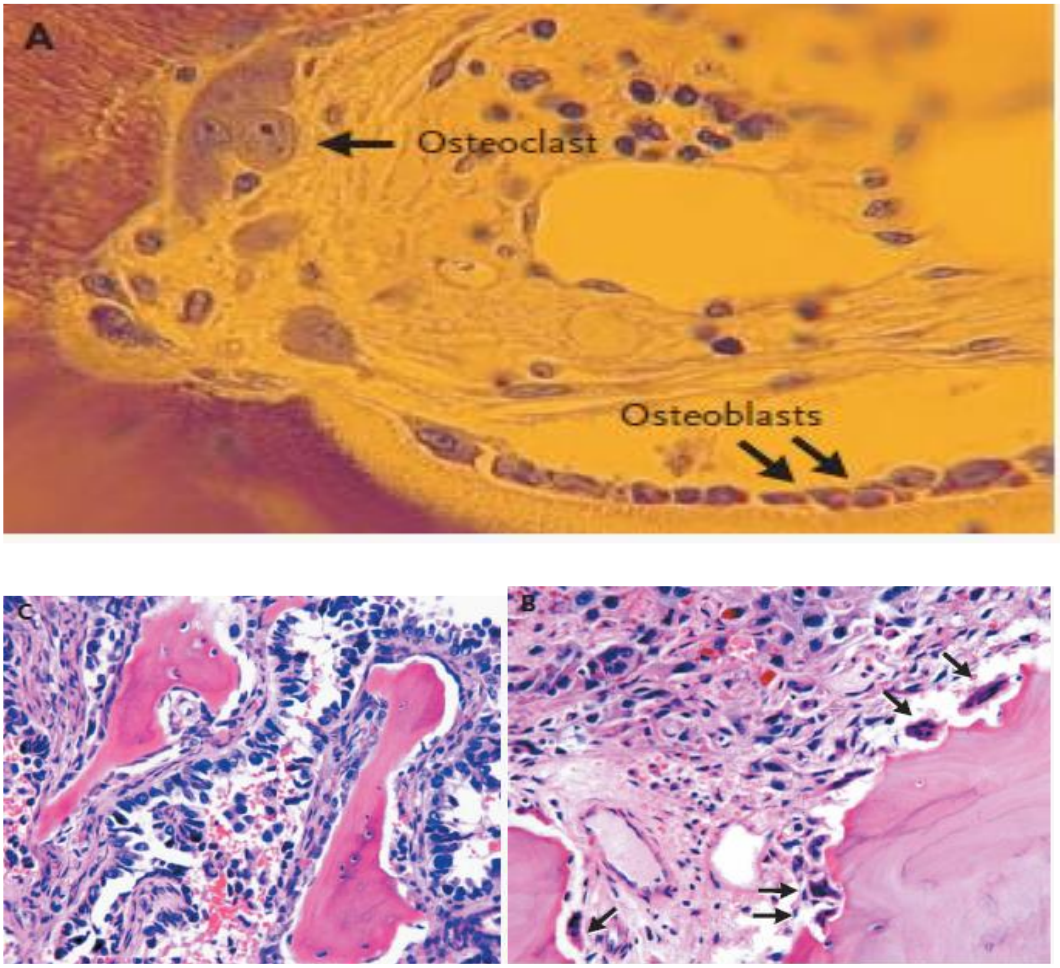

Figure 2.3 Osteoclasts and Osteoblasts in Normal Bone and Bone Metastasis.

Panel A shows osteoclasts and osteoblasts in normal bone (toluidine blue, ¬100). The large osteoclast is actively resorbing bone. Osteoblasts are small, cuboid cells that actively lay down bone matrix. Panel B shows osteolytic bone metastasis (hematoxylin and eosin, ¬200). Renal carcinoma cells are invading the bone marrow, and osteoclasts (arrows) are actively resorbing bone adjacent to the tumor cells. Panel C shows osteoblastic metastasis (hematoxylin and eosin, ¬200).

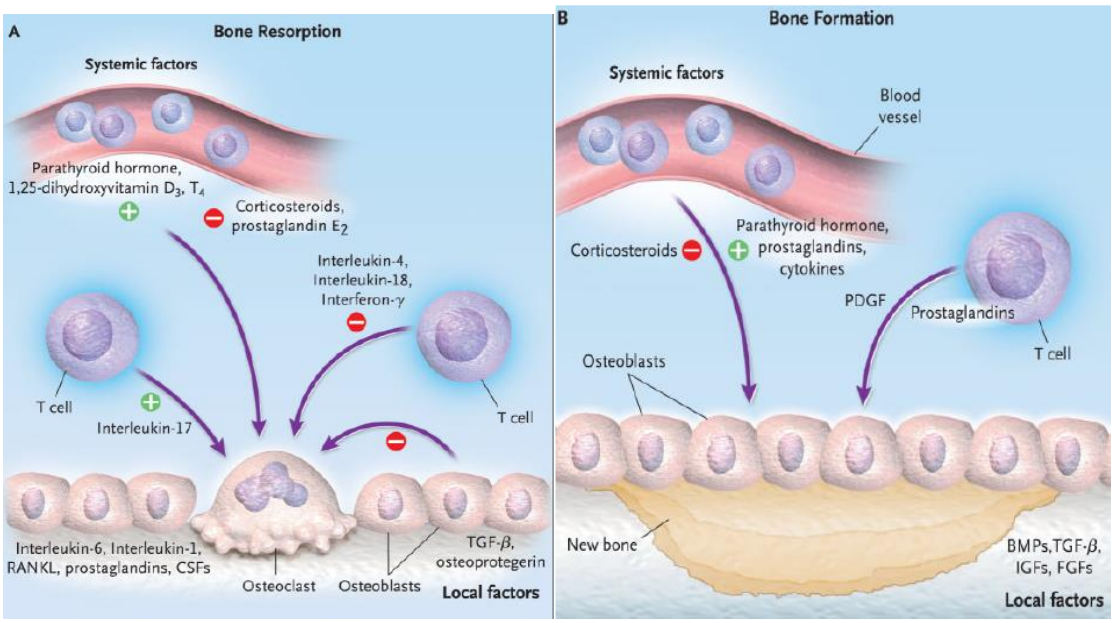

Figure 2.4 Regulation of Bone Resorption (Panel A) and Bone Formation (Panel B). Both systemic factors and locally acting factors induce the formation and activity of osteoclasts (Panel A). Systemic hormones such as parathyroid hormone, 1,25-dihydroxyvitamin D 3, and thyroxine (T 4) stimulate the formation of osteoclasts by inducing the expression of receptor activator of nuclear factorB ligand (RANKL) on marrow stromal cells and osteoblasts. Also, osteoblasts produce interleukin-6, interleukin-1, prostaglandins, and colony-stimulating factors (CSFs), which induce the formation of osteoclasts. Accessory cells such as T cells can produce cytokines that can inhibit the formation of osteoclasts, such as interleukin-4, interleukin- 18, and interferon*g*. TGF*b*denotes transforming growth factor *b*. Plus signs indicate stimulation, and minus signs inhibition.

2.7.2.bone as a preferred site of metastasis

Several factors account for the frequency of bone metastasis. Blood flow is high in areas of red marrow,7 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.8 Bone is also a large repository for immobilized growth factors, including transforming growth factor b, insulin-like growth factors I and II, fibroblast growth factors, platelet-derived growth factors,

bone morphogenetic proteins, and calcium.9 These growth factors, which are released and activated during bone resorption,10 provide fertile ground in which tumor cells can grow. This "seed-and-soil hypothesis" of the mechanism of bone metastasis was first advanced by Stephan Paget in 188911 and is supported by findings in animal models of bone metastasis.

2.7.3. control of normal bone remodeling

The adult skeleton continually turns over and remodels itself through the coordinated activity of osteoclasts and osteoblasts on trabecular surfaces and the Haversian system. In normal bone, there is a balanced remodeling sequence: first, osteoclasts resorb bone, and then osteoblasts form bone at the same site.

2.7.4.osteocytes metastasis from breast cancer the vicious circle

Tumor cells in breast cancer produce factors that directly or indirectly induce the formation of osteoclasts. In turn, bone resorption by osteoclasts releases growth factors from the bone matrix that stimulate tumor growth and bone destruction.63 This reciprocal interaction between breast-cancer cells and the bone microenvironment results in a vicious circle that increases both bone destruction and the tumor burden (Fig. 2.3). Bone is an abundant source of inactive growth factors, which are activated during the bone-resorptive process10 and which can then stimulate the growth of breast-cancer cells. Parathyroid hormone-related peptide is probably the factor produced by breast-cancer cells and most solid tumors that stimulates the formation of osteoclasts.64,65 Both parathyroid hormone-related peptide and parathyroid hormone bind the same receptor (PTHR1) and induce the expression of RANKL on marrow stromal cells. Parathyroid hormone is the main peptide regulator of calcium homeostasis, and

parathyroid hormone-related peptide has biologic effects on bone similar to those of parathyroid hormone.66 In the amino acid sequences of parathyroid hormone and parathyroid hormone-related peptide, 8 of the first 13 amino acids are identical and both peptides have similar three-dimensional structures.66 The production of parathyroid hormone-related peptide is increased in metastases of breast cancer to bone. Only 50 percent of primary breast cancers express parathyroid hormone-related peptide, whereas 92 percent of metastases of breast cancer to bone produce the peptide.67 However, it is unclear whether this difference results from induction of the peptide in the bone microenvironment or whether tumors that produce the peptide are more likely to metastasize to bone. When breast-cancer cells from patients are injected into nude mice and metastasize to bone, they increase the production of parathyroid hormone-related peptide.64 The peptide inducesthe formation of osteoclasts and bone resorption, which releases transforming growth factor b. Transforming growth factor b, in turn, further increases production of the peptide by the breast-cancer cells.68 An antibody against parathyroid hormone-related peptide is being evaluated in patients with bone metastases from breast cancer. In the vicious circle of breast-cancer metastases (**Fig.2.5**).

Bone destruction increases local calcium levels, which promotes tumor growth and the production of parathyroid hormone-related peptide.69 Breast-cancer cells also produce, or induce, interleukin-6, prostaglandin E2, macrophage colony-stimulating factor, interleukin-1, and tumor necrosis factor a, 70,71 which may also play an important role in the induction of osteoclast formation by breast cancer metastases. Prostaglandin E2 can increase the expression of RANKL and directly enhance the effects of RANKL on the formation of osteoclasts.71 Together, these data suggest that parathyroid hormone-related peptide is a major mediator of osteolytic bone destruction by breast cancer and other solid tumors.

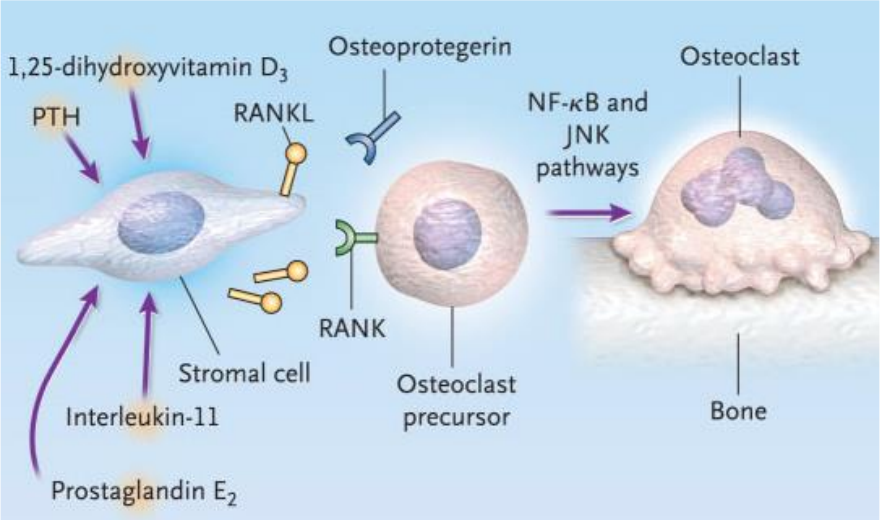

Figure 2.5.Receptor Activator of Nuclear FactorB Ligand (RANKL) and Osteoclast Formation.

2.8.Type of bone metastasis treatment:-

2.8.1.Hormone therapy

Hormone therapy drugs block the actions of certain hormones or reduce how much is made. This therapy is most often used to treat breast and prostate cancer, and it can be used when these cancers spread to the bone as well.

For instance, estrogen is a hormone that causes many breast cancers to grow. Drugs can lower estrogen levels or block the effect that estrogen has on breast cancer cells. When breast cancer has spread to the bones, this may stop cell growth and even cause tumors to shrink.

Likewise, male sex hormones, called androgens, make most prostate cancers grow. Drugs that lower androgen levels or block their effect can help stop or slow growth of these cancers.(Coleman RE and holen, I,2014)

2.8.2.Targeted therapy

Targeted therapy drugs attack specific parts of cancer cells or other cells or proteins that help cancer cells grow. These drugs work differently from standard

chemo drugs. They can be used alone or along with other treatments to treat bone metastases(Conway JL, et al02016)

2.8.3.Immunotherapy

Immunotherapy is a systemic therapy that boosts the body's immune system or uses man-made versions of immune system proteins to kill cancer cells. Immunotherapy may be used to treat bone metastases.

To see if immunotherapy is used to treat cancer you have, see information about that type of cancer.

2.8.4.Radiopharmaceuticals

Radiopharmaceuticals are a group of drugs that carry radioactive elements. These drugs are injected into a vein and settle in areas of bone with active turnover (like those containing cancer spread). Once there, the radiation they give off kills cancer cells.(Finlay IG, mason MD 2005)

If the cancer has spread to many bones, radiopharmaceuticals work better than trying to aim external beam radiation at each affected bone. (External beam radiation is discussed below as a local treatment.) In some cases, radiopharmaceuticals may be used along with external beam radiation that's aimed at the most painful bone metastases.

Some of the radiopharmaceuticals approved for use in the United States include:

-Strontium-89

– Samarium-153

-Radium-223

Treatment with a radiopharmaceutical can often reduce pain from bone metastases for several months. Re-treatment is possible when the pain returns, but the pain might not be reduced for as long as it was with the first treatment.

These drugs work best when the metastases are blastic, meaning cancer has stimulated certain bone cells (osteoblasts) to form new areas of bone.(*Howell DD et al. 2013*)

2.8.5.Other drugs for bone metastases

2.8.5.1.Bisphosphonates

Bisphosphonates are a group of drugs that may be used to treat cancer that has spread to the bones. These drugs work by slowing down the action of osteoclasts. These bone cells normally dissolve small bits of bones to help remodel them and keep them strong. But osteoclasts are often overactive when cancer spreads to the bones, which can cause problems.

Bisphosphonates can help with cancer that has spread to the bones by Reducing bone pain Slowing down the bone damage caused by cancer Reducing high blood calcium levels (hyperkalemia) Lowering the risk of broken bones Bisphosphonates tend to work better when x-rays show the metastatic cancer is thinning and weakening the bone (lytic metastases). They don’t work as well for treating blastic metastases, where the bones become denser.

The most common side effects of bisphosphonates are fatigue, fever, nausea, vomiting, anemia (a low red blood cell count), and bone or joint pain. But other drugs or cancer itself can cause many of these effects, too. These drugs can lower calcium levels, so they can't be given to someone whose calcium levels are already low. Bisphosphonates can cause kidney damage and often can't be given to people with poor kidney function.(*Howell DD et al. 2013*)

2.8.5.2.Medication-related osteonecrosis of the jaw

A rare but very serious side effect of bisphosphonates is osteonecrosis (OS-tee-o-nuh-CROW-sis) of the jaw or ONJ. In ONJ, part of the jaw bone loses its blood supply and dies. This can lead to tooth loss and infections or open sores of the jaw bone that won’t heal and are hard to treat.

ONJ is very hard to treat, and prevention is very important. ONJ sometimes seems to be triggered by having a tooth pulled while taking bisphosphonates. Many cancer doctors advise patients to get a dental check-up and have any tooth or jaw problems treated before they start taking a bisphosphonate. Maintaining good oral hygiene by flossing and brushing, making sure that dentures fit properly, and having regular dental check-ups might also help prevent ONJ.(*ringeki, panzica m 2016)*

2.8.5.3.Denosumab

Denosumab is another drug that can help when cancer spreads to bone. Like the bisphosphonates, this drug keeps osteoclasts from being turned on, but it does so in a different way, by blocking a substance called *RANKL*.

Common side effects include nausea, diarrhea, and feeling weak or tired. Like the bisphosphonates, denosumab can cause osteonecrosis of the jaw (ONJ), so doctors recommend taking the same precautions (such as having tooth and jaw problems treated before starting the drug). Unlike the bisphosphonates, this drug is safe to give to patients with kidney problems(*rosella d et al 2016*).

2.8.5.4.Local treatments for bone metastases

Local treatments, including radiation therapy, surgery, and other techniques, are directed at one part instead of the entire body.

Local treatments can be useful if cancer has spread to only one bone, or if there are areas of cancer spread that are worse than others and need to be treated right away. These treatments can help relieve pain or other symptoms caused by one or a few bone metastases.

Sometimes, local treatments such as surgery are used to stabilize a bone that's in danger of breaking because it's been weakened by cancer. It's much easier to keep a damaged bone from breaking than to try and fix it after it has broken.

2.8.6.External radiation therapy

Radiation therapy uses high-energy rays or particles to destroy cancer cells or slow their growth. When cancer has spread to a small number of spots in bones, radiation can be used to help relieve symptoms such as pain. If the bone is treated with radiation before it gets too weak, it may also help prevent a later fracture.

The most common way to give radiation to bone metastasis is to focus a beam of radiation from a machine outside the body. This is called external beam radiation.

Radiation therapy for bone metastasis can be given as 1 or 2 large doses or in smaller amounts over 5 to 10 treatments that result in a somewhat larger total dose. Both schedules give the same degree of pain relief. The major advantage of the 1- or 2-dose treatment is that fewer trips are needed for treatment. The advantage of more treatments is that patients are less likely to need re-treatment because of the pain coming back.

See our Radiation Therapy section to learn more about different kinds of external beam radiation, what it's like to get radiation and treatment side effects.

2.8.7.Ablation techniques

Putting a needle or probe right into a tumor and using heat, cold, or a chemical to destroy it is called ablation. It may be used if only 1 or 2 bone tumors are causing problems.(*Zugaro L, et al. 2016*)

2.8.8. Radiofrequency ablation (RFA)

Is a common type. It uses a needle that carries an electric current. The tip of the needle is put into the bone tumor. CT scans may be used to be sure the needle is in the right place. An electric current is then sent through the needle to heats the tumor to destroy it. RFA is usually done while the patient is under general anesthesia (deeply asleep and not able to feel pain).

In another type of ablation, called cryoablation, a very cold probe is put into the tumor to freeze it, killing the cancer cells. Other methods use alcohol to kill the

cells or other ways to heat the tumor (such as laser-induced interstitial thermotherapy). After the cancer tissue is destroyed, the space left behind may be filled with bone cement .(*Zugaro L et al 2016*).

2.8.9. Bone cement

Another option to strengthen and stabilize a bone is to use injections of quick-setting bone cement or glue called PMMA.When (PMMA) is injected into a spinal bone, it's called vertebroplasty or kyphoplasty. This helps stabilize the bone and relieves pain in most people. Vertebroplasty often reduces pain right away and can be done in an outpatient setting.

When the bone cement is injected to strengthen bones other than the spine, it's called cementoplasty. Sometimes, it's used along with surgery, radiation, radiofrequency ablation, or other treatments.(*Liu xw, et al 2016*)

2.8.10. Surgery

Surgery used to treat a bone metastasis is done to relieve symptoms and stabilize the bone to prevent fractures (breaks).

Bone metastases can weaken bones, leading to fractures that tend to heal very poorly. Surgery can be done to put in screws, rods, pins, plates, cages, or other devices to make the bone more stable and help prevent fractures. If the bone is already broken, surgery can often relieve pain quickly and help the patient return to their usual activities.

Sometimes a person can't have surgery because of poor general health, other complications of cancer, or side effects of other treatments. If doctors can't surgically reinforce a bone that has metastasis, a cast or splint may help stabilize it to reduce pain so the person can move around.

2.8.11.Clinical trials

Clinical trials are carefully controlled research studies that are done with patients who volunteer for them. If you would like to take part in a clinical trial, you should

start by asking your doctor if your clinic or hospital conducts clinical trials. You can also call our clinical trials matching service for a list of clinical trials that meet your medical needs.

Clinical trials are one way to get state-of-the-art cancer treatment. In some cases, they may be the only way to get access to newer treatments. They are also the only way for doctors to learn better methods to treat cancer. Still, they're not right for everyone.

2.9. The breast anatomy

Is one of two prominences located in the upper ventral region of the torso of primates. In females, it serves as the mammary gland, which produces and secretes milk and feeds infants. Both females and males develop breasts from the same embryological tissues. At puberty, estrogens, in conjunction with growth hormone, cause breast development in females.

Subcutaneous fat covers and envelops a network of ducts that converge on the nipple, and these tissues give the breast its size and shape. At the ends of the ducts are lobules, or clusters of alveoli, where milk is produced and stored in response to hormonal signals. During pregnancy, the breast responds to a complex interaction of hormones, including estrogens, progesterone, and prolactin, that mediate the completion of its development, namely lobuloalveolar maturation, in preparation of lactation and breastfeeding.

Along with their major function in providing nutrition for infants, female breasts have social and sexual characteristics. Breasts have been featured in notable ancient and modern sculpture, art, and photography. Female breasts can figure prominently in a woman's perception of her body image and sexual attractiveness. Some Western cultures associate breasts with sexuality and tend to regard bare breasts in public as immodest or indecent. Breasts and especially the nipples are an erogenous zone on women(*Adam W.M. Mitchell 2005*)

2.10.Chemotherapy for breast cancer

Chemotherapy (chemo) is treatment with cancer-killing drugs that may be given intravenously (injected into your vein) or by mouth. The drugs travel through the bloodstream to reach cancer cells in most parts of the body.Occasionally, chemo may be given directly into the spinal fluid which surrounds the brain and spinal cord.

Not all women with breast cancer will need chemo, but there are several situations in which chemo may be recommended:(*Callahan RD and Ganz PA 2014*)

2.10.1. After surgery (adjuvant chemotherapy):

Adjuvant chemo is used to try to kill any cancer cells that might have been left behind or have spread but can't be seen, even on imaging tests. If these cells were allowed to grow, they could form new tumors in other places in the body. Adjuvant chemo can lower the risk of breast cancer coming back .(*Dang C and Hudis CA 2014)*

2.10.2.Before surgery (neoadjuvant chemotherapy):

Neoadjuvant chemo can be used to try to shrink the tumor so it can be removed with less extensive surgery. Because of this, neoadjuvant chemo is often used to treat cancers that are too big to be removed by surgery at the time of diagnosis (called locally advanced cancers). Also, by giving chemo before the tumor is removed, doctors can better see how cancer responds to it. If the first set of chemo drugs doesn't shrink the tumor, your doctor will know that other drugs are needed.It should also kill any cancer cells that have spread but can't be seen. Just like adjuvant chemo, neoadjuvant chemo can lower the risk of breast cancer coming back.

2.10.3.For advanced breast cancer:

Chemo can be used as the main treatment for women whose cancer has spread outside the breast and underarm area, either when it diagnosed or after initial treatments.The length of treatment depends on how well the chemo is working and how well you tolerate it.

Sometimes it is not clear if chemotherapy will be helpful. There are tests available, such as Oncotype DX and Mammoprint, that can help determine which women will most likely benefit from chemo after breast surgery. See Breast Cancer Gene Expression Tests for more information. (*Morrow M, et, al 2009)*

The most common drugs used for adjuvant and neoadjuvant chemo include ,Anthracyclines,suchas doxorubicin (Adriamycin) and epirubicin (Ellence),Taxanes, such as paclitaxel (Taxol) and docetaxel (Taxotere),5-fluorouracil (5-FU),Cyclophosphamide (Cytoxan),Carboplatin (Paraplatin),Most often, combinations of22 or 3 of these drugs are used.*(Osborne CK,2015*)

2.10.4.Cisplatin:-

Continues to play a central role in cancer chemotherapy in spite of its toxicity. It is used as first-line chemotherapy against epithelial malignancies of lung, ovarian, bladder, testicular, head and neck, esophageal, gastric, colon and pancreatic but also as second- and third-line treatment against a number of metastatic malignancies including cancers of the breast, melanoma, prostate, mesothelioma, leiomyosarcomas, malignant gliomas and others. Cisplatin has become the standard gold treatment against cervical cancer in combination with radiotherapy. This review summarizes the state of the art in clinical trials published mainly in 2002 using cisplatin and carboplatin in their combinations with other anticancer drugs. For most advanced cancers the response rate to chemotherapy is about 50% in first-line treatments and about 15% in second- or third-line treatments; for example response rates of 25-50% have been observed for chemo-naive patients

with advanced non-small cell lung cancer treated with cisplatin or carboplatin in combination with gemcitabine or taxanes and in exceptional cases these rates are up to 80% with addition of radiotherapy. Response rates are very discouraging in second- or third-line chemotherapy treatments (7-25%). Despite an increase in response rate from the use of modern-day chemotherapy drugs, no major difference in long-term survival has been achieved. It is a high priority to invent novel approaches for cancer treatment. It is hoped that a fraction of the numerous experimental drugs will show virtues in the anticancer arena especially combined with existing treatment regimens. Efforts should focus on the diminution of side effects improving the quality of life of the patient. A preferential tumor targeting of chemotherapy treatments would bring a revolution in molecular medicine and would greatly advance cancer therapy in the upcoming years.

2.10.5.Cisplatin combinations in breast cancer

The combination of gemcitabine and cisplatin has proven effective as first-line chemotherapy for patients with breast cancer, inducing a response rate of 80% in one phase II study. Five additional studies as second or third-line chemotherapies in breast cancer patients demonstrated a median response rate of 43% with a moderate toxicity profile, particularly for patients whose disease progressed after treatment with anthracyclines and taxanes (*Heinemann V,2002*).

Eliminating minimal residual disease in breast cancer patients and with the aim to achieve the highest rate of complete response to enhance disease-free survival is a challenge in the treatment of advanced or metastatic breast cancer. In a phase II trial, 60 women with metastatic breast cancer and at least a partial response to induction chemotherapy received three separate high-dose cycles of chemotherapy with peripheral blood progenitor support and G-CSF. The first intensification was paclitaxel (825 mg/m2), the second melphalan (180 mg/m2) and the third consisted of cyclophosphamide 6,000 mg/m2 (1,500 mg/m2 /day x 4), thiotepa 500

mg/m2 (125 mg/m2 /day x 4) and c 800 mg/m2 (200 mg/m2 /day x 4) (CTCb). Following the paclitaxel infusion, most patients developed a reversible, predominantly sensory polyneuropathy. Of the 30 patients with measurable disease, 12 converted to CR, nine converted to a PR, and 5 had a further PR, giving an overall response rate of 87%. The toxic death rate was 5% (*Vahdat LT, et, al 2002*).

Both paclitaxel and cisplatin are active as second-line chemotherapy for patients with breast carcinoma. A synergistic cytotoxicity of these two drugs has been demonstrated in vitro. A phase II clinical trial using 175 mg/m2 paclitaxel as 3-h infusion plus 50 mg/m2 cisplatin as the 24-h infusion every three weeks was administered as first-line chemotherapy; when appropriate, chemotherapy was followed by resection of the primary tumor (mastectomy) and adjuvant radiotherapy. There were three complete responses (CRs) and 24 partial responses (PRs) among 46 patients, for an overall response rate of 58.7%. Grade 3-4 nausea and emesis and grade 3-4 myelosuppression occurred in 6 and four patients, respectively (*Hsu C et al. 2002)*

2.10.6.Cisplatin Cellular Mechanisms:-

Platinum complexes are clinically used as an adjuvant therapy for cancers aiming to induce tumor cell death. Depending on cell type and concentration, cisplatin induces cytotoxicity, e.g., by interference with transcription and DNA replication mechanisms. Additionally, cisplatin damages tumors via induction of apoptosis, mediated by the activation of various signal transduction pathways, including calcium signaling, death receptor signaling, and the activation of mitochondrial pathways. Unfortunately, neither cytotoxicity nor apoptosis is exclusively induced in cancer cells. Thus, cisplatin might also lead to diverse side-effects such as neuro- and renal-toxicity or bone marrow-suppression. Moreover, the binding of cisplatin to proteins and enzymes may modulate its biochemical

mechanism of action. While a combination-chemotherapy with cisplatin is a cornerstone for the treatment of multiple cancers, the challenge is that cancer cells could become cisplatin-resistant. Numerous mechanisms of cisplatin resistance were described including changes in cellular uptake, drug efflux, increased detoxification, inhibition of apoptosis and increased DNA repair. To minimize cisplatin resistance, combinatorial therapies were developed and had proven more effective to defeat cancers. Thus, understanding of the biochemical mechanisms triggered by cisplatin in tumor cells may lead to the design of more efficient platinum derivates (or other drugs) and might provide new therapeutic strategies and reduce side effects.(*Frezza, M. et al. 2010*)

2.11.Anatomy and physiology of the kidneys

The kidneys are part of the urinary system. There are two kidneys deep inside the upper part of the abdomen, one on either side of the spine under the lower ribs. The left kidney is slightly higher than the right kidney.

There is an adrenal gland just above each kidney. These glands are part of the body's endocrine system, which is the group of glands and cells in the body that make and release hormones into the blood. These hormones control many functions such as growth, reproduction, sleep, hunger, and metabolism shows in (*fig 2.6*).

The ureters are thin tubes about 25–30 cm (10–12 inches) long that connect the kidneys to the bladder. The urethra is a small tube that connects the bladder to the outside of the body(*Martini FH et, al,2002*).

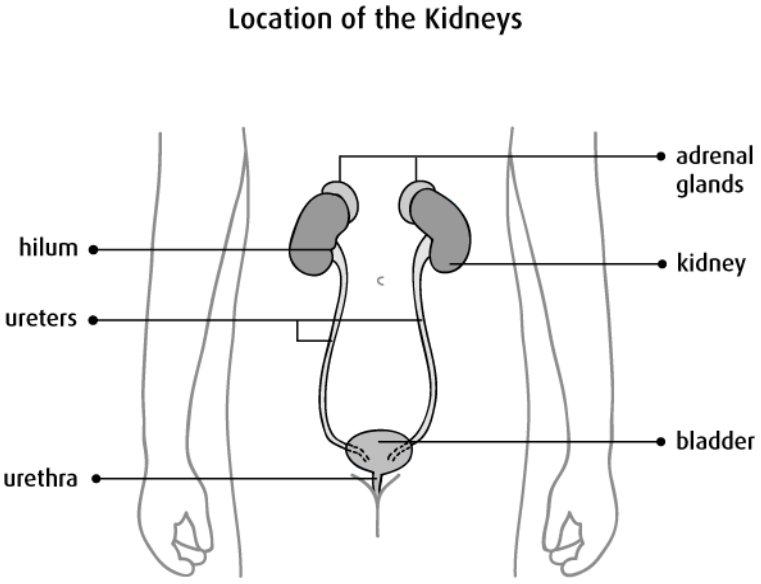

Fig 2.6 location of the kidneys

2.11.1. Structure

The kidneys are bean-shaped organs, about the size of one's fist. An adult kidney is about 12 cm (4–5 inches) long, 6 cm (2–3 inches) wide and 3 cm (1–2 inches) thick.

Each kidney is surrounded by the renal capsule, which is a layer of fibrous tissue. A layer of fatty tissue holds the kidneys in place against the muscle at the back of the abdomen. Outside the layer of fat is Gerota's fascia, or renal fascia. It is a thin, fibrous tissue shows in (*fig 2.7***)**.

The inside of the kidney is made up of an outer part called the cortex, and an inner part called the medulla. The renal pelvis is a hollow, funnel-shaped area in the center of each kidney where urine collects(*Martini FH et, al,2002).*

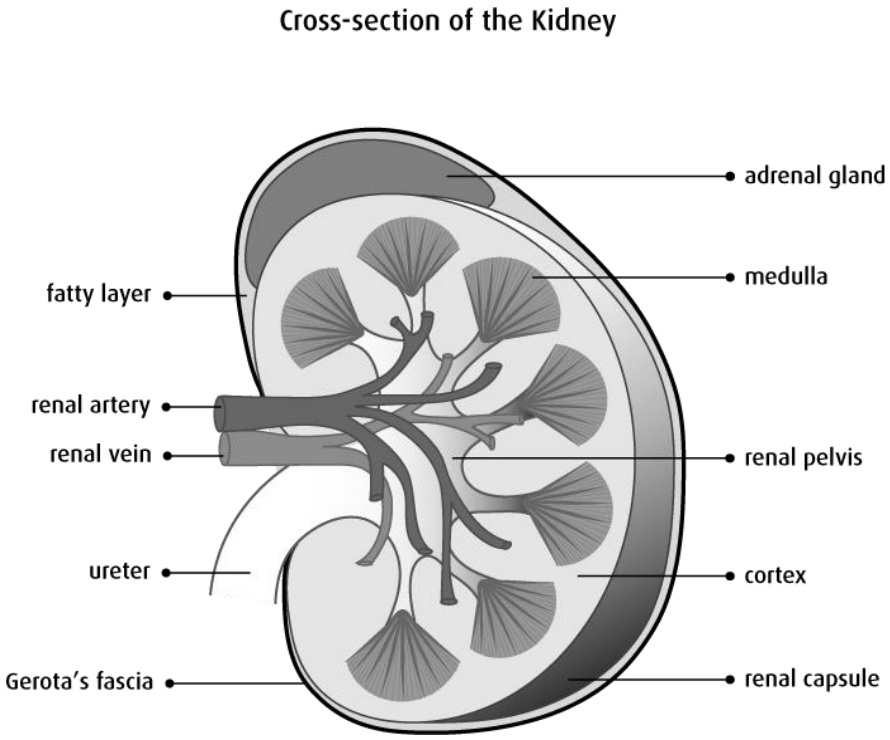

Figure 2.7 shows cross-section of kidney

The renal artery brings blood to the kidney, and the renal vein takes blood away from the kidney. The area where the renal artery, renal vein, and ureter enter the kidney is called the renal hilum.

Inside each kidney is a network of millions of small tubes called nephrons. Each nephron has corpuscles and tubules. The corpuscles contain tiny blood vessels called glomeruli that filter the blood. A glomerulus is surrounded by a layer of cells called Bowman's capsule. Tubules are tiny tubes that collect the waste materials and chemicals from the blood as it moves through the kidney(*Martini FH et, al,2002).*

2.11.2. Function

The main function of the kidneys is to filter extra water, impurities, and wastes from the blood.

Blood from the body enters the kidneys through the renal arteries. The blood passes through the nephrons, where waste products and extra water are removed. The clean blood is returned to the body through the renal veins.

The waste products filtered from the blood are then concentrated into the urine. The urine is collected in the renal pelvis. The ureters move the urine to the bladder, where it is stored. Urine travels from the bladder and out of the body through the urethra.

The kidneys also make certain hormones, which are substances that control certain body functions. Hormones made by the kidneys are:

- Erythropoietin (EPO) stimulates the bone marrow to make red blood cells.
- Calcitriol, a form of vitamin D, helps the intestines absorb calcium from the diet, Renin helps control blood pressure(*Martini FH et, al,2002)*.

2.11.3.Evaluation of kidney function in cancer patients

It is important to remember that the nephrotoxic potential of most anti-cancer agents is dramatically increased in the presence of borderline or overt preexisting chronic kidney disease and the presence of concomitant comorbidities
such as heart failure and sepsis. In some cases, this may be explained by the altered pharmacokinetics of drugs predominantly excreted by the kidneys, but in other circumstances, the reasons for this potentiation are unclear (*Safirstein RL. 2007*) Evaluation of renal function is therefore of utmost importance in the cancer patient before any treatment is initiated. This is all the more important because of the well-known decline in renal function with age and the increasing prevalence of elderly cancer patients (*Janus N et al.,2009*). Primarily for reasons of convenience, the most common

Method for evaluation of renal function is at present the estimation of the patient's glomerular filtration rate by equations (e.g., Cockcroft-Gault, the abbreviated MDRD, and CKD-EPI) based upon a stable Cr concentration. The caveats associated with the use of these formulae in cancer patients have previously been discussed (*Lameire N,2008*) The SCr concentration may be falsely low in cancer patients owing to cachexia, low muscular mass or fluid overload, which may lead to substantial errors in the estimation of the GFR. Despite these limitations, the abbreviated MDRD formula has become the reference method in cancer patients (Dietz K et al2008). Using this formula, a study of 4684 adults (mean age 58 years) undergoing treatment for cancer in 15 French centres [the Renal Insufficiency and Anticancer Medications (IRMA) study] found that 50–60% had biochemical evidence of impaired glomerular function (*Bauchmuller K et al.,2007*) Of the patients who were treated with an anti-cancer drug, 79.9% received at least one drug that required a dosage adjustment or for which there were no data for use in patients with renal insufficiency and 80.1% received at least one drug that was potentially nephrotoxic. The Belgian Renal Insufficiency and Anticancer Medications (BIRMA) study including 1137 cancer patients with solid tumours and in whom an SCr was available found a prevalence of an elevated SCr≥ 1.2 mg % (≥106 μmol/L) of 14.9%, but 64.0% had an eGFR≤ 90 mL min/per 1.73 m2 (Byloos E et al.2010) This apparently ‘high’ prevalence of ‘disturbed kidney function’ should be corrected since it is well known that the eGFR estimated by MDRD is not reliable for accurate calculation of GFR above a value of 60 mL/min 1.73 m2. Classifying only patients with an eGFR< 60 mL/min as having CKD, the prevalence of ‘true’ CKD in the BIRMA.

2.11.4.GFR calculation:-

In adults, the normal GFR number is more than 90. GFR declines with age, even in people without kidney disease.See chart below for average estimated GFR based on age show in (table2.1)

Age (years)	Average estimated GFR
20–29	116
30–39	107
40–49	99
50–59	93
60–69	85
70+	75

Table no 2.1 Normal rang in depend calculate in this study.

2.11.5.eGFR And Chemotherapy

Chemotherapeutic agents, such as carboplatin, are eliminated from the body mainly via glomerular filtration. GFR correlates strongly with renal clearance of carboplatin *(Ekhart C, 2006)*.

Consequently, it is essential to individualize chemotherapy dosages during courses of treatment to the patient's underlying renal function to optimize treatment. Submaximal chemotherapy dosages can be avoided for patients with high carboplatin clearance and can also prevent overdosing of patients with reduced clearance. Significant drops in GFR can occur during treatment because of the nephrotoxic nature of the therapies, and thesedrops can be chronic or acute. Chemotherapy doses are hence based on the patient's GFRresults(*Gumbrell LA et*

al,2008). The GFR-based Calvert formula (1), which is commonly used clinically for chemotherapy dosing, is as follows:

Eq= Dose 5* target AUC *ðGFR 1 25Þ;.

2.12.Gamma camera : -

A gamma camera was used for imaging the tracer within the patient, and which is consists of one or more flat crystal planes or, detectors, optically coupled to an array of photomultiplier tubes, the assembly is known as a "head," mounted on a gantry .The gantry is connected to a computer system that both controls the operation of the camera as well as acquisition and storage of acquired images (*Dougherty G,2009*)

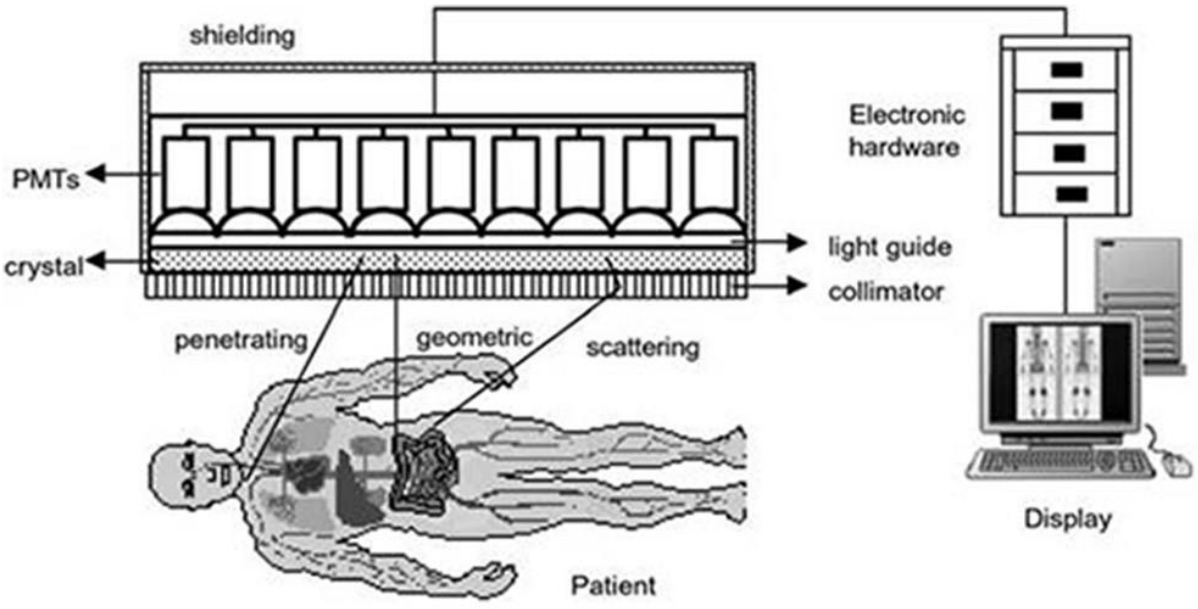

Figure 2-8: System of image acquisition using e.cam single-photo emission computed tomography system

2. 12.1.Gamma camera quality control:-

It is now widely recognized the attainment of high standards of efficiency and reliability in the practice of nuclear medicine; as in other specialties' based on advanced technology, requires an appropriated quality assurance program (*Dougherty G,2009*)

The concept of quality in term quality assurance expresses the closeness with which the out come of a given procedure approaches some ideal, free from all errors and artifacts. The term quality control is used about the specific measures taken to ensure that one particular aspect of the procedure is satisfactory (*Dougherty G,2009*)

The quality of the gamma camera image depends on the performance of the instrument and the correct handling of the instrument. Factors affecting image quality and formation include parameters such as:

- Distribution of the radiopharmaceutical
- Collimator selection
- Spatial resolution
- Energy resolution and window setting
- Uniformity
- Spatial positioning at different energies
- Scattered radiation
- Attenuation
- Noise

The quality control of the gamma camera should include tests of parameters such as Uniformity, Energy resolution, Sensitivity, Pixel size, Center of rotation, Linearity, Count losses at high count-rates, multiple window positioning, background and total performance Some of the parameters should be checked

daily, such as the uniformity, background and energy window settings, while others should be checked at a lower frequency but never less than once a year *(Dougherty G,2009).*

A set of phantoms and sources are necessary to perform the regular quality control. These include flood source, line source, bar phantom and a total performance phantom planar or homographic *(Dougherty G,2009)*

2.12.2.Acquisition of bone scintigrams

Tc99m methylene diphosphonate was prepared in the hot laboratory of the Nuclear Medicine Unit and intravenously administered to patients immediately after preparation. Anterior and posterior whole‐body planar images were acquired three hours after administration of the radiopharmaceutical. Administered activity typically ranged from 0.555 to 1.110 MBq depending on a patient's weight and age. Patients were made to drink four to six glasses of water between the time of injection and time of image acquisition to aid in rapid clearance of radioisotope from the bladder. A 256 × 1024 matrix size was used in acquiring the bone scintigrams. The acquired images were displayed in grayscale for a resident nuclear medicine physician's interpretation and diagnosis (*Burger Iand Burge M.2007)*

2.13.MatLab

(Matrix Laboratory) is a high performance interactive software package for scientific and engineering computation developed by MathWorks (Mathworks Inc., 2009). MatLab allows matrix computation, implementation of algorithms, simulation, plotting offunctions and data, signal and image processing by the Image Processing Toolbox. It enables quantitative analysis and visualisation of nuclear medical images of several modalities, such as Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET) or a

hybrid system (SPECT/CT) where a Computed Tomography system (CT) is incorporated to the SPECT system. The Image Processing Toolbox (*Mathworks Inc., 2009*) is a comprehensive set of reference-standard algorithms and graphical tools for image processing, analysis, visualization and algorithm development. It offers the possibility to restore noisy or degraded images, enhance images for improved intelligibility, extract features, analyse shapes and textures, and register two images. Thus, it includes all the functions that MatLabutilises in order to perform any sophisticated analysis needed after the acquisition of an image. Most toolbox functions are written in open MatLab language offering the opportunity to the user to inspect the algorithms, to modify the source code and create custom functions (*Wilson et al., 2003, Perutka, 2010*). This chapter emphasises on the utility of MatLab in nuclear medicine images' processing. It includes theoretical background as well as examples. After an introduction to the imaging techniques in nuclear medicine and the quality of nuclear medicine images, this chapter proceeds to a study about image processing in nuclear medicine through MatLab. Image processing techniques presented in this chapter include organ contouring, interpolation,MatLab (Matrix Laboratory) is a high performance interactive software package forscientific and engineering computation developed by MathWorks*(Mathworks,Inc.2009).* MatLab allows matrix computation, implementation of algorithms, simulation, plotting of functions and data, signal and image processing by the Image Processing Toolbox. It enables quantitative analysis and visualisation of nuclear medical images of several modalities, such as Single Photon Emission Computed Tomography (SPECT), Positron Emission Tomography (PET) or a hybrid system (SPECT/CT) where a Computed Tomography system (CT) is incorporated to the SPECT system. The Image Processing Toolbox (Mathworks Inc., 2009) is a comprehensive set of reference-standard algorithms and graphical tools for image processing, analysis,

visualisation and algorithm development. It offers the possibility to restore noisy or degraded images, enhance images for improved intelligibility, extract features, analyse shapes and textures, and register two images. Thus, it includes all the functions that MatLabutilises in order to perform any sophisticated analysis needed after the acquisition of an image. Most toolbox functions are written in open MatLab language offering the opportunity to the user to inspect the algorithms, to modify the source code and create custom functions (Wilson et al., 2003, Perutka, 2010). This chapter emphasises on the utility of MatLab in nuclear medicine images' processing. It includes theoretical background as well as examples. After an introduction to the imaging techniques in nuclear medicine and the quality of nuclear medicine images, this chapter proceeds to a study about image processing in nuclear medicine through MatLab. Image processing techniques presented in this chapter include organ contouring, interpolation, filtering, segmentation, background activity removal, registration and volume quantification. A section about DICOM image data processing using MatLab is also presented as this type of image is widely used in nuclear medicine

2.14 Image quality in nuclear medicine

Image quality plays an important role in nuclear medicine imaging as the goal is a reliable image of the projected organ to be provided, for accurate diagnosis or therapy. The physical characteristics that are used to describe image quality are (1) contrast, (2) spatial resolution and (3) noise. Image contrast is the difference in intensity corresponding to different concentration of activity in the patient. For high diagnostic accuracy, nuclear medicine images must be of high contrast. The image contrast is principally affected by the radiopharmaceutical that is used for imaging and the scattered radiation. In general, it is desirable to use a radiopharmaceutical which has a high uptake within the target organ. Spatial resolution is defined as the ability of the imaging modality to reproduce the details

of a nonuniform radioactive distribution. The spatial resolution is separated into intrinsic resolution (scintillator, photomultiplier tubes and electronic circuit) and system resolution (collimator, scintillator, photomultiplier tubes and electronic circuit).

2.14.1The intrinsic resolution

depends on the thickness of scintillation crystal while the system resolution depends mainly on the distance from the emitting source to collimator.

The resolution of a gamma camera is limited by several factors. Some of these are the patient motion, the statistical fluctuation in the distribution of visible photons detected and the collimators geometry (*Wernick&Aarsvold, 2004*).

Noise refers to any unwanted information that prevents the accurate imaging of an object. Noise is the major factor in the degradation of image quality. Image noise may be divided into random and structured noise. Random noise (also referred as statistical noise) is the result of statistical variations in the counts being detected. The image noise is proportional to N1/2 where N is the number of detected photons per pixel. Therefore, as the number of counts increases the noise level reduces. Image noise is usually analysed in terms of signal-to-noise-ratio (SNR). SNR is equal to N/ N1/2. If the SNR is high, the diagnostic information of an image is appreciated regardless of the noise level. Structured noise is derived from non-uniformities in the scintillation camera and overlying structures in patient body.

2.14.2. Image analysis and processing in nuclear medicine

In the last several decades, medical imaging systems have advanced in a dynamic progress. There have been substantial improvements in characteristics such as sensitivity, resolution, and acquisition speed. New techniques have been introduced and, more specifically, analogue images have been substituted by digital ones. As a result, issues related to the digital images' quality have emerged.

The quality of acquired images is degraded by both physical factors, such as Compton scattering and photon attenuation, and system parameters, such as intrinsic and extrinsic spatial resolution of the gamma camera system. These factors result in blurred and noisy images. Most times, the blurred images present artefacts that may lead to a fault diagnosis. In order the images to gain a diagnostic value for the physician, it is compulsory to follow a specific series of processing. Image processing is a set of techniques in which the data from an image are analysed and processed using algorithms and tools to enhance certain image information that is more useful to human interpretation (*Nailon,A. 2010*). The processing of an image permits the extraction of useful parameters and increases the possibility of detection of small lesions more accurately. Image processing in nuclear medicine serves three major purposes: a) the reconstruction of the images acquired with tomographic (SPECT) techniques, b) the quality improvement of the image for viewing in terms of contrast, uniformity and spatial resolution and, c) the preparation of the image in order to extract useful diagnostic qualitative and quantitative information.

2.14.3. Image processing techniques - MatLab

Image processing techniques include all the possible tools used to change or analyse an image according to individuals' needs. This subchapter presents the most widely performed image processing techniques that are applicable to nuclear medicine images. The examples used are mostly come from nuclear medicine renal studies, as kidneys' planar images and SPECT slices are simple objects to show the application of image processing MatLab tools.

2.14.4. Contrast enhancement

One of the very first image processing issues is the contrast enhancement. The acquired image does not usually present the desired object contrast. The improvement of contrast is absolutely needed as the organ shape, boundaries and

internal functionality can be better depicted. In addition, organ delineation can be achieved in many cases without removing the background activity. The command that implements contrast processing is the adjust. Using this, the contrast in an image can be enhanced or degraded if needed. Moreover, a very useful result can be the inversion of colours, especially in greyscale images, where an object of interest can be efficiently outlined. The general function that implements contrast enhancement is the following:

J = adjust(I,[low in high in],[low out high out],gamma);

while the function of color inversion is the following:

J = adjust(I,[0 1],[1 0],gamma); or J = complement(I);

suppose that J, is the new image, I, is the initial image and gamma factor depicts the shape of the curve that describes the relationship between the values of I and J. If the gamma factor is omitted, it is considered to be 1.

2.15.previous study.

(Gihad ,kh 2010) That where are a direct linear relationship between the acquired counts and the elapsed time after chemotherapy .The coefficient of this relationship indicates that the count will be increased by 0.018 mega counts per day starting from 0.81 mega counts .Therefore the count reaches the appropriate level after one month which is equal to 1.5 mega counts .This result was agreed with(Pollen , el Shlaer 1979) and from the observation of the researcher the counts rate reach the acceptable level after 28 days ,that when the weight of the patient increase must be increasing the doses, that to get the optimum counts for detecting to show the bone scan clearly, because if the dose is low and the weight of the patients is high result in increasing scattered counts which are not detected.

The study also showed that there is a direct positive relationship between the potent weight (kg)and the administered dose (mci)

The trend of the graph indicates that the administered dose increased as a result of the weight increment, whose the coefficient shows that the dose increased by 0.285 mic\kg starting from 0.072mci for zero weight ,this result agreed with the equation that used to the calculated dose fore patient (weight of patient *normal dose/normal weight) the confirmative result with the calculated equation used in the department is that the counts which detected must be increased in patients with high weight due to avoid the scattered counts to get the best counts for a clear bone scan and that as the researcher mentioned, require increasing the dose in the patient of overweight.

Conclusion:The suitable time of bone scan post-chemotherapy is one month.

The Results of research show that chemotherapy would lead to more influence on the bone scan and their refers to the decrease in the level of absorption of bone material, and each piece is attributed to those who.

-Biochemical effect within the cells

-Direct impact of the chemical in the formation of blood cells and circulatory system that lead to an imbalance in the rate of absorption of bone cell material pharmaceutical there are secondary causes such as loss of appetite for the patient and the presence of vomiting and diarrhea in some cases all of those reasons hinder the absorption of pharmaceutical material adequately staged to turn, lead to the emergence of bone scan required

2-(*Ozhan, O, et al., 2008*) Objective of this studyBone scan is the accepted initial imaging modality for skeletal metastases. Cisplatin is a cell-cycle nonspecific cantineoplastic agent used in some chemotherapy regimens. Knowing that platinum reacts with phosphate compounds such as the methylenediphosphonic acid (MDP), decreases bone resorption and new bone formation, it can be proposed that cisplatin chemotherapy may decrease Tc-99m MDP bone uptake. We aimed to demonstrate, if present, the decrease in bone uptake and to determine the duration

of this effect. *Methods* Thirty male Wistar rats were randomized into fi ve groups, namely, placebo group (G1) and cisplatin groups (G2, G3, G4, G5). Pre-therapy bone scintigraphies were obtained in all the groups. Cisplatin chemotherapy was given as the infusion. Post-therapy bone scintigraphies were obtained 10 min, one h, 24 h, and 72 h after chemotherapy in groups G2–G5, respectively. A placebo bone scintigraphy was obtained 10 min after infusion of serum physiologic in G1. Plasma samples for cisplatin plasma values were obtained. The graphite furnace atomic absorption spectrophotometry technique

was used for cisplatin analysis. Quantitative analysis (bone uptake ratios) was performed by drawing regionsof interest on the right femur, vertebral column, and adjacent soft tissues. The injection/examination time delay and the net injected MDP doses were also noted. Results There was no statistically significant difference in bone uptake values, injected MDP doses or injection/ examination time delay in any group. Cisplatin plasma values were significantly different in G2, G3, G4, and G5 ($P < 0.05$) but not in G1. Conclusions Cisplatin chemotherapy seems to not affect the Tc-99m MDP uptake of normal bone.

Results

Pre- and post-therapy cisplatin plasma values, Tc-99m MDP doses, injection/examination delays, and bone uptake ratios are given in Tables 1, 2, 3, 4, respectively. There was no significant difference in the pre-therapy

bone uptake values between the groups (ANOVA, $P > 0.05$). So, the randomization of rats into groups was

deemed successful. There was no significant difference in the pre- and post-therapy cisplatin plasma values in G1, but pre- and post-therapy cisplatin plasma values were significantly different in the rest of the groups ($P < 0.05$).

There was no significant difference in the pre- and post-therapy Tc-99m MDP doses or the injection/examination delays in any group ($P > 0.05$). There was no

significant difference in the pre- and post-therapy bone uptake ratios in any group ($P > 0.05$).

Limitation There are some factors that can account for the negative results such as randomization of the rats, factors related to the bone scintigraphy, and factors related to the chemotherapy. The randomization, however, was successful as shown by the pre-therapy bone uptake values, as noted earlier. We did not consider the injected

Tc-99m MDP doses, the injection/examination time delays or status of hydration of the rats as possible contributing factors for the negative results either; all the rats were hydrated with three cc SF for one h following

radiopharmaceutical injection in both the pre- and post-therapy studies. There were no statistically signifi -

cant differences between the pre- and post-therapy MDP doses or pre- and post-therapy injection/examination

time delays in the groups.

Conclusions Cisplatin chemotherapy does not seem to decrease Tc-99m MDP uptake of normal bone in rats. According to the results of our study, Tc-99m MDPbone scintigraphy, which is the preferred imaging technique

for detecting bone metastases, can be performed at any time following chemotherapy with cisplatin.

Table 1 Cisplatin plasma values before and after cisplatin chemotherapy

Cisplatin (µg/l)	G1 (placebo)	G2 (10 min)	G3 (1 h)	G4 (24 h)	G5 (72 h)
Pre-therapy	32.4 ± 28.7	41.7 ± 42.7	34.2 ± 25.0	16.7 ± 19.0	18.5 ± 17.2
Post-therapy	37.2 ± 28.5	1349.7 ± 774.7	2259.8 ± 1042.2	620.5 ± 506.2	386.9 ± 398.8
P	0.75	0.028	0.028	0.028	0.028

The pre- and post-therapy cisplatin plasma values were significantly different in all groups except in the placebo group

Table 2 Tc-99m methylenediphosphonate (MDP) net doses injected for pre-therapy and post-therapy bone scintigraphies

MDP (µCi)	G1 (placebo)	G2 (10 min)	G3 (1 h)	G4 (24 h)	G5 (72 h)
Pre-therapy	112 ± 14	118 ± 16	112 ± 7	114 ± 6	116 ± 17
Post-therapy	95 ± 10	112 ± 13	112 ± 11	114 ± 14	121 ± 13
P	0.115	0.715	0.917	0.893	0.674

There was no statistically significant difference in Tc-99m MDP injected doses between pre- and post-therapy bone scintigraphies

Table 3 Injection/examination time delay for bone scintigraphy

Delay (min)	G1 (placebo)	G2 (10 min)	G3 (1 h)	G4 (24 h)	G5 (72 h)
Pre-therapy	163 ± 26	181 ± 24	243 ± 95	199 ± 20	219 ± 27
Post-therapy	174 ± 37	178 ± 18	232 ± 103	201 ± 12	224 ± 31
P	0.201	0.670	0.058	0.809	0.363

There was no statistically significant difference in injection/examination time delay between pre- and post-therapy bone scintigraphies in the groups

Table 4 Bone uptake

	G1 (placebo)	G2 (10 min)	G3 (1 h)	G4 (24 h)	G5 (72 h)
(a) *F/S* (right femur to soft tissue ratio)					
Pre-therapy	4.67 ± 1.71	4.60 ± 0.92	7.75 ± 1.49	5.45 ± 2.70	7.06 ± 2.74
Post-therapy	3.93 ± 0.76	4.97 ± 1.72	7.97 ± 1.83	5.91 ± 2.20	6.58 ± 3.26
P	0.469	0.406	0.814	0.806	0.691
(b) *V/S* (vertebrae to soft tissue ratio)					
Pre-therapy	4.98 ± 1.00	4.41 ± 0.20	5.81 ± 1.77	5.22 ± 1.13	5.84 ± 2.07
Post-therapy	4.06 ± 1.16	4.66 ± 0.83	6.12 ± 1.26	4.90 ± 2.01	4.60 ± 0.92
P	0.153	0.507	0.790	0.736	0.127

There was no statistically significant difference in bone uptake ratios between pre- and post-therapy bone scintigraphies in the groups according to the right femur to soft tissue ratios (a) and vertebrae to soft tissue ratios (b)

3-(*Ronald P.et al 2010*) Cisplatin is a widely used and highly effective cancer chemotherapeutic agent. One of the limiting side effects of cisplatin use is nephrotoxicity. Research over the past ten years has uncovered many of the cellular mechanisms which underlie cisplatin-induced renal cell death. It has also become apparent that inflammation provoked by injury to renal epithelial cells serves to amplify kidney injury and dysfunction in vivo. This review summarizes recent advances in our understanding of cisplatin nephrotoxicity and discusses how these advances might lead to more effective prevention Nephrotoxicity is a serious

and dose-limiting toxicity of cisplatin. Cisplatin nephrotoxicity is the composite result of the transport of cisplatin into renal epithelial cells, injury to nuclear and mitochondrial DNA, activation of a multiple cell death and survival pathways and initiation of a robust inflammatory response. Although this scheme presents many possible therapeutic targets, single interventions in animal models have provided only incomplete protection. Moreover, the impact of many interventions on the chemotherapeutic efficacy of cisplatin has not been adequately examined. Moving forward, combinatorial strategies which target multiple mechanisms, such as reducing cisplatin uptake and reducing inflammation, may offer the best chance for clinically meaningful prevention. Any proposed strategy, however, must be carefully studied in tumor-bearing animals to ensure that the chemotherapeutic efficacy of cisplatin is not compromised. (*Ronald P.et al 2010*)

2-(*Macleod PM, et, al 1988*)Retrospective analysis of 22 patients with testicular cancer treated with 1 to 5 cycles of cisplatin-based chemotherapy reported a reduction in mean GFR from 137 ml/min to 106 ml/min. GFR was evaluated by serial measurement of 51Cr-EDTA clearanceMedical records of 17 patients indicated normalization of GFR and improvement of renal function in respectively 12 and 18% of patients. Impaired renal function remained stable in 41% and continued to decline in 29% of patients. Patients received a cumulative cisplatin dose of 180 to 900mg(*Macleod PM, et, al 1988*).

3-(*Daugaard G, Abildgaard U,1999*) Kidney function throughout three cycles of high dose cisplatin was monitored in 30 patients (age 18to 52 years) undergoing treatment for poor prognosis germ cell tumors.

The chemotherapy regimen included cisplatin 40 mg/m2/day for five days and etoposide 200 mg/m2/day for five days. Patients received a cumulative cisplatin dosage of 800 to 1200mg. All patients had a normal rate of glomerular filtration (78 to 139 ml/min/1.73 m2), as assessed by 51Cr-EDTA clearance, at study entry.

Mean plasma clearance of 51Cr-EDTA decreased significantly, from 123 ml/min to 92 ml/min, after the first cycle of chemotherapy. GFR continued to decline throughout subsequent cycles of chemotherapy. The mean GFR 6 months following the initiation of chemotherapy, was 89 ml/min. Additional chemotherapy drugs administered included etoposide and bleomycin.(*Daugaard G, Abildgaard U,1999)*

4-(*Murphy KJ1, Line BR 1997*) To define the nature, incidence, and consequence of a possible interaction between etidronate (for the treatment of hypercalcemia) and methylene diphosphonate labeled with technetium-99m (99mTc-MDP) (for bone scanning).

The authors reviewed hospital pharmacy records for two years and identified 18 patients who had received etidronate. Of this group, six patients (4 men and two women, ranging in age from 56 to 76 years) had undergone bone scanning with 99mTc-MDP while receiving etidronate. Five of the patients had hypercalcemia associated with metastatic disease, and the sixth had hyperparathyroidism. All bone scans demonstrated poor uptake of tracer by bone accompanied by high soft-tissue background. There was the loss of bone definition below the mid-thigh, and in 5 of the six patients, there was indistinguishable rib uptake. In 1 of the patients, there was an absence of uptake in 2 previously defined metastatic lesions. Recent oral or intravenous administration of etidronate is a contraindication to bone scintigraphy, as it markedly decreases sensitivity for bone disease. Bone scintigraphy should be timed so that it is performed before etidronate treatment or, if that is not possible, more than 2 to 4 weeks after the therapy has been completed.

An important point to consider before diagnosing a flare reaction on the bone scan is the period that has elapsed between the pretreatment scan and the beginning of therapy .If there is the substantial delay, even as short as 3-6 weeks, between the first scan and onset of treatment, interval progression of metastases could go

unrecognized .For correct interpretation of serial scans, the pretreatment scan should be obtained as close to the onset of therapy as possible.The overall accuracy of the radionuclide bone scan for monitoring bony metastases from carcinoma of the breast cancer is excellent .In our review of scans obtained three months after initiation of treatment, this early scan provided misleading information in 6 %of studies, showing apparent deterioration in the face of clinical improvement .It is emphasized, however, that this phenomenon is exceptional.(*Pollen and Gerber 1981)*

5-(*Pollen and Shlaer 1979*) this study related it is concluded of The radionuclide bone scans 1 month after the initiation of treatment for advanced cancer of the prostate occasionally shows apparent details of bone To determine the incidence and clinical significance , serial bone scans were reviewed in 33 patients with carcinoma of the prostate and bony metastases, who were receiving chemotherapy treatment for the first time .Was seen clearance 60%of 33 bone scans obtained 1months after initiation of treatment. (Pollen and Shlaer 1979)

7-(*Murphy KJ, et, al 1997*)this objective of study: To define the nature, incidence, and consequence of a possible interaction between etidronate (for the treatment of hypercalcemia) and methylene diphosphonate labeled with technetium-99m (99mTc-MDP) (for bone scanning). Materials and methods: The authors reviewed hospital pharmacy records for two years and identified 18 patients who had received etidronate. Of this group, six patients (4 men and two women, ranging in age from 56 to 76 years) had undergone bone scanning with 99mTc-MDP while receiving etidronate. Five of the patients had hypercalcemia associated with metastatic disease, and the sixth had hyperparathyroidism.

Results: All bone scans demonstrated poor uptake of tracer by bone accompanied by high soft-tissue background. There was a loss of bone definition below the mid-thigh, and in 5 of the six patients, there was indistinguishable rib uptake. In 1 of the

patients, there was the absence of uptake in 2 previously defined metastatic lesions. Conclusion: Recent oral or intravenous administration of etidronate is a contraindication to bone scintigraphy, as it markedly decreases sensitivity for bone disease. Bone scintigraphy should be timed so that it is performed before etidronatetreatment or, if that is not possible, more than 2 to 4 weeks after the therapy has been completed.

Chapter Three

Method & Material

3.1Material

3.1.1 Patient

This study include (150) female with breast cancer their age ranged between 25-75 years refer to the department of nuclear medicine in king Abdulla medical city , for bone scan study examination ,all patient has base line have no other diseases such as diabetes, hypertension and kidney disease

all patient with normal GFR before chemotherapy treatment all patient are successfully bone scan done and included in the study. Original sample was 410 patient weexcluded 260 patient in depended for many reasons (disease ,age, previous history, test before don't done requested)

150 female confirm diagnoses single breast cancer in the first stage were distributed intofive groups, namely, control group (G1) and chemotherapy (cisplatin combination) groups (G2, G3, G4, G5). Pre-therapy and after GFR bone scintigraphies were obtained in all the groups. Cisplatincombination chemotherapy was given as infusion by same type of chemotherapy company and calculated the dos independ on patient weight and other clinical criteria . Post-therapy bone scintigraphies were obtained after 7 days from one cycle(G2), 14 days from one cycle(G3), ,21 days from one cycle(G4) and 28 days from one cycle(G5), respectively. alll groups bone scintigraphy was obtained GFR base lineThey were also measured after chemotherapy and before bone scan at same time withintwo days of bone scan also dose of radiopharmaceutical (TC99m +MDP) is giving by weight factor.

3.1. 2 Machine

The study is carried out in king Abdulla medical city hospital in KSA using SPECT gamma camera GE general electric - made in USA 2014 in the period from FEB 2015 – MAY 2017.

3.2 Method

3.2.1 Technique

(The following as Experimental and retrospective study for 150 breast cancer patients (150 females; age range, 25-75 years) refer to the department of nuclear medicine in king Abdulla medical city during 2015-2017, have been examined using SPECT gamma camera GE general electric - made in USA 2014. SPECT gamma camera protocol: All the cases were examined in supine position with standard position of bone scan using the following sequences. Spots views and whole body sped stander (10m/m) pixel 1024*256.system software included all data inter such as age Weight height control the data that helps in scanning.

3.2.2preparation of 99mTc-MDP injection:

The MDP kits contains sterile component in lyophilized form which after reconstitution with pertechnetatesolution a complex of methylenediphosphate (MDP) with technetium99mTCformed, which show an affinity to hydroxyapatite of the bone tissue.

Under sterile condition 5ml of sodium pertechnetate solution with maximum activityOf 100-500mCi was added to the MDP vial content through the stopper . The vialContent 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(shelf life) .

3.2.3 patientpreparations:

All Patient was instructed to be will hydrated by drinking about 2 liter before and 2 of water during (between injection and scan) the patient must drink at least 2 liter of fluid between injection and image that is done for all patient .

The patient was encouraged to avoid immediately prior to imaging, if the catheter is present the back should be emptied before imagine (this excluded in this sample)

3.2.4 Patient positioning

Patient was laid in supine position for most patients feet in , a pillow was placed under the patients knees for comfort if necessary (.Metal objects were removed e.g . coin and keys (prior imagin).

3.2.5. 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)99mTc-MDP (in depend for Wight equation using syringe shield and butter fly for protection purposes .Then the patient was left to stay for 3hrs at specially waiting room.During this period the patient was allowed to have alot of 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 start at 1 hour after administration.

3.2.6 Imaging Procedure

Image was obtained after 3 hours following administration .A longer delay image is helpful in elderly patients with slower bone uptake but we have three hours only the waiting time for the sample, 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 wasunable to empty the bladder masking the retained urinary activity with lead shielding will allow improved detail in the rest of the pelvis. In this study we used xelelaris software This system analyzes, displays and converts the image from the digital system after it is sent from the main control penal as row data an invisible data set.

3.2.7.GFR calculation

The level of the eGFR was measured from the laboratory by criatinine equation (equation No 2)After that we certainly confirmed the result with a program(https://www.davita.com/gfr-calculator/) equation that calculate GFR by the patient's age ,gender and criatinine level the patient's type and the creatinine levels in the blood, and the measurement sensitivity was highWe found the difference between the two readings almost negligible and this is attributed to the different design programs on the population of South America.

eGFR = 141 × min (Scr /ê, 1)á × max(Scr /ê, 1)-1.209 × 0.993Age × 1.018 [if female] × 1.159 [if black]

where:
Scr is serum creatinine in mg/dL,
ê is 0.7 for females and 0.9 for males,
á is -0.329 for females and -0.411 for males,
min indicates the minimum of Scr /ê or 1, and
max indicates the maximum of Scr /ê or 1.

3.2.2 Method of data analysis

MATLAB program 2016 was used analyze the row data image and extract the highest value of the bones and the highest value of the background is subtracts then the actual value is extracted for three should.

Also used in the study the SPSS program to analyze the variables and extract the values of the difference group and compare them with other readings(scatter plots depict the result of MRS and histopathology) and excel to fine the significant defiance's between variables with chemotherapy treatment and non-treated.

Variable used for data collection are age weight counts and GFR level .

3.2.8 Ethical Consideration

There is no patient identification or individual patient details will be published. Also confidentiality will be ensured by making the collected data accessible only to the researcher and consultant of nuclear medicine and the head of radiology department. And also keep all data collected during the study will be stored on computer protected by password. All paper format data will be stored in locked cabinet.

Chapter Four

Result

4-1 Result

The following results highlighting the bone scan in Saudi Arabia during the period of 2015-2017, incidence% based on GFR , duration of chemotherapy before bone scan , and variation incidence with patient taking chemotherapy , the involved Includes period of chemotherapy before bone scan and role of image enhancement ..

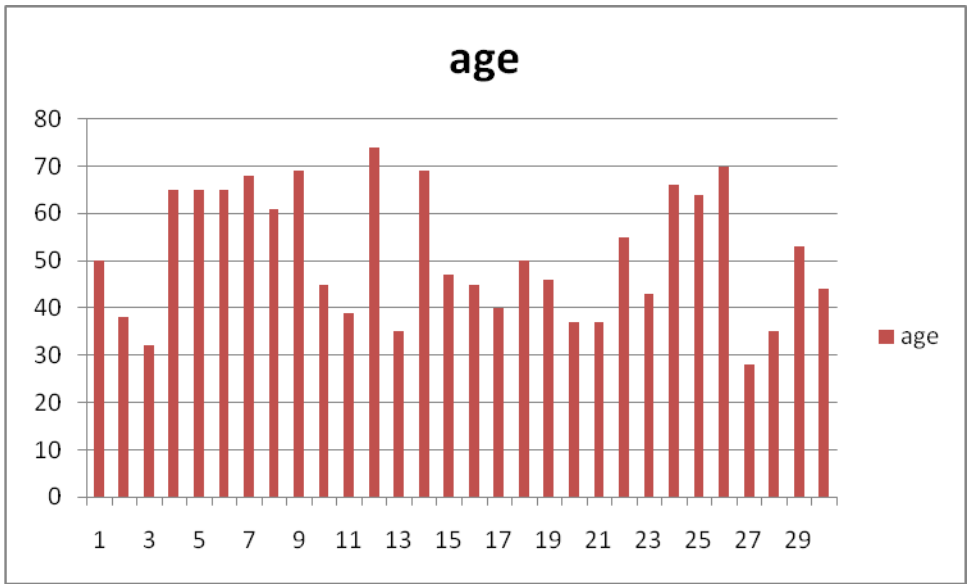

Figure 4-1 age frequency of control patient

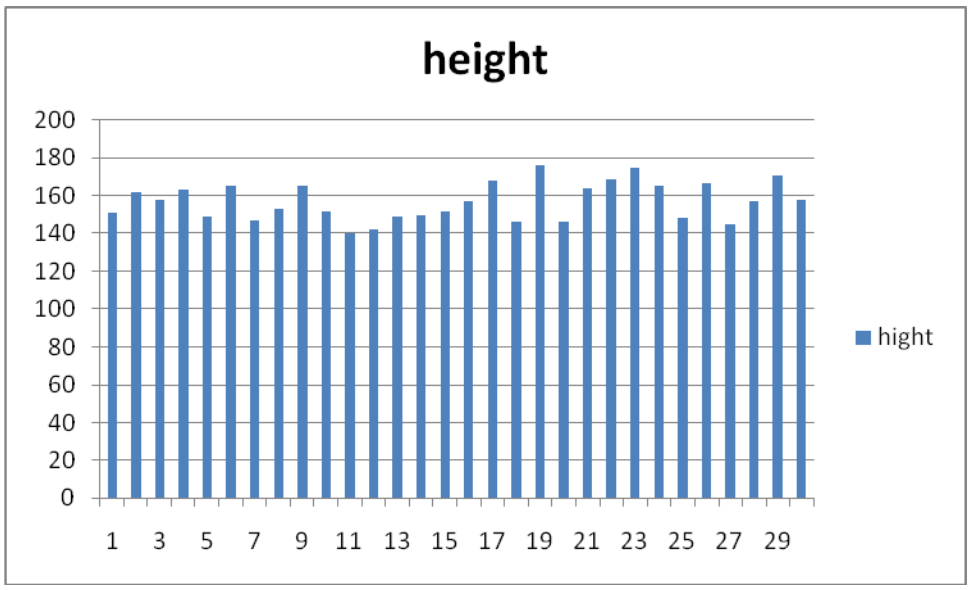

Figure 4-2 height frequency of control group patient

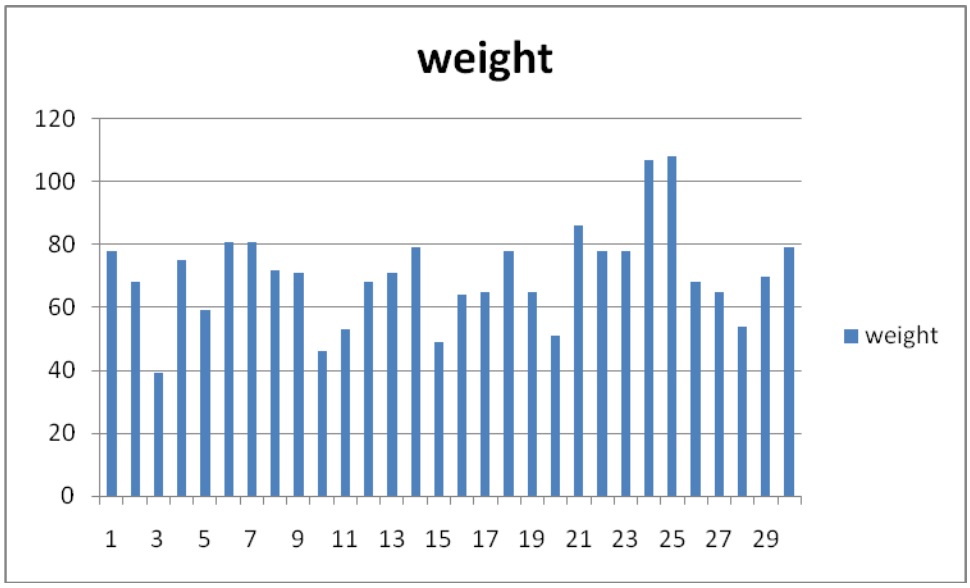

Figure 4-3 weight frequency of all patient

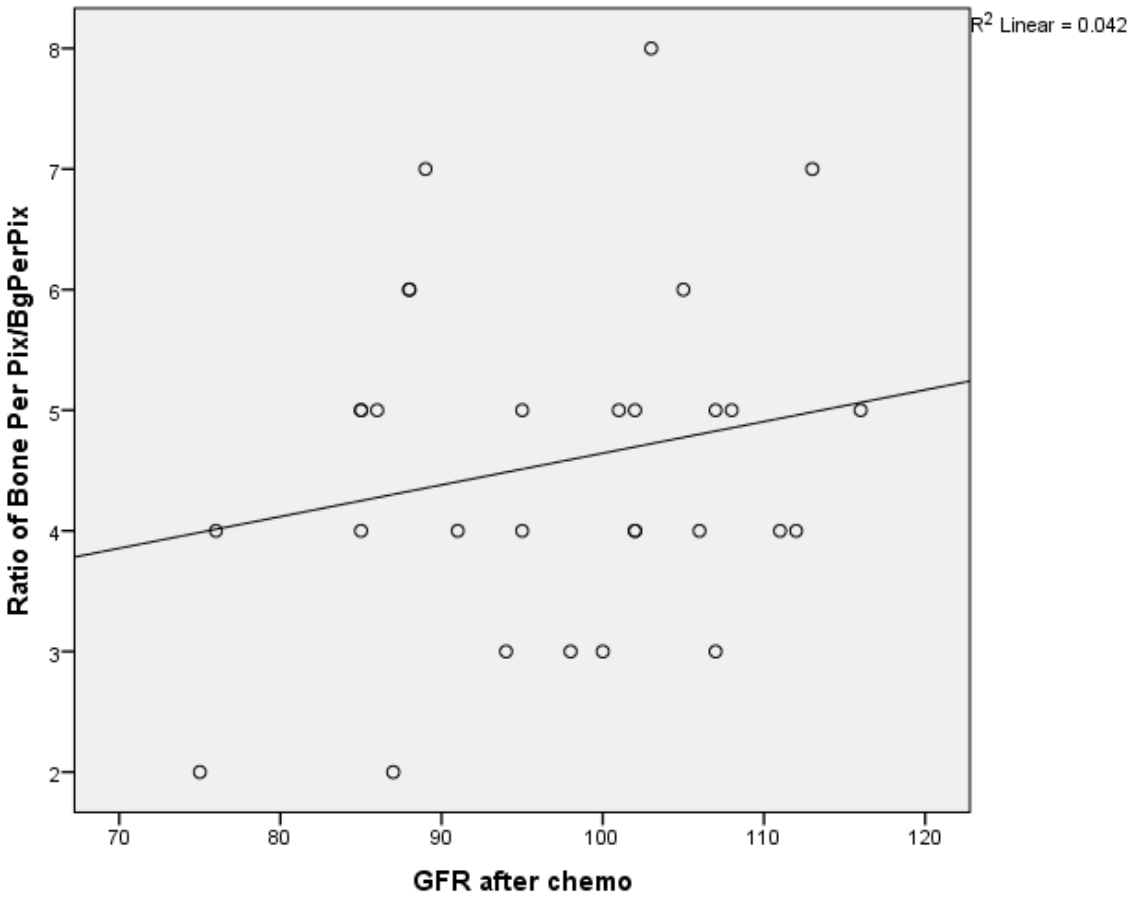

Figure 4-4 scatter plot shows the correlation of GFR after chemotherapy and ratio of bone per/background per pixel For controlling group:

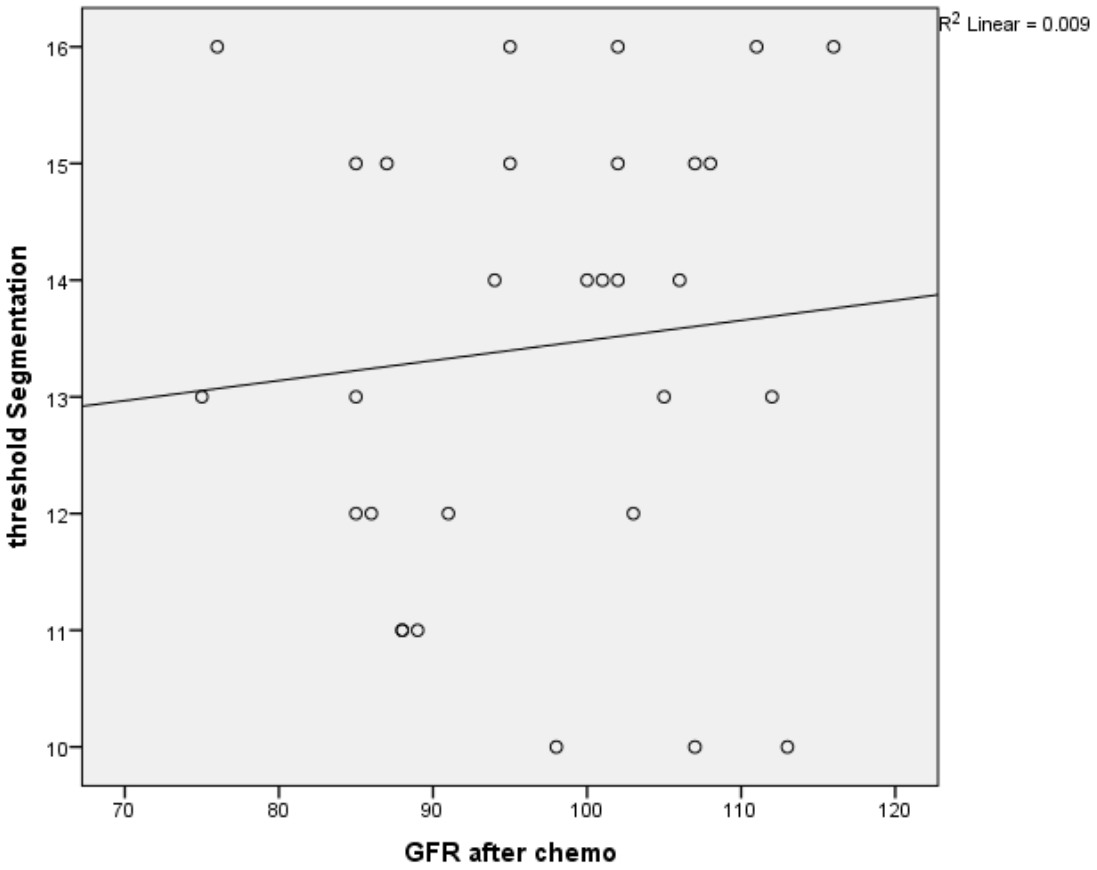

Figure 4-5 scatter plot shows the correlation of GFR after chemotherapy and threshold segmentation For controlling group

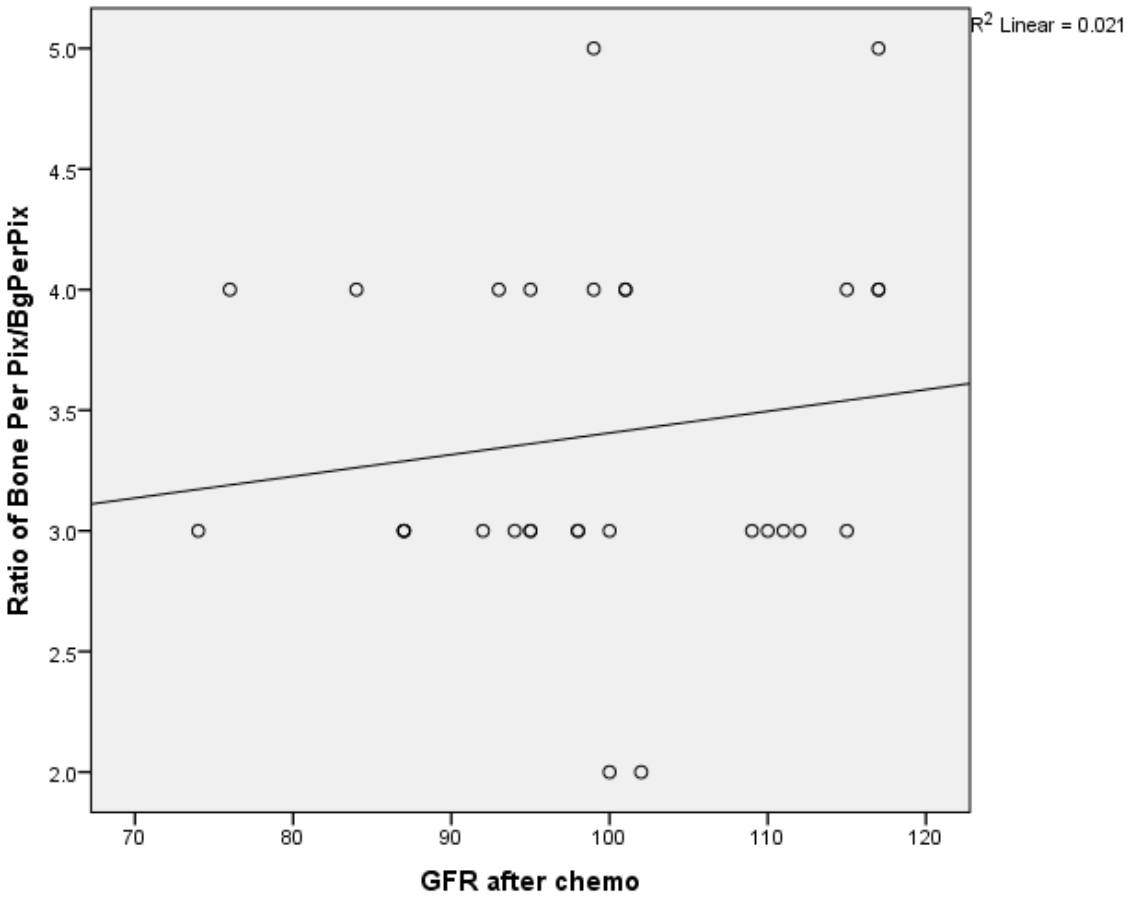

Figure 4-6 scatter plot shows the correlation of GFR after chemotherapy and ratio of bone per/background per pixel For Group G1

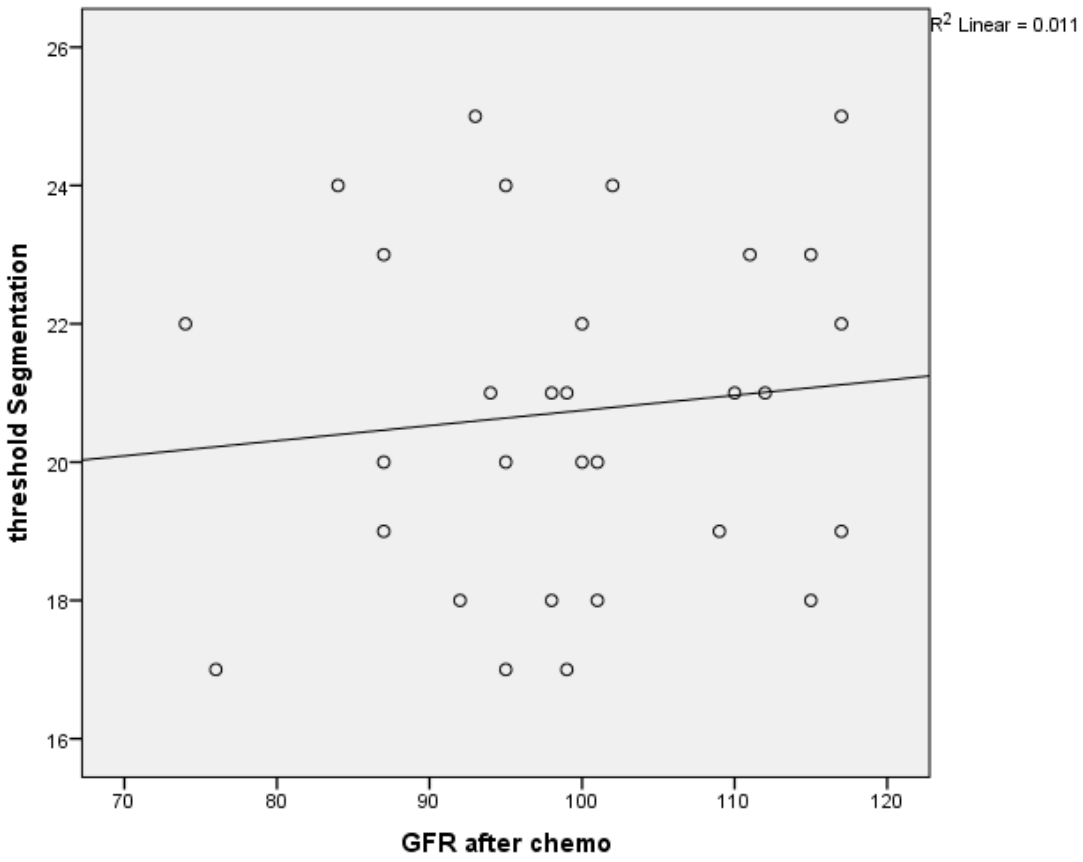

Figure 4-7 scatter plot shows the correlation of GFR after chemotherapy and threshold segmentation For group G2

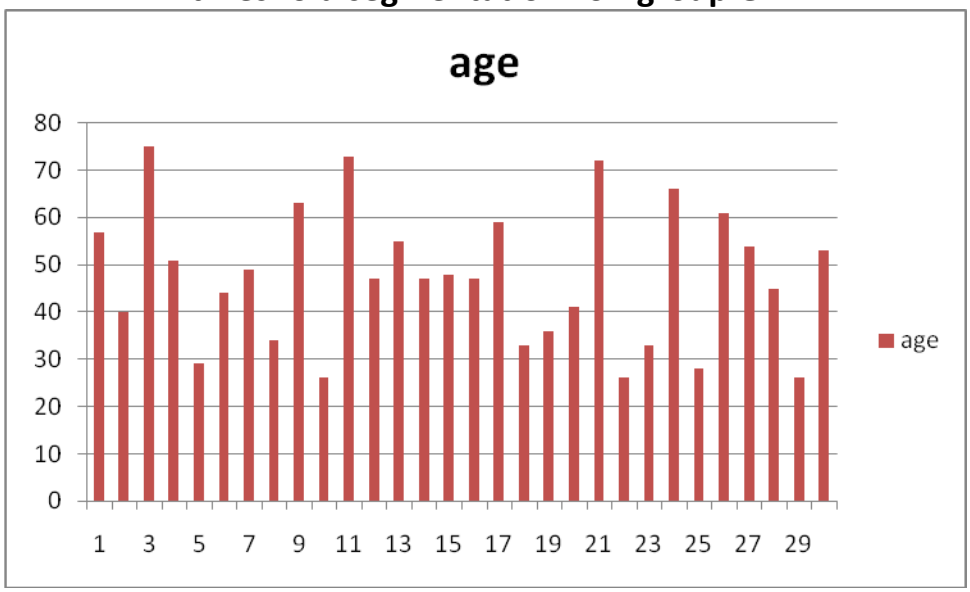

Figure 4-8 age frequency of group G2 patient

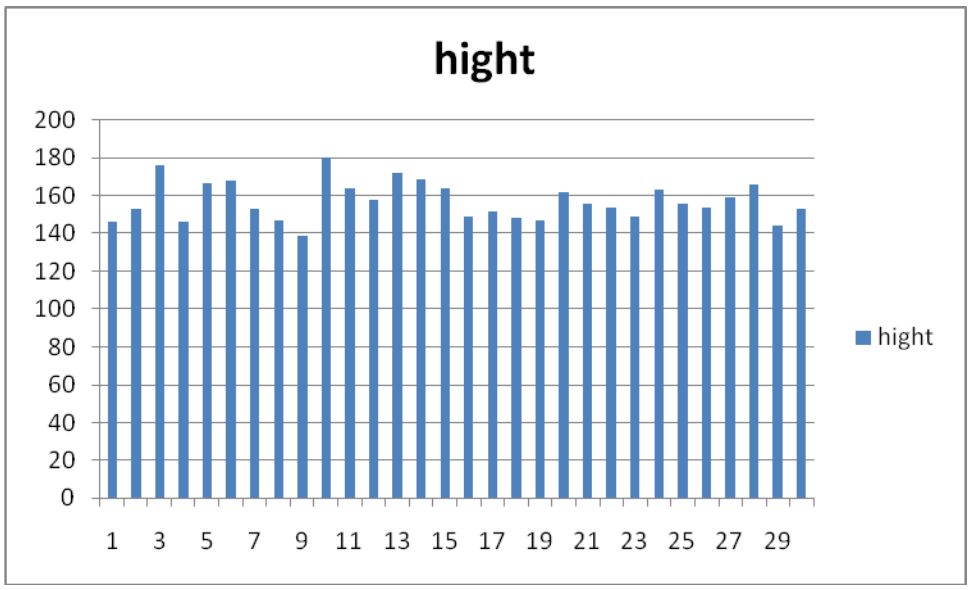

Figure 4-9 height frequency of group G2 patient

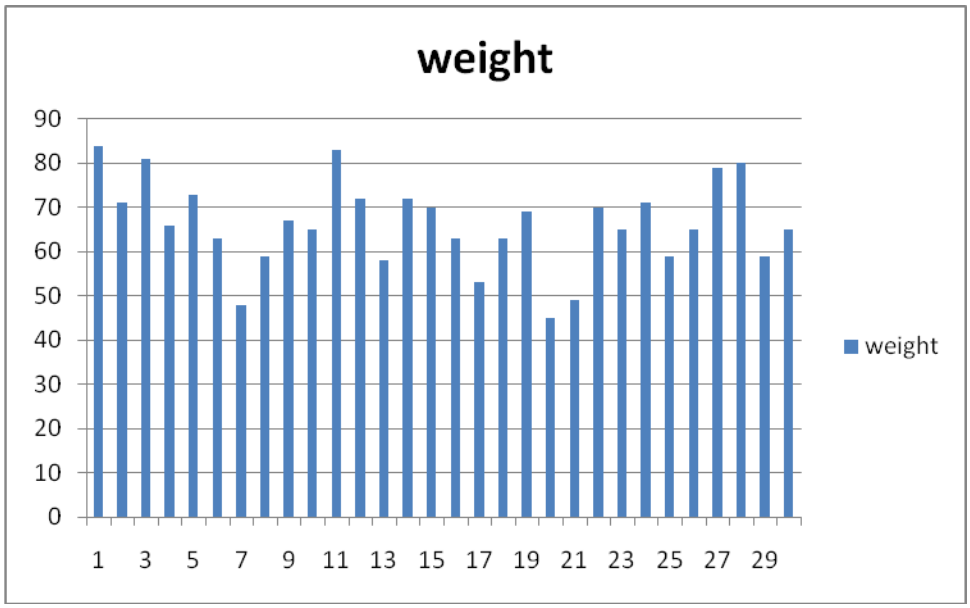

Figure 4-10 weight frequency of group G2 patient

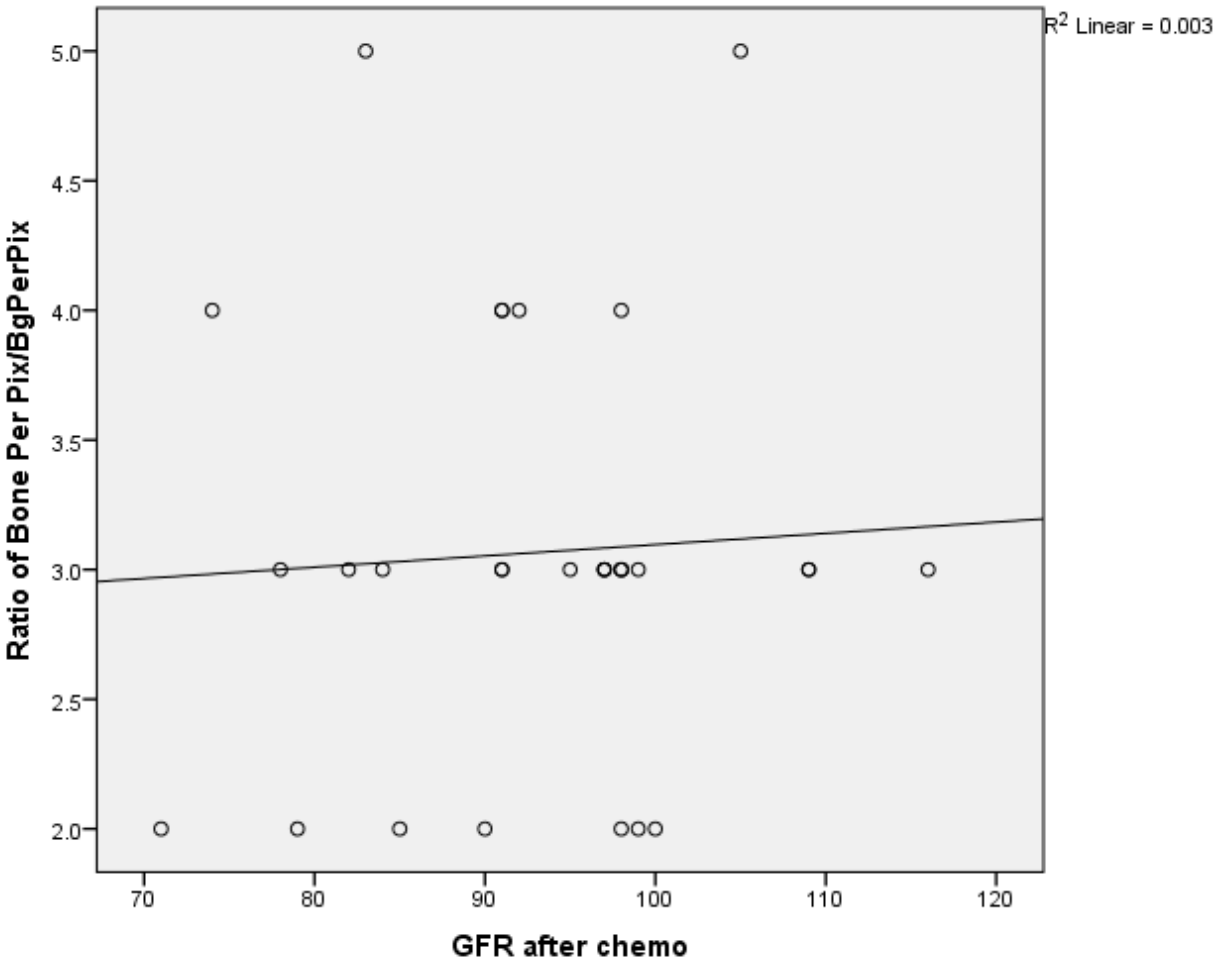

Figure 4-11 scatter plot shows the correlation of GFR after chemotherapy and ratio of bone per/background per pixel For G3 group

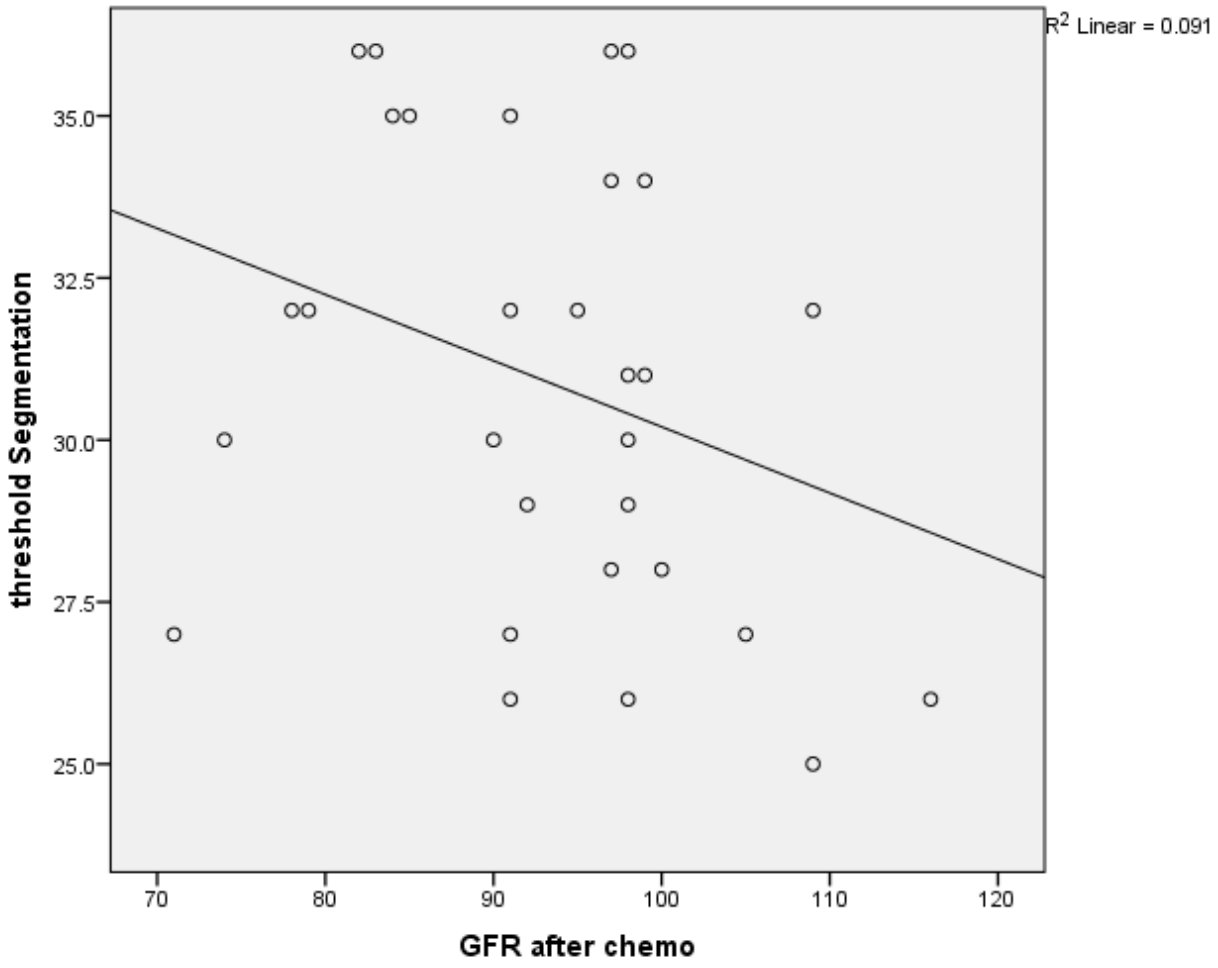

Figure 4-12 scatter plot shows the correlation of GFR after chemotherapy and threshold segmentation For group G3

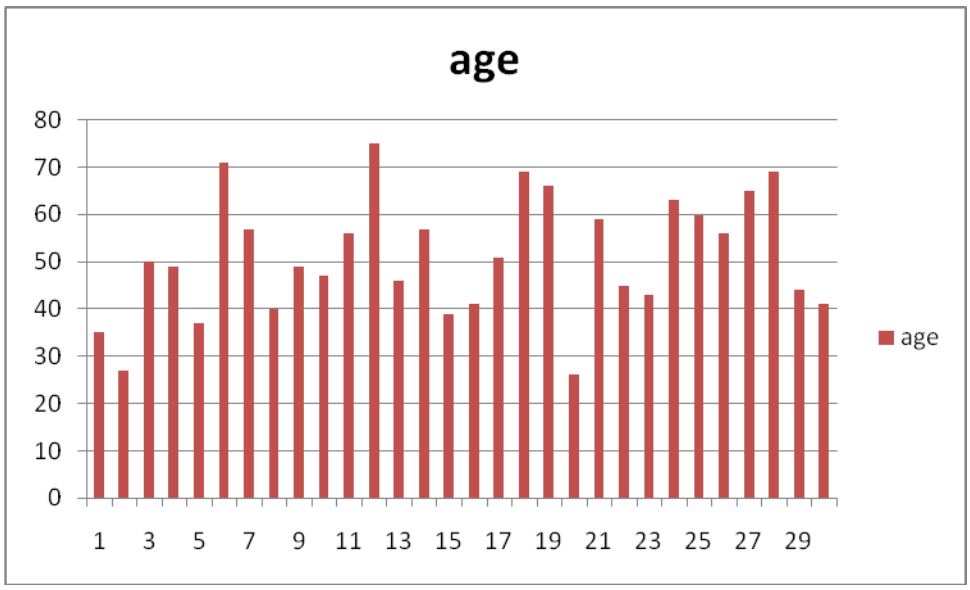

Figure 4-13 age frequency of group G3 patient

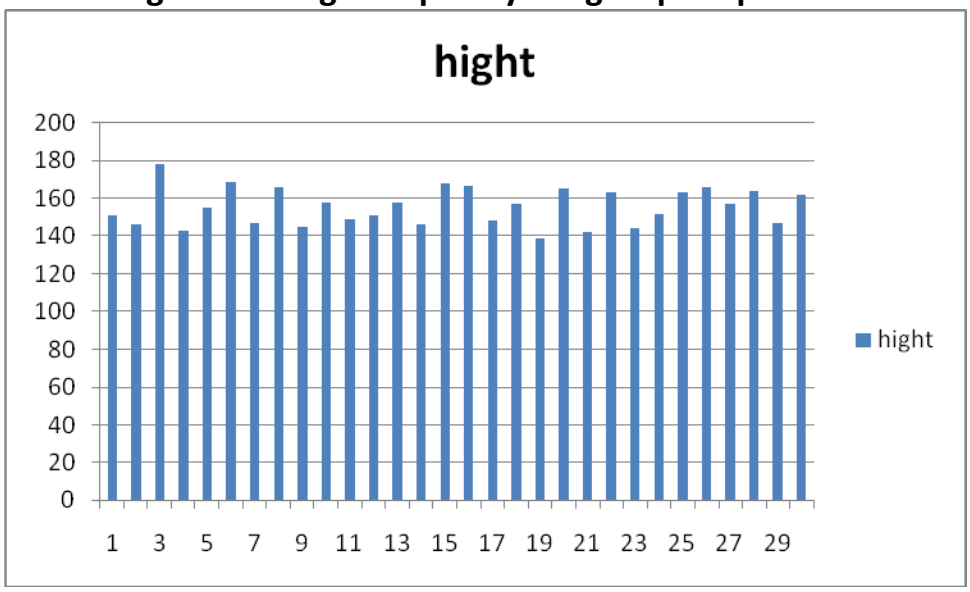

Figure 4-14 height frequency of group G3patient

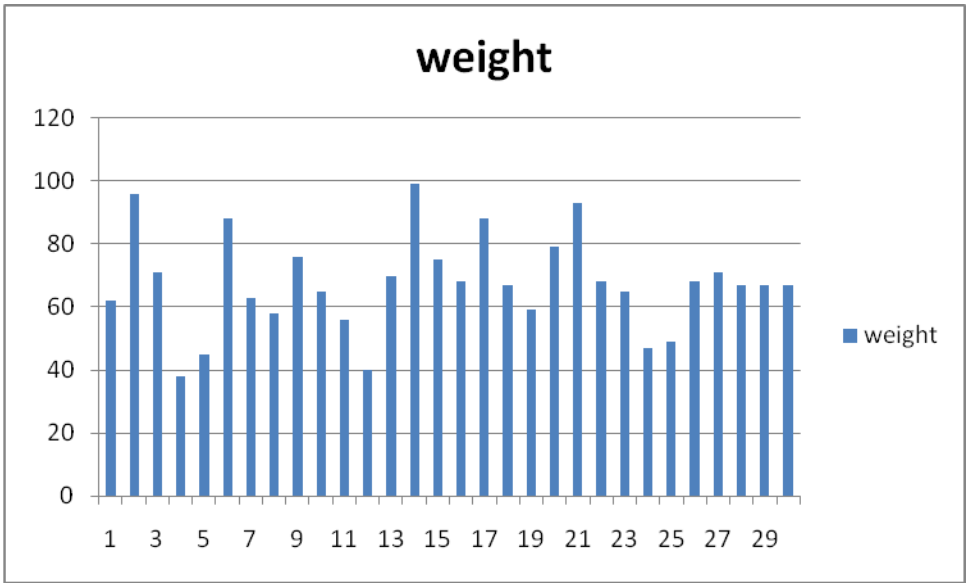

Figure 4-15 weight frequency of group G3patient

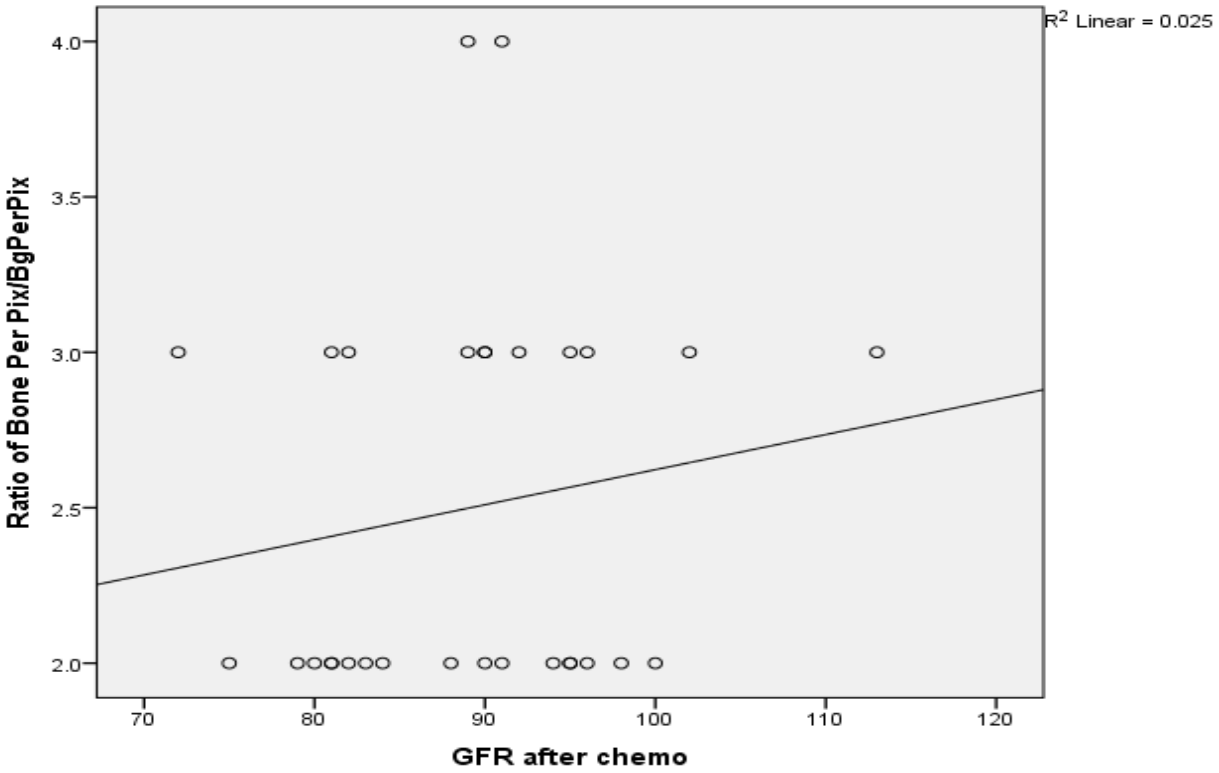

Figure 4-16 scatter plot shows the correlation of GFR after chemotherapy and ratio of bone per/background per pixel For G4 group

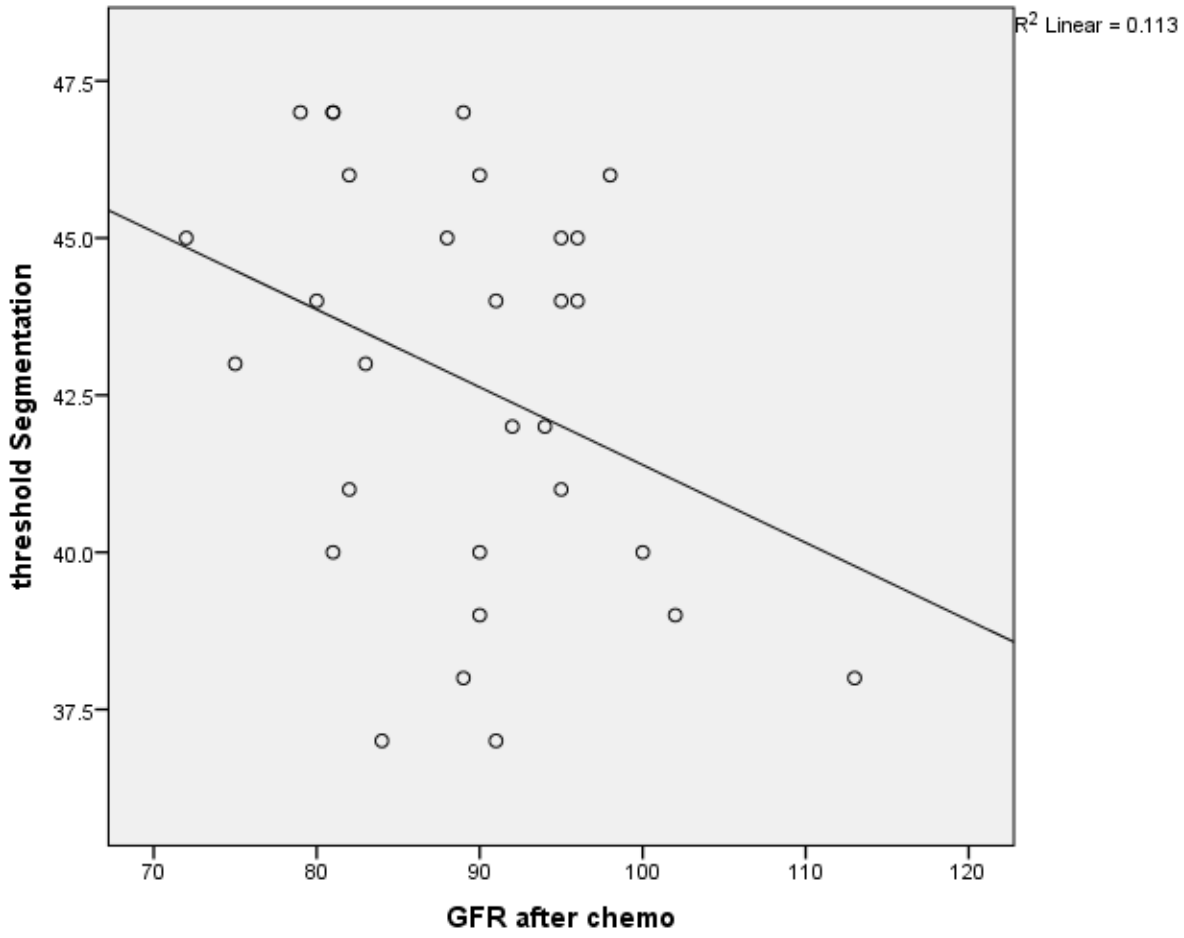

Figure 4-17 scatter plot shows the correlation of GFR after chemotherapy and threshold segmentation For group G4

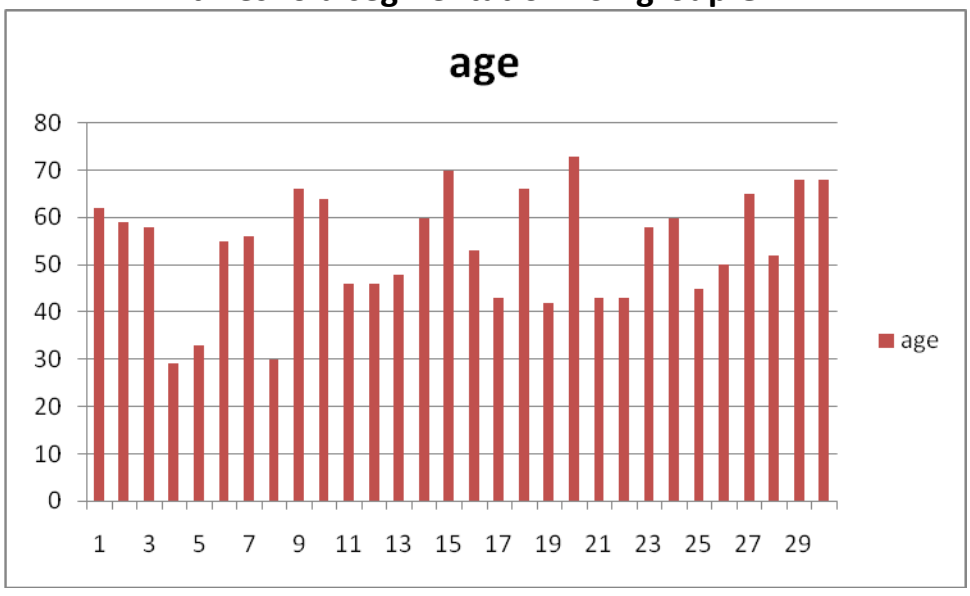

Figure 4-18 age frequency of group G4 patient

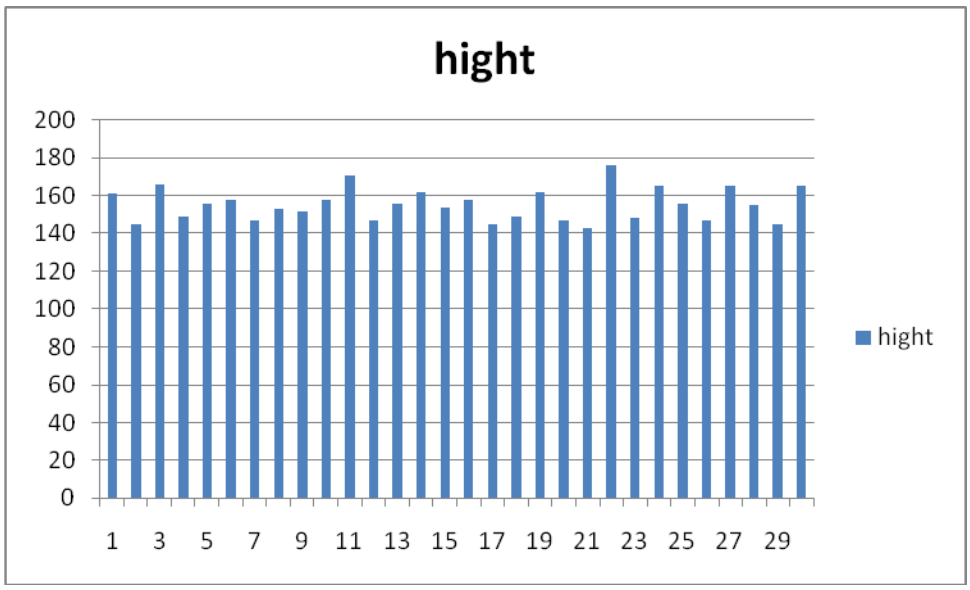

Figure 4-19 height frequency of group G4 patient

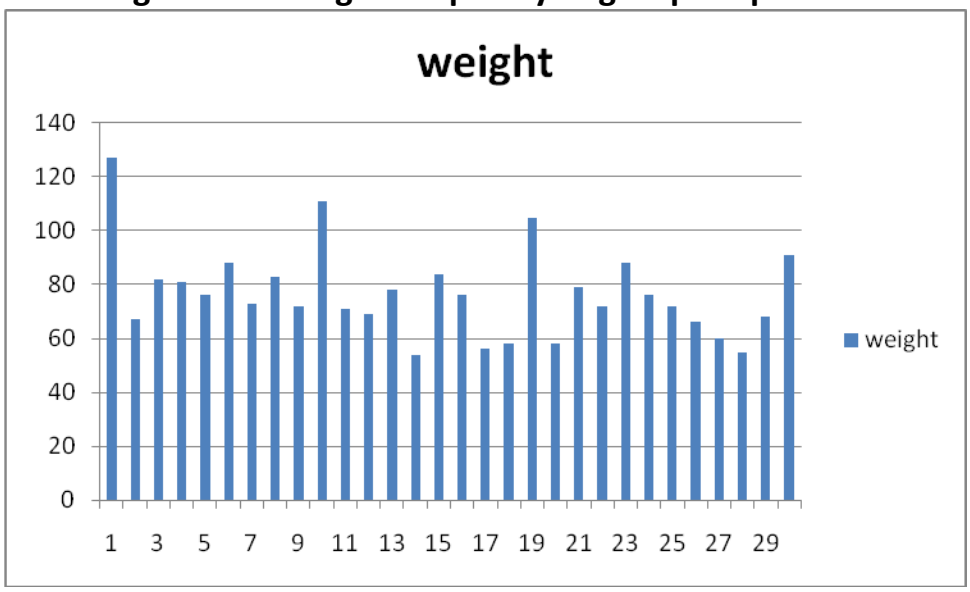

Figure 4-20 weight frequency of group G4 patient

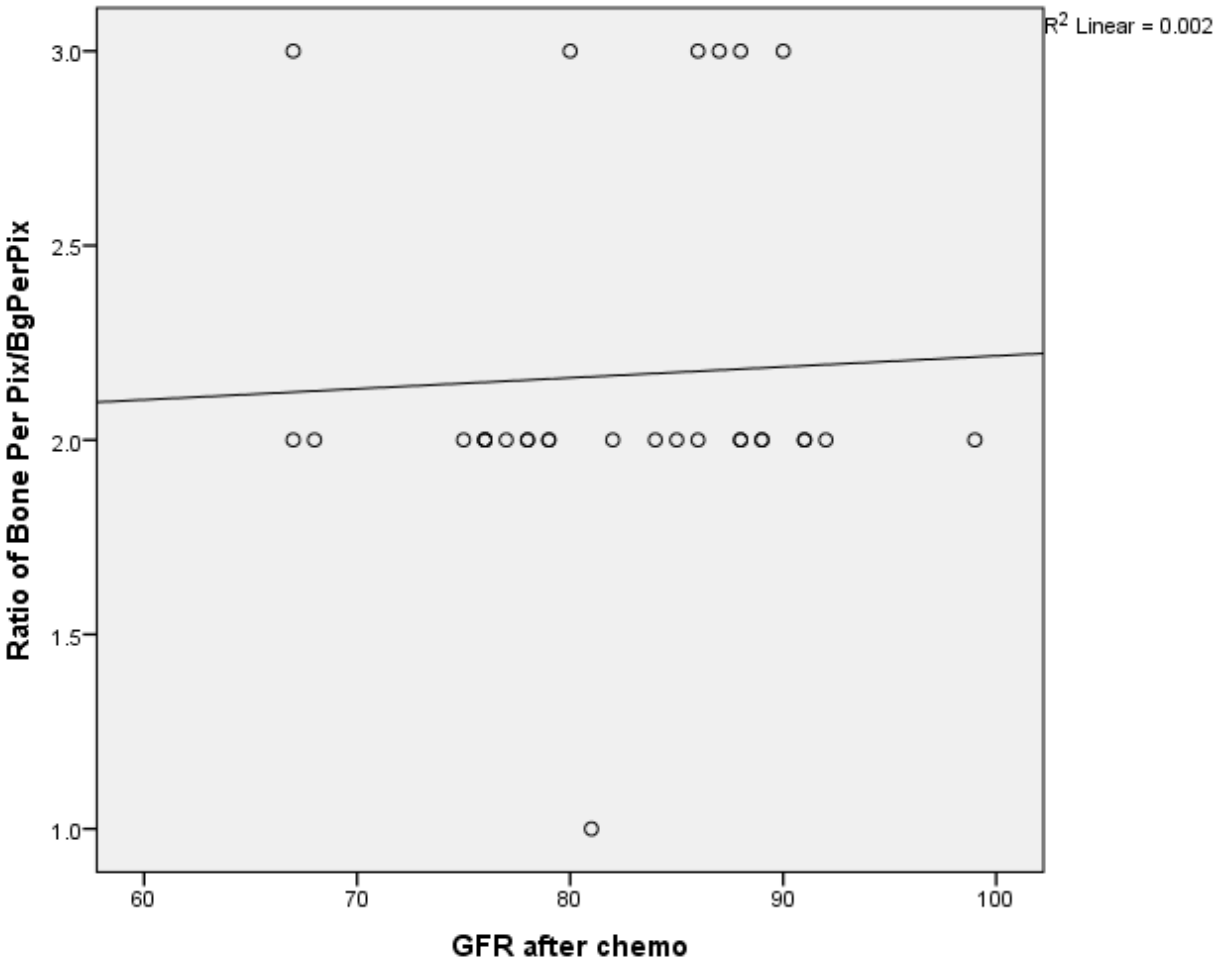

Figure 4-21 scatter plot shows the correlation of GFR after chemotherapy and ratio of bone per/background per pixel For G5 group:

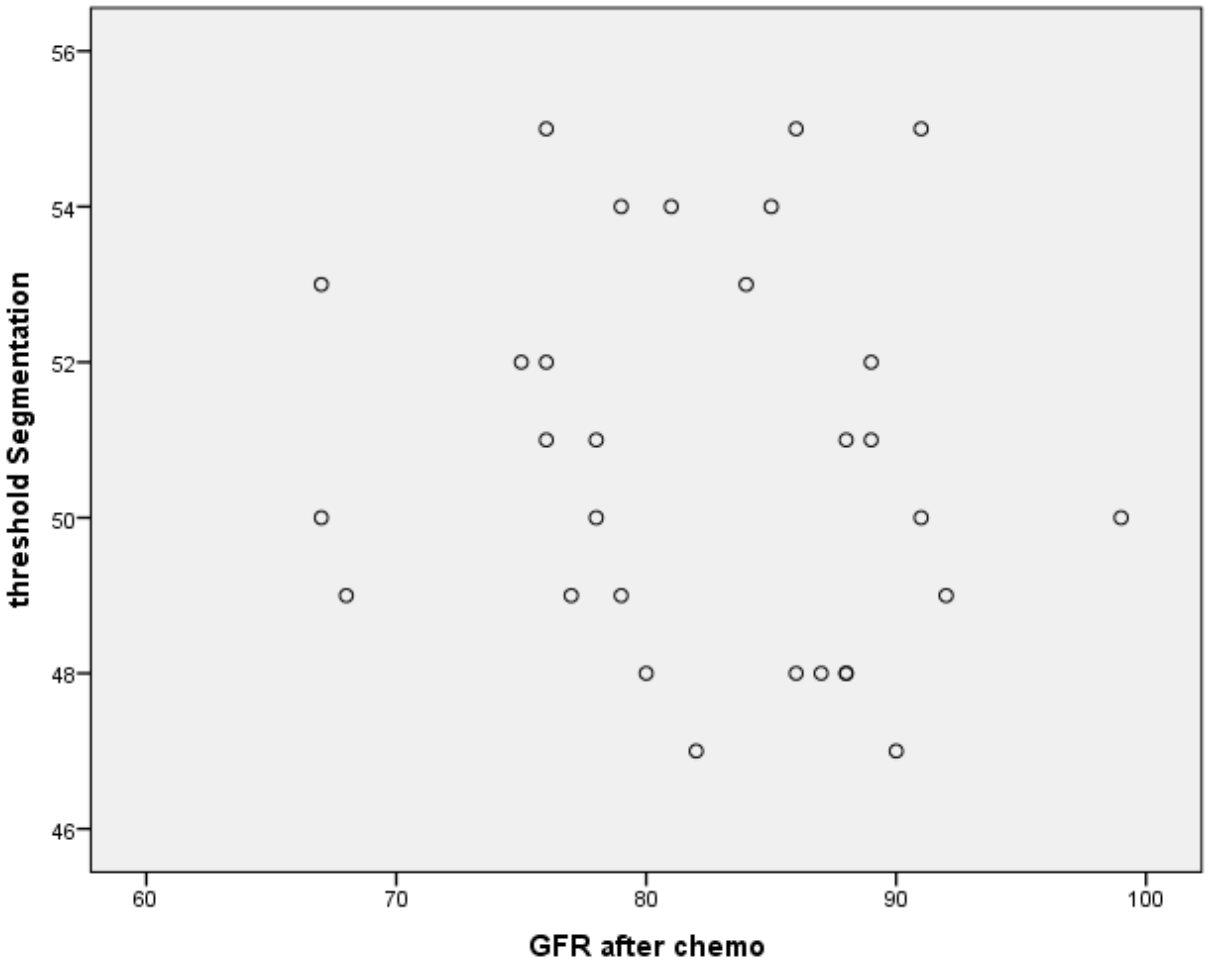

Figure 4-22 scatter plot shows the correlation of GFR after chemotherapy and threshold segmentation For group G5

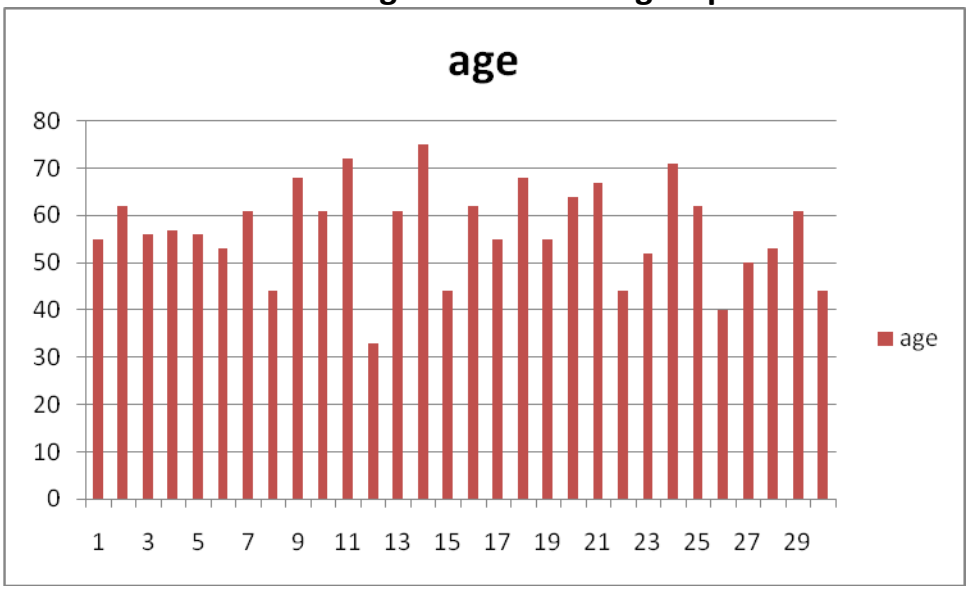

Figure 4-23 age frequency of group G5 patient

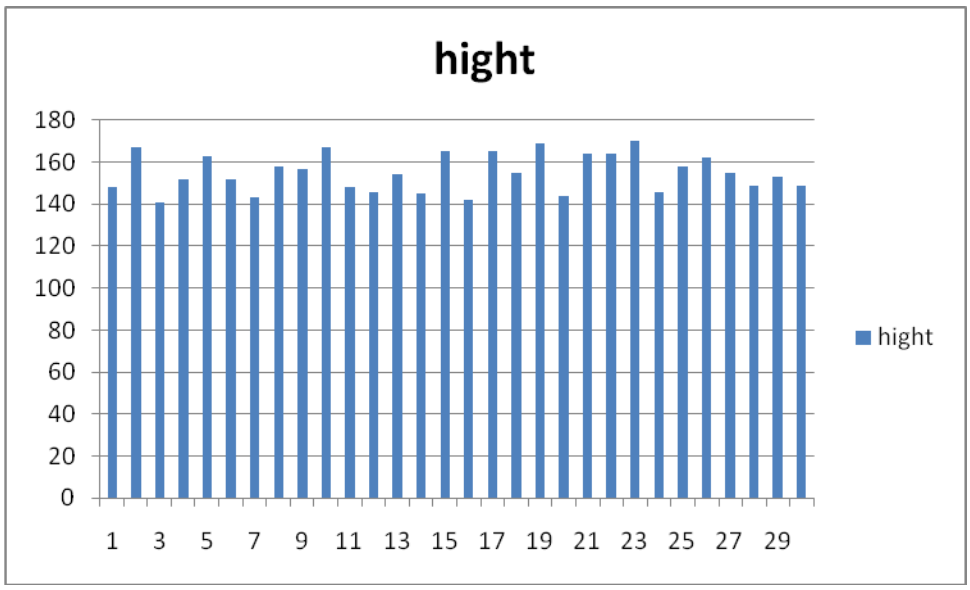

Figure 4-24 height frequency of group G5 patient

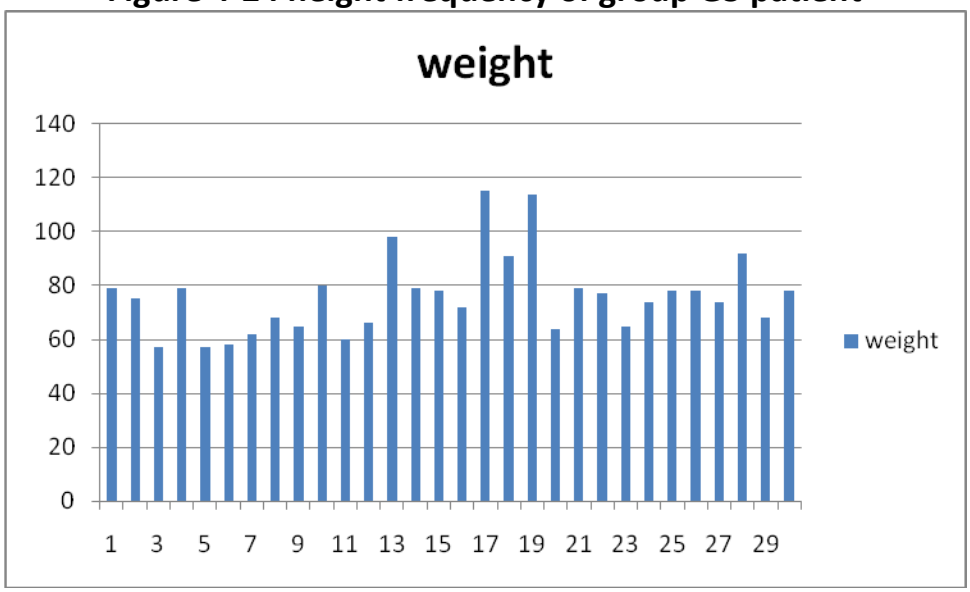

Figure 4-25 weight frequency of group G5 patient

Statistics

		age	hight	weigh t	counts in row data image	threshold Segment ation	BgPe rPix	Bone Per Pix	Ratio	NewImM ax bone highest value	FiImEnR Val (bone highest val/255)	GFR	Base line	BMI
N	Valid	120	120	120	120	120	120	120	120	120	120	120	120	120
	Missi ng	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean		52.23	155.7 7	71.57	2085887. 00	36.28	10.65	27.66	2.78	244.35		91.01	96.27	29.60
Median		53.00	155.0 0	70.00	1988231. 00	36.50	10.00	28.00	3.00	245.00		91.00	95.50	29.00
Mode		44	147[a]	65	1053950	47	9	28	2[a]	246		91[a]	94[a]	31
Std. Deviation		12.77 5	9.306	14.92 3	648184.7 76	11.838	3.219	4.403	.822	3.219		11.47 8	10.06 1	6.559

a. Multiple modes exist. The smallest value is shown

Table 4-1*statestic for all Patients groups (G2,G3G,4,G5):*

Correlations

		threshold Segmentation	Ratio	GFR
threshold Segmentation	Pearson Correlation	1	-.615**	-.552**
	Sig. (2-tailed)		.000	.000
	N	120	120	120
Ratio	Pearson Correlation	-.615**	1	.381**
	Sig. (2-tailed)	.000		.000
	N	120	120	120
GFR	Pearson Correlation	-.552**	.381**	1
	Sig. (2-tailed)	.000	.000	
	N	120	120	120

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4-2 statestic correlation of GFR threshold and bone ration for allPatients groups (G2,G3G,4,G5):

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	4812.887	2	2406.444	25.916	.000[b]
	Residual	10864.104	117	92.856		
	Total	15676.992	119			

a. Dependent Variable: GFR

b. Predictors: (Constant), Ratio, threshold Segmentation

Table 4-3 that shows anova sig for all group between GFR and threshold Segmentation

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	106.371	6.554		16.231	.000
	threshold Segmentation	-.495	.095	-.511	-5.232	.000
	Ratio	.933	1.363	.067	.685	.495

a. Dependent Variable: GFR

Table 4-4 that shows coefficients for all group between GFR and threshold Segmentation and ratio of bone value

Correlations

		threshold Segmentation	Ratio	GFR
threshold Segmentation	Pearson Correlation	1	-.615**	-.552**
	Sig. (2-tailed)		.000	.000
	N	120	120	120
Ratio	Pearson Correlation	-.615**	1	.381**
	Sig. (2-tailed)	.000		.000
	N	120	120	120
GFR	Pearson Correlation	-.552**	.381**	1
	Sig. (2-tailed)	.000	.000	
	N	120	120	120

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4-5 that shows correlation for all group between GFR after chemotherapy and threshold Segmentation and ratio of bone value

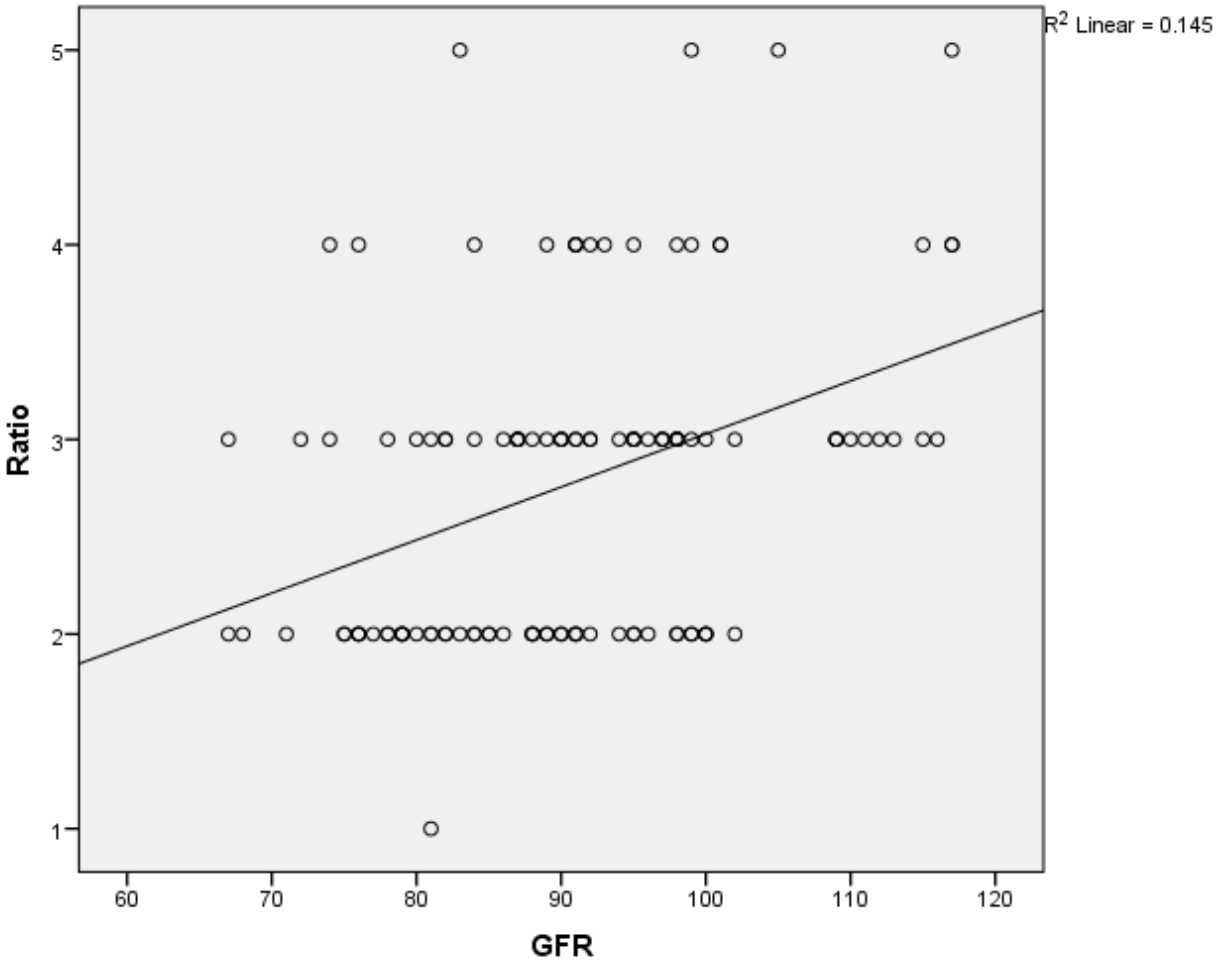

Figure 4-26shows' the scatter blot and linier regration between bone ratio value and GFR after chemotherapy in all groups (G2G3G4G5)

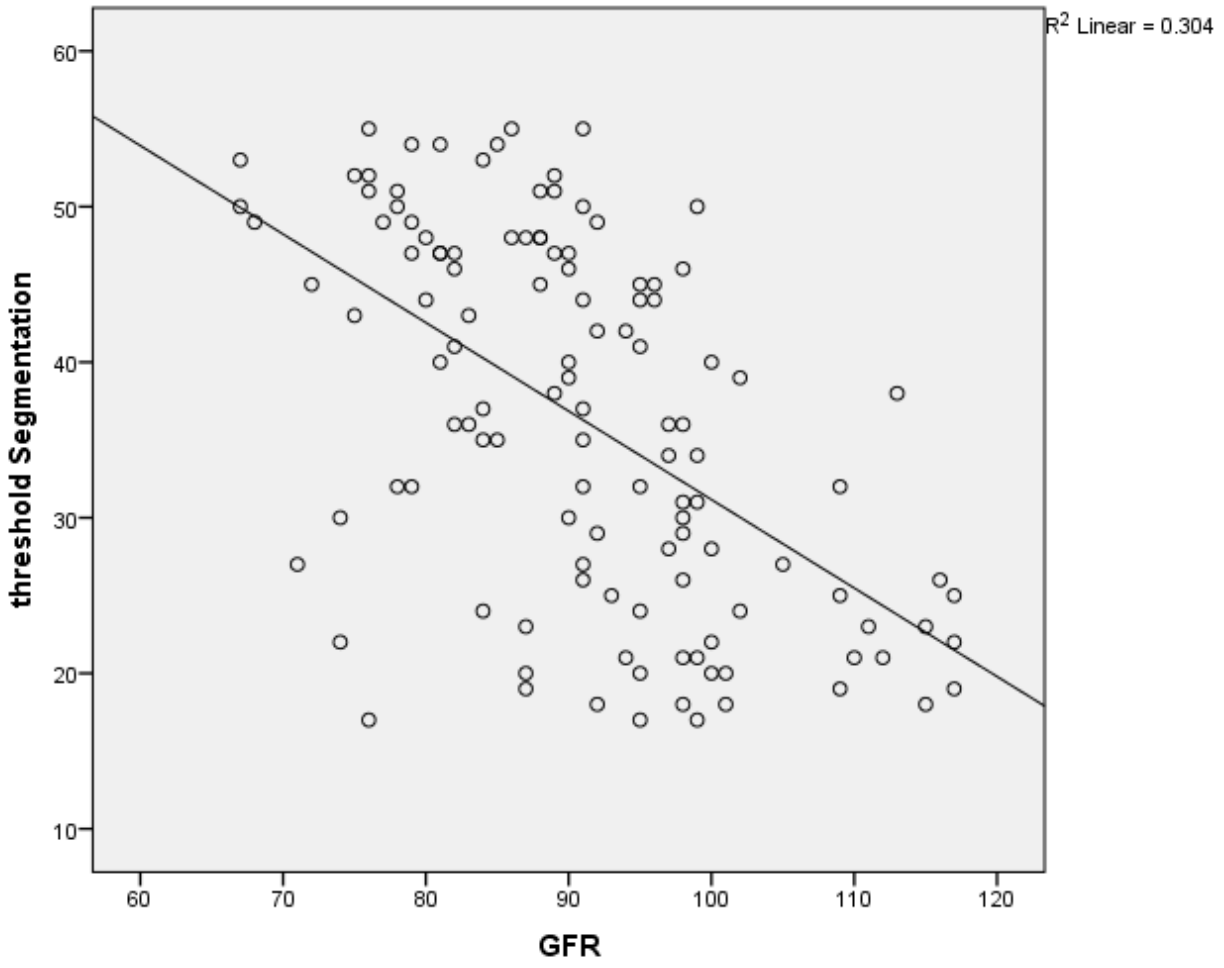

Figure 4-27shows'the scatter blot and linier R2 between threshold value and GFR after chemotherapy in all groups (G2G3G4G5)

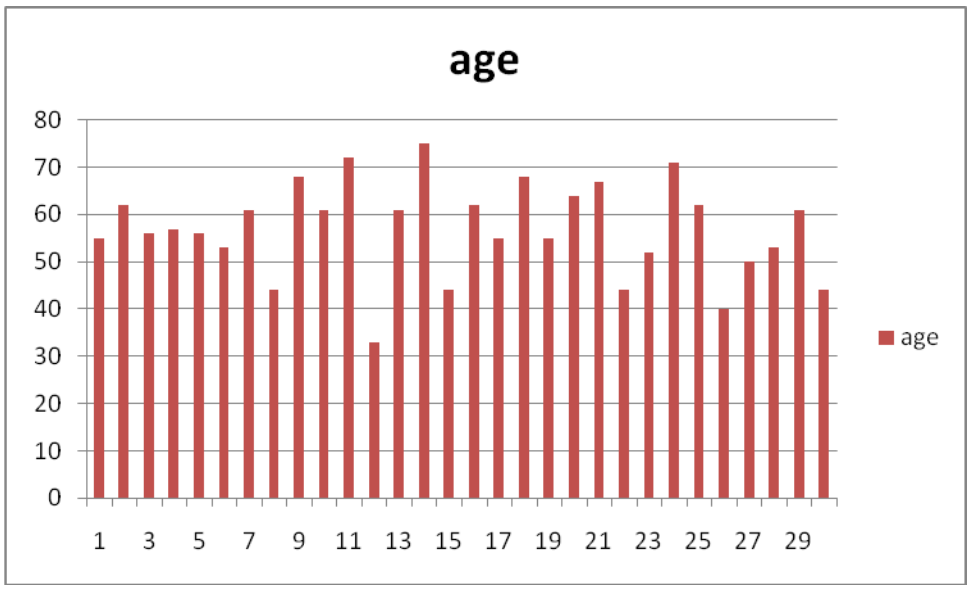

Figure 4-28 age frequency of all Patients groups (G2,G3G,4,G5)

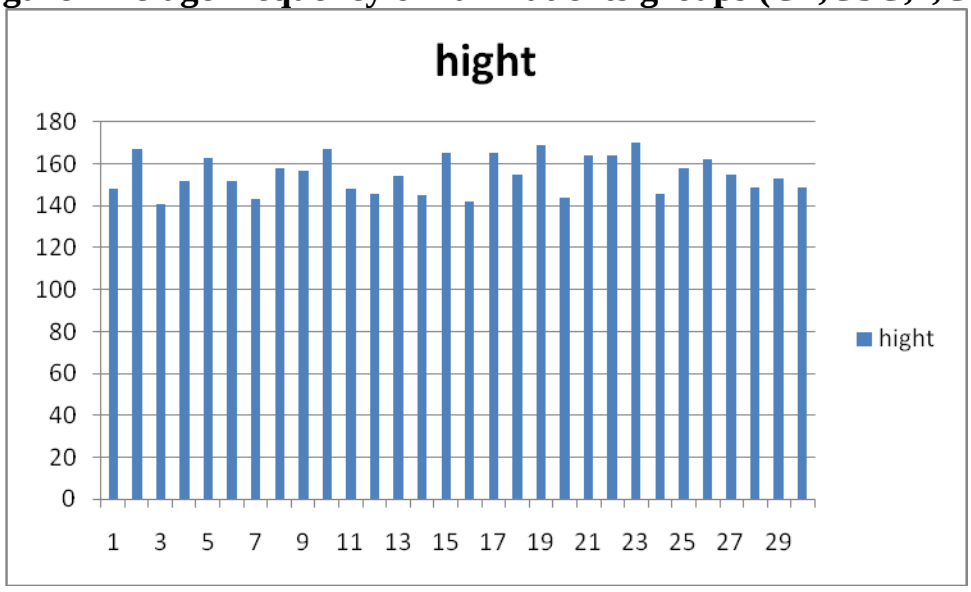

Figure 4-29 height frequency of all Patients groups (G2,G3G,4,G5)

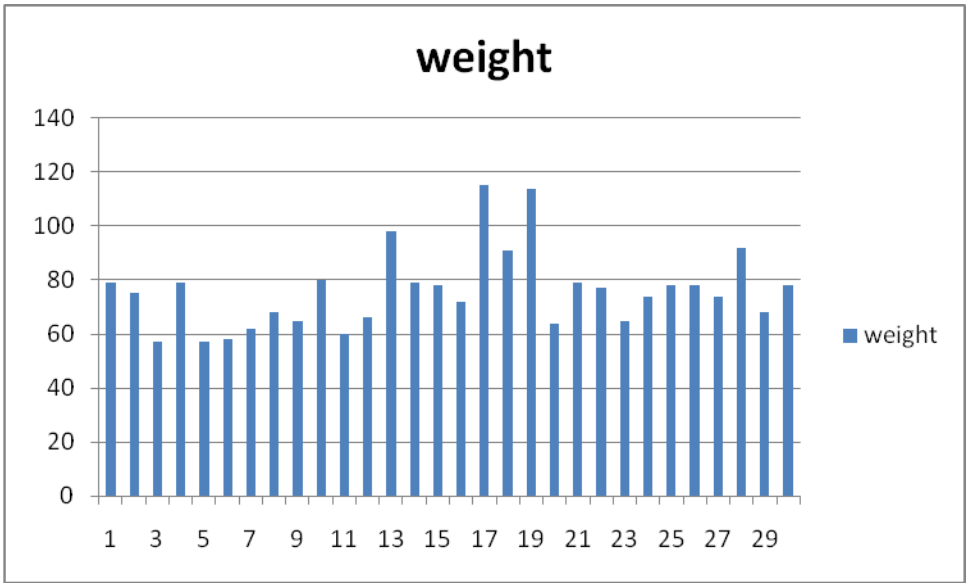

Figure 4-30 weight frequency of all Patients groups (G2,G3G,4,G5)

For controlling group:

Statistics

		age	weight	hight	counts in row data image	threshold Segmentation	BgPerPixvalu	Bone Per Pix	Ratio of Bone Per Pix/BgPerPix	NewIm Max bone highest value	rtio of (bone highest val/255)	GFR after chemo	Base line GFR	BMI
N	Valid	30	30	30	30	30	30	30	30	30	30	30	30	30
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean		51.17	70.20	157.00	2313103.13	13.43	4.77	20.43	4.57	250.23	.98	97.07	97.07	28.60
Median		48.50	70.50	157.00	2354016.50	14.00	5.00	20.50	4.50	250.00	.98	99.00	99.00	27.00
Mode		65	78	165	1232590[a]	15	6	20[a]	4[a]	249	1	85[a]	86	26
Std. Deviation		13.626	15.410	10.017	678077.430	1.960	1.104	4.508	1.406	1.104	.004	10.983	10.352	6.770

a. Multiple modes exist. The smallest value is shown

Table 4-6 that shows statistics of group G1

Correlations

		Ratio of Bone Per Pix/BgPerPix	rtio of (bone highest val/255)	Base line GFR	GFR after chemo
Ratio of Bone Per Pix/BgPerPix	Pearson Correlation	1	.733**	.142	.205
	Sig. (2-tailed)		.000	.455	.277
	N	30	30	30	30
rtio of (bone highest val/255)	Pearson Correlation	.733**	1	-.074	-.007
	Sig. (2-tailed)	.000		.698	.971
	N	30	30	30	30
Base line GFR	Pearson Correlation	.142	-.074	1	.975**
	Sig. (2-tailed)	.455	.698		.000
	N	30	30	30	30
GFR after chemo	Pearson Correlation	.205	-.007	.975**	1
	Sig. (2-tailed)	.277	.971	.000	
	N	30	30	30	30

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4-7 that shows correlation for G1 group between GFR after chemotherapy, GFR base line and Ratio of Bone Per Pix/BgPerPix and ratio of bone value

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	293.225	2	146.612	1.235	.307[b]
	Residual	3204.642	27	118.690		
	Total	3497.867	29			

a. Dependent Variable: GFR after chemo

b. Predictors: (Constant), threshold Segmentation, Ratio of Bone Per Pix/BgPerPix

Table 4-8 that shows anova sig for G1 group between GFR after chemotherapy , threshold Segmentation and Ratio of Bone Per Pix/BgPerPix

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	69.240	19.721		3.511	.002
	Ratio of Bone Per Pix/BgPerPix	2.361	1.593	.302	1.482	.150
	threshold Segmentation	1.269	1.143	.226	1.110	.277

a. Dependent Variable: GFR after chemo

Table 4-9 that shows coefficients for G1 group between GFR and threshold Segmentation and ratio of bone value (Ratio of Bone Per Pix/BgPerPix)

For group 2:

Statistics

		age	hight	weight	counts in row data image	threshold Segmentation	BgPerPixvalu	Ratio of Bone Per Pix/BgPerPix	Bone Per Pix	rtio of (bone highest val/255)	NewIm Max bone highest value	Base line GFR	GFR after chemo	BMI
N	Valid	30	30	30	30	30	30	30	30	30	30	30	30	30
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean		47.27	157.13	66.23	20966400.07	20.73	7.27	3.40	24.57	.97	247.73	100.87	99.33	27.00
Median		47.00	155.00	65.50	2023968.50	21.00	7.00	3.00	24.00	.97	248.00	102.00	99.00	27.50
Mode		26[a]	153	65	1354720[a]	21	7	3	22	1	248	102[a]	87[a]	20[a]
Std. Deviation		14.501	10.105	9.964	566139.670	2.434	.828	.724	4.199	.003	.828	11.599	11.751	4.871

a. Multiple modes exist. The smallest value is shown

Table 4-10 that shows statistics of group G2

Correlations

		Ratio of Bone Per Pix/BgPerPix	rtio of (bone highest val/255)	GFR after chemo	Base line GFR
Ratio of Bone Per Pix/BgPerPix	Pearson Correlation	1	.357	.146	.154
	Sig. (2-tailed)		.053	.442	.415
	N	30	30	30	30
rtio of (bone highest val/255)	Pearson Correlation	.357	1	-.235	-.216
	Sig. (2-tailed)	.053		.211	.252
	N	30	30	30	30
GFR after chemo	Pearson Correlation	.146	-.235	1	.992**
	Sig. (2-tailed)	.442	.211		.000
	N	30	30	30	30
Base line GFR	Pearson Correlation	.154	-.216	.992**	1
	Sig. (2-tailed)	.415	.252	.000	
	N	30	30	30	30

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4-11 that shows correlation for G2 group between GFR after chemotherapy, GFR base line and Ratio of Bone Per Pix/BgPerPix and ratio of bone value

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	137.158	2	68.579	.479	.625[b]
	Residual	3867.509	27	143.241		
	Total	4004.667	29			

a. Dependent Variable: GFR after chemo

b. Predictors: (Constant), threshold Segmentation, Ratio of Bone Per Pix/BgPerPix

Table 4-12 that shows anova sig for G2 group between GFR after chemotherapy , threshold Segmentation and Ratio of Bone Per Pix/BgPerPix

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	79.526	22.251		3.574	.001
	Ratio of Bone Per Pix/BgPerPix	2.470	3.074	.152	.803	.429
	threshold Segmentation	.550	.914	.114	.602	.552

a. Dependent Variable: GFR after chemo

Table 4-13 that shows coefficients for G2 group between GFR and threshold Segmentation and ratio of bone value (Ratio of Bone Per Pix/BgPerPix)

For group 3:

Statistics

		age	hight	weight	counts in row data image	threshold Segmentation	BgPer Pixvalu	Bone Per Pix	Ratio of Bone Per Pix/BgPerPix	NewIm Max bone highest value	rtio of (bone highest val/255)	GFR after chemo	Base line GFR	BMI
N	Valid	30	30	30	30	30	30	30	30	30	30	30	30	30
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean		51.10	155.53	67.50	1986369.13	30.90	9.10	27.77	3.07	245.90	.96	93.17	96.63	28.13
Median		49.50	156.00	67.00	2022784.00	31.00	9.00	28.50	3.00	246.00	.96	96.00	99.00	26.50
Mode		41[a]	146[a]	67	1477987	32	9	30	3	246	1	98	94[a]	26
Std. Deviation		12.829	9.933	15.359	502988.836	3.517	.885	4.216	.828	.885	.003	10.406	10.005	7.811

a. Multiple modes exist. The smallest value is shown

Table 4-14 that shows statistics of group G3

Correlations

		Ratio of Bone Per Pix/BgPerPix	rtio of (bone highest val/255)	GFR after chemo	Base line GFR
Ratio of Bone Per Pix/BgPerPix	Pearson Correlation	1	.622**	.055	.049
	Sig. (2-tailed)		.000	.774	.798
	N	30	30	30	30
rtio of (bone highest val/255)	Pearson Correlation	.622**	1	.122	.116
	Sig. (2-tailed)	.000		.522	.540
	N	30	30	30	30
GFR after chemo	Pearson Correlation	.055	.122	1	.993**
	Sig. (2-tailed)	.774	.522		.000
	N	30	30	30	30
Base line GFR	Pearson Correlation	.049	.116	.993**	1
	Sig. (2-tailed)	.798	.540	.000	
	N	30	30	30	30

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4-15 that shows correlation for G3 group between GFR after chemotherapy, GFR base line and Ratio of Bone Per Pix/BgPerPix and ratio of bone value

ANOVAa

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	286.869	2	143.434	1.357	.274b
	Residual	2853.298	27	105.678		
	Total	3140.167	29			

a. Dependent Variable: GFR after chemo

b. Predictors: (Constant), threshold Segmentation, Ratio of Bone Per Pix/BgPerPix

Table4-16 that shows anova sig for G3 group between GFR after chemotherapy , threshold Segmentation and Ratio of Bone Per Pix/BgPerPix

Coefficientsa

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	120.121	19.372		6.201	.000
	Ratio of Bone Per Pix/BgPerPix	.160	2.329	.013	.069	.946
	threshold Segmentation	-.888	.548	-.300	-1.620	.117

a. Dependent Variable: GFR after chemo

Table 4-17 that shows coefficients for G3 group between GFR and threshold Segmentation and ratio of bone value (Ratio of Bone Per Pix/BgPerPix)

For group 4:

Statistics

		age	hight	weight	counts in row data image	threshold Segmentation	BgPerPixvalu	Bone Per Pix	Ratio of Bone Per Pix/BgPerPix	NewIm Max bone highest value	rtio of (bone highest val/255)	Base line GFR	GFR after chemo	BMI
N	Valid	30	30	30	30	30	30	30	30	30	30	30	30	30
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean		53.70	155.37	76.53	2120879.27	42.73	11.37	28.17	2.50	243.63	.96	95.07	89.13	31.67
Median		55.50	155.50	74.50	1988231.00	43.50	12.00	28.00	2.00	243.00	.95	94.50	90.00	31.50
Mode		43	147	72	764250	44	12	28	2	243	1	94[a]	81[a]	32
Std. Deviation		11.931	8.536	16.571	741744.846	3.216	1.426	4.161	.630	1.426	.006	8.948	8.740	6.551

Table 4-18 that shows statistics of group G4

Correlations

		Ratio of Bone Per Pix/BgPerPix	rtio of (bone highest val/255)	GFR after chemo	Base line GFR
Ratio of Bone Per Pix/BgPerPix	Pearson Correlation	1	.634**	.157	.171
	Sig. (2-tailed)		.000	.409	.365
	N	30	30	30	30
rtio of (bone highest val/255)	Pearson Correlation	.634**	1	.433*	.464**
	Sig. (2-tailed)	.000		.017	.010
	N	30	30	30	30
GFR after chemo	Pearson Correlation	.157	.433*	1	.976**
	Sig. (2-tailed)	.409	.017		.000
	N	30	30	30	30
Base line GFR	Pearson Correlation	.171	.464**	.976**	1
	Sig. (2-tailed)	.365	.010	.000	
	N	30	30	30	30

**. Correlation is significant at the 0.01 level (2-tailed).

*. Correlation is significant at the 0.05 level (2-tailed).

Table 4-19 that shows correlation for G4 group between GFR after chemotherapy, GFR base line and Ratio of Bone Per Pix/BgPerPix and ratio of bone value

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	252.674	2	126.337	1.738	.195[b]
	Residual	1962.793	27	72.696		
	Total	2215.467	29			

a. Dependent Variable: GFR after chemo

b. Predictors: (Constant), threshold Segmentation, Ratio of Bone Per Pix/BgPerPix

Table 4-20 that shows anova sig for G4 group between GFR after chemotherapy , threshold Segmentation and Ratio of Bone Per Pix/BgPerPix

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	125.376	26.051		4.813	.000
	Ratio of Bone Per Pix/BgPerPix	.496	2.712	.036	.183	.856
	threshold Segmentation	-.877	.531	-.323	-1.652	.110

a. Dependent Variable: GFR after chemo

Table 4-21 that shows coefficients for G4 group between GFR and threshold Segmentation and ratio of bone value (Ratio of Bone Per Pix/BgPerPix)

Statistics

		age	hight	weight	counts in row data image	threshold Segmentation	BgPerPixvalu	Bone Per Pix	Ratio of Bone Per Pix/BgPerPix	NewImMax bone highest value	rtio of (bone highest val/255)	GFR after chemo	Base line GFR	BMI
N	Valid	30	30	30	30	30	30	30	30	30	30	30	30	30
	Missing	0	0	0	0	0	0	0	0	0	0	0	0	0
Mean		56.87	155.03	76.00	2139659.53	50.77	14.87	30.13	2.17	240.13	.94	82.40	92.50	31.60
Median		56.50	154.50	76.00	1957884.50	50.50	15.00	30.00	2.00	240.00	.94	83.00	93.50	30.50
Mode		44[a]	146[a]	78[a]	1053950	48	13[a]	30	2	239[a]	1[a]	76[a]	88[a]	29
Std. Deviation		10.061	8.888	14.546	765321.516	2.501	2.403	3.213	.461	2.403	.009	7.811	7.904	5.575

a. Multiple modes exist. The smallest value is shown

Table 4-22 that shows statistics of group G5

For group 5:

Correlations

		Ratio of Bone Per Pix/BgPerPix	rtio of (bone highest val/255)	GFR after chemo	Base line GFR
Ratio of Bone Per Pix/BgPerPix	Pearson Correlation	1	.695**	.048	-.137
	Sig. (2-tailed)		.000	.802	.470
	N	30	30	30	30
rtio of (bone highest val/255)	Pearson Correlation	.695**	1	.107	-.036
	Sig. (2-tailed)	.000		.573	.849
	N	30	30	30	30
GFR after chemo	Pearson Correlation	.048	.107	1	.945**
	Sig. (2-tailed)	.802	.573		.000
	N	30	30	30	30
Base line GFR	Pearson Correlation	-.137	-.036	.945**	1
	Sig. (2-tailed)	.470	.849	.000	
	N	30	30	30	30

**. Correlation is significant at the 0.01 level (2-tailed).

Table 4-23 that shows correlation for G5 group between GFR after chemotherapy, GFR base line and Ratio of Bone Per Pix/BgPerPix and ratio of bone value

ANOVA[a]

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	34.030	2	17.015	.265	.769[b]
	Residual	1735.170	27	64.266		
	Total	1769.200	29			

a. Dependent Variable: GFR after chemo

b. Predictors: (Constant), Ratio of Bone Per Pix/BgPerPix, threshold Segmentation

Table 4-24 that shows anova sig for G5 group between GFR after chemotherapy , threshold Segmentation and Ratio of Bone Per Pix/BgPerPix

Coefficients[a]

Model		Unstandardized Coefficients		Standardized Coefficients	t	Sig.
		B	Std. Error	Beta		
1	(Constant)	108.874	41.950		2.595	.015
	threshold Segmentation	-.492	.720	-.158	-.683	.500
	Ratio of Bone Per Pix/BgPerPix	-.692	3.907	-.041	-.177	.861

a. Dependent Variable: GFR after chemo

Table 4-25 that shows coefficients for G5 group between GFR and threshold Segmentation and ratio of bone value (Ratio of Bone Per Pix/BgPerPix)

CHAPTER FIVE

DISCUSSION, CONCLUSION, AND RECOMMENDATION

5.1 Discussion:

Chemotherapy used for the treatment of many tumors. Some of these tumors have a high affinity to metastasize to bone, such as genitourinary system tumors, and neuroblastoma, Bone scintigraphy is a screening test to demonstrate bone metastases and is sometimes performed during or within a few days following chemotherapy studied the renal accumulation index of Tc-99m MDP following chemotherapy. They observed a high renal uptake of Tc-99m MDP within 28 days after chemotherapy(*Daugaard G, Abildgaard U,1999*).-(*Macleod PM, et, al 1988*)also observed this high renal accumulation following chemotherapy (.*Ozhan, O, et al., 2008*) Thestudy results differed with this research relative to their application to non- human rabbits. This difference is different to the difference of the biological factor between humans and animals, as well as the method of measuring the effect of blood, the difference in measurement and the time period of measurement and can not be considered a study identical to this research due to the difference of all factors,Most of the results of this research have been agreed with(Gihad ,kh 2010) observation of this study the counts rate reach the acceptable level after 28 days ,(*Murphy KJ1, Line BR 1997*) also observed in this study as it markedly decreases sensitivity for bone disease. Bone scintigraphy should be timed so that it is performed before etidronate treatment orcisplatin, if that is not possible, more than 2 to 4 weeks after the therapy has been completed.

The aim of the study is to evaluate the effects of chemotherapy on bone scintigraphy to enhance the reliability of the acquired image and hence the diagnostic quality,to compare measured glomerular filtration rate brfor and after taking chemotherapy treatment This study focuses on oncology patients considered

for chemotherapy. We evaluated the impact of different GFR methods on the reduction of cisplatindose.

The study population consisted of 150 consecutive oncology patients female confirm diagnoses single breast cancer in the first stage were distributed into five groups, namely, control group (G1) and chemotherapy (cisplatin combination) groups (G2, G3, G4, G5). Pre-therapy and after GFR bone scintigraphies were obtained in all the groups before and after chemotherapy treatment

Treatment and demographic data are presented in Tables and figures for this study revealed that for control group(G1) patients their mean of age ,weight and height is 51.2 years , 70 Kg and 157 Cm respectively . The bone and background counts per pixel for this group mean of counts are 20.43 and 13.43 respectively with a ratio of 4.57 and 250.23 as maximum pixel counts, and the mean of GFR is 97.07 with 28.60 mean BMI, a significant correlation was found between the base line GFR and ration of the bone highest value of -.074, and this significant correlation increased significantly when comparing the value of GFR after chemotherapy treatment to the values of maximum bone counts to be -.007. There is strong significant correlation between the highest bone values counts in the image of the bone scan and ration between the background to bone ratio which indicate strongly to the hypothesis that the chemotherapy somehow affects the absorption of bone-seeking agents in the bone which result in increased the background, increasing in background result in the poor imaging quality of the bone scan, the value of this strong significant correlations between the maximum bone absorption per pixel and the ratio between the bone to background values is .733. the strong significant correlation is also founded between the baseline GFR and GFR value after chemotherapy (0.975) which indicate the renal impairments in term of GFR affected by chemotherapy.

Table (4-9)showed that the patient's bone scan after four weeks of chemotherapy treatment, the mean values of counts in row data image is 2096640.07 counts compare with the 2313103.13 counts for control group patients (table 4-6), the threshold applied for this group of patients is 20.73 compare to the 13.43 to the control group in order to provide the same image resolution of the bone, the background per pixel means in this patients group is 7.27 which is more than the value of control group patients (4.77) while the mean value of the bone target per pixel is 24.57, and the mean ratio of the bone to the backgrounds pixels is 3.40, the mean values of base line GFR for this group of patients is 100.87 while the mean values after the chemotherapy is 99.33.

Table (4-12) for the group of patients examined for bone scan after three weeks from receiving a chemotherapy treatment cycle with dysplatine, showed that the mean counts in row data image is 1986369.13 counts with 30.9 mean threshold segmentation applied for the image to be adequate interpreted image, the mean value of backgrounds per pixel is 9.10 and the bone pixel means value is 27.77 while the mean values of the ratio of the bone per pixel per background is 3.07, from the renal profile of this group of patients, the mean value of the baseline GFR is 96.63 while the mean values of GFR after the chemotherapy treatment is 93.17. Table (4-16) for the group of patients whom scanned using ^{99m}Tc-MDP bone seeking agent after two weeks from chemotherapy received intravenously, the values showed 2120879.27 counts as mean value of counts in the row data images of the all patients in this group before any type of processing, while the mean threshold segmentation value applied for processing the image is 42.73 with 43.50 median and 3.216 standard deviation, the value of background non-target per pixel is 11.37 mean, 12 median with 1.426 standard deviations, for this group of patients the mean, median and standard deviation of the counts from bone region per pixel

is 28.17, 28, and 4.161 respectively, the ratio of bone region per pixel per backgrounds region per pixel is measured to be 2.50, 2 and 0.630 mean, median and standard deviation respectively, the GFR baseline for this group of patients is 95.07 mean with 8.948 standard deviations compared to 89.13 mean value and 8.740 standard deviations for the GFR values measured after the patients treated with a chemotherapy cycle. Values of patients scanned after one week from chemotherapy line represented in table (4-20), the mean, median and standard deviation values of the counts in the row data images of the patients before any filter added or processing carried out is 2139659.53 counts, 1957884.50 counts, and 765321.516 counts respectively while the mean threshold segmentation values applied for image processing in order to increase the image resolution is 50.77 with 2.501 as standard deviation value, the mean values of background per pixel for this group of patients is 14.87 with 15 as median and 2.403 as standard deviation while the value of bone per pixels measured to be 30.13, 30 and 2.403 as mean, median and standard deviation respectively.

Table (4-20) showed that the mean value of ratio between the bone and the background counts per pixel is 2.17 with 0.461 standard deviation, the mean value of base line GFR for this group of patients is 92.5 with 7.904 standard deviations compared to 82.4 mean value of the GFR after the patients treated with cycle of chemotherapy.

From tables (5-8) with compare to the tables (1-4) and tables (9,13,17) the result showed that for groups of patients whom scanned after four weeks from chemotherapy treatment the counts in the row data image before added filter of threshold segmentation was decreased (2096640.07) compared to the mean values of the same parameter of the control group patients (2313103.13), and this values is decreased in the patients scanned after three weeks from chemotherapy cycle

treatments with mean values of 1986369.13 while this value is also decreased for the other rest of groups i.e. patients scanned two and one week after chemotherapy treatment compare to the control group, but this value was found to be considered more than the mean value of the same parameters for the other groups which includes the patients scanned for bone scan after four weeks from treated with chemotherapy and those scanned after three weeks from received intravenously chemotherapy cycle which indicate that the overall counts in the row data image was decreased after chemotherapy compared to the patients without and history of cancer nor chemotherapy treatments but without defined factors for measuring the percentage of decreasing. The mean value of background/pixel is showed to be increased as the time between chemotherapy treatments and bone scan imaging decreased, the value is 4.77 for normal control group patients, and these value increased to be 7.27 for patients scanned for bone using gamma camera SPECT system after four weeks from administration of chemotherapy as treatments essential for cancer, and then this value showed being 9.10 for group of patients whom scanned for bone after three weeks from chemotherapy treatments, then increased up to the value of 11.37 for the patients scanned after two weeks from chemotherapy administration and the value be 14.87 for the patients group which were scanned after only one week from chemotherapy treatments line. Physiologically the unbound ^{99m}Tc must be execrated from the body via renal system, this free ^{99m}Tcwhich can came from hydrolyzed reduced technetium inventory or can be result from in vivo dissociation of the components after injected to the patients intravenously, so any impairments in the renal system lead to slower clearness of these Tc^{99m}, when compared to the value of background per pixel to the GFR values the researcher find that there was strong significant correlation of 0.381between these parameters, this is so clear from the change that happened and showed in the GFR values after chemotherapy, when compare this

values to the normal control group of patients the researcher found that there is a proportional relationship between the GFR value and the chemotherapy treatments, the mean value of normal patients is 97.07 while this value was decreased rapidly for patients received chemotherapy and then increased as the time interval between chemotherapy treatments and the GFR value measured increased, so that the impairments of the renal system from chemotherapy treatments was found and considered to be temporarily impairments with the value function of time, this hypothesis explained the increased the background per pixel values in all the patients group after chemotherapy when scanned by gamma camera to evaluate the bone, and also found to be function of time values as this values increased as the time between the chemotherapy treatments and bone scanned decreased, the GFR mean values were 99.33, 93.17, 89.13 and 82.40 for the patients treated with chemotherapy and GFR measured 4,3,2 and 1 weeks after chemotherapy treatments respectively. Form the all above mentioned tables the result showed that the values of the bone counts per pixel have a direct relationship with the time between the bone scan and chemotherapy treatments. The threshold segmentation applied in image processing to the image to result in a diagnosable resolution image has a proportional relationship to the time between bone scan and chemotherapy , which indicate that the little bone absorption of the ^{99m}Tc-MDP and low image resolution can be increased by changed the threshold segmentation applied to the image, when compared the mean value of threshold for all groups of patients treated with chemotherapy to the threshold segmentation for patient without history of chemotherapy (13.43), this value changed to be 20.73, 30.90, 42.73 and 50.77 for the 4,3,2, and 1 week between chemotherapy treatments and bone scan respectively, this value showed strong significant correlation of 0.693. when compared the value of ratio of mean background pixel counts to the mean bone region pixel counts the researcher found that there is direct relationship

between the value measured and the time interval between the chemotherapy treatments and bone scan imaging, the mean value of this ratio to the normal patients whom dose not treated with chemotherapy is 0.98 and the ratio showed to be decreased after the patients having chemotherapy to be 0.94, 0.96, 0.96 and 0.97 for patients scanned for bone after one, two, three and four weeks from chemotherapy treatments respectively. When the researcher applied the specific threshold segmentation in order to increase the image quality by decreasing the values of the counts per background pixel and increased the value of counts per bone region pixel and increasing the ratio between the background counts to the bone region counts per pixel, the result showed a strong significant correlation of 0.733 between the applied threshold significant and the ratio of bone counts to the background counts the researcher set a values of recommended threshold segmentation which should be applied for bone scan image to the patients treated with chemotherapy, these set of segmentation values was depends on the time intervals between the bone scan and the chemotherapy treatments in order to increase the image quality to be quite diagnosable, the threshold segmentation should be increased by a factors of 54.4%, 130%, 218.2% and 278.2% form the threshold segmentation of the normal control groups of patients for bone scan after 4,3,2 and 1 weeks from chemotherapy treatments respectively.

5.2 Conclusion:

- It was observed that there was a significant reducing in the reading of the counts at adjusted levels according to the time period before and after the chemotherapy.This effect increases as the period of time between bone scan study and chemotherapy decreases.
- Tc-99m MDP bone scintigraphy, can be performed imaging technique for detecting bone metastases, can be performed at a period of four weeks after chemotherapy.
- The study findings revealed that the duration of effect of Chemotherapy on bone scintigraphy
- Oncology patients are a very special group of patients who differ from general population; there are significant individual differences between GFR before and after chemotherapy

5.3 Recommendation

- There has been considerable under-reporting of drug and radiopharmaceutical interactions, security and adverse reactions.
- it should be wary of the interpretations of the findings of the 99mTc MDP bone scintigraphy after the chemotherapy treatment
- The increasing use of radiopharmaceuticals has come to the attention of nuclear medicine staff and regulatory bodies.
- A study can be used to add the threshold coefficient to the software to improve the quality of the image after inserting all the parameters and time periods affecting the image after chemotherapy .
- The aim is to provide reference for adverse reactions which could help all nuclear medicine staff in their daily routine.
- Another recommendation was that the modality that gave the most definitive image of bone metastases at diagnosis should be used again to assess the response of bone metastases to treatment.
- In this study, we used the bone scan as a basic imaging method to monitor the treatment, and the effect of chemotherapy on the quality of image diagnosis by nuclear medicineeffect of patients with breast cancer and the response we observed correlates well with the worldwide studied .
- Criteria for applying nuclear imaging protocols should be selected to improve the quality of diagnosis of patient benefits.
- Current methods of assessment of therapy responses for metastatic breast cancer to the bone remain problematic with wide variations in clinical practice. Imaging techniques including PET scans and WB-MRI have the potential to address the unmet need of a robust methodology of tumour detection and therapy evaluation.

- in this study, we recommend the continuation of the researcher in the various chemotherapy and drugs effects on all study of nuclear medicine with different effects and increase the samples to give better results

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