TO DETERMINE THE PATTERN OF SKELETAL METASTASES IN PROSTATE CANCER PATIENTS USING RADIONUCLIDE IMAGING.

A DESSERTATION SUBMITTED IN PART FULFILLMENT FOR THE DEGREE OF MASTER OF MEDICINE IN DIAGNOSTIC IMAGING AND RADIATION MEDICINE OF THE UNIVERSITY OF NAIROBI.

A CROSS-SECTIONAL STUDY, CARRIED OUT IN MITC (NAIROBI)

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2009

DECLARATION

I declare that this dissertation is my original work and it has not been submitted to any other university or organization:

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DEDICATION

I dedicate this work to lovely wife Ann and our two sons Leon and Nathan for their unfailing support throughout the period of writing this dissertation.

ACKNOWLDGEMENT

I am highly grateful to my supervisors Dr. Onyambu and Dr. Thuku J. Njoroge, The Chairman and all the lecturers of the department of diagnostic imaging and radiation medicine for their assistance in writing the proposal and finally during the preparation of this work. I am also quite indebted to the following.

- Dr Adamali for allowing me access to his patients, his records and files.
- Dr Muriuki Johnson for assisting me to come up with the research topic and drafting the proposal,
- Mr. Julius the radiographer MITC radionuclide department for helping me to access patients, files and records during the study.
- Alex Mwaniki for his assistance in data analysis.
- KNH ethical committee for the guidance and approval for the study.
- The government of Kenya for sponsoring me for the MMED course.

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ABBREVIATIONS

RNI	Radionuclide Imaging
^{99m}Tc-MDP	Technetium 99-metastable labeled Methylene Diphosphonate
18F-Fluoride	Fluorine 18 labeled Fluoride
PET	Positron emission tomography
FDG-PET	Fluoro-Deoxy-Glucose-Positron emission tomography
SPECT	Single Photon Emission Computerized Tomography
MRI	Magnetic Resonance Imaging
CT	Computerized Tomography
US	Ultrasound
MBq	MegaBecquerel
MeV	Mega electron volt
SPSS	Statistical Package for Social Sciences
IVU	Intravenous Urogram
UoN	University of Nairobi
MITC	Medical Imaging and Therapeutic centre
KNH	Kenyatta National Hospital
BPH	Benign prostatic hyperplasia
PSA	Prostatic specific antigen
ENT	Ear, nose and throat
NVB	Neural vascular bundle
Ca	Cancer
T1WI	T1 weighted images
T2WI	T2 weighted images
Tc	Technetium
Tn	Tin
Na	Sodium

ABSTRACT

Prostate cancer is a common disease which occurs all over the world, affecting males as young as those in their 40's and as many as 90% of those who are in their 90's. Skeletal metastasis is a common complication of ca prostate and is known to cause high morbidity and mortality.

Scintigraphy is an imaging modality that is available and reveals the presence of disease prior to the appearance of any symptoms or structural expressions of the disease by providing information about the level of function within a body system unlike CT and plain radiography which provide structural information.

OBJECTIVES

The aim of the study was to describe the distribution of skeletal metastases in patients with metastatic ca prostate. To determine the prevalence of bone metastases in patients with prostate cancer with no skeletal symptoms and to compare RNI findings with those of plain radiography in patients with bone metastases.

METHODS

A nine month cross-sectional descriptive study was carried out between May 2008 and January 2009 at MITC. All consecutive patients with a histological diagnosis of prostate cancer and evaluated using radiography and RNI for bone metastasis were included in the study after giving consent.

RESULTS

A total of 121 patients were recruited into the study over a period of one year. The age distribution of the patient was between 51 to 94 years with a mean age of 68.9 years. Majority were referred by the oncologist and surgeons. Using radionuclide it was established that the axial skeleton was the most commonly involved site in skeletal metastases at 80.9% of the cases while metastases to the appendicular skeleton were seen in 36.7% of the patients. Majority of the patients had multiple metastases.

CONCLUSION

The study demonstrated that whole body ^{99m}Tc-MDP is a very effective way of determining the distribution of skeletal metastases in patients with prostate cancer. RNI should be included in the initial work-up of these patients. Plain radiography should be used to complement assessment areas of increased uptake. Primary health care providers should be sensitized about the potency of RNI as a modality during the management of ca prostate patients. Resources should also be mobilized to acquire gamma cameras to increase accessibility and reduce the cost of this crucial examination in the management of patients with prostate cancer.

CHAPTER ONE

INTRODUCTION

Prostate cancer is one of the most common human cancers in men; it is seen in 30% of those at 50 years of age and in 90% of men at 90years during autopsy. While it is not known just how old the disease is, it was first documented by doctors in 1853 and this is seen as the beginning of the prostate cancer history. Carcinoma of the prostate was not considered a common disease until Scott et al. found what they called "epithelioma adenoide" in specimens after prostatectomy for benign prostatic hypertrophy. Detection methods were poor at this period in history and thus prostate cancer was thought to have been a rare disease.[1]

Investigations on the use of radioactive agents for diagnosis as well as for treatment was first started by Antonio Becquerel in 1896 and continued, thanks to the work of Marie Curie, whose discovery of radioactive elements polonium and radium led to increased research on their use in the management of prostate cancer among many other malignancies.[2] In Kenya as well as in the rest of Africa the presence of this common disease is well recognized and over the last five decades there has been a recorded increase in the prevalence of prostate cancer leading to higher morbidity and mortality. This has been attributed to the late diagnosis and inadequate management of the disease and its complications.[3]

Skeletal metastasis as a complication of ca prostate is common and it is found in almost 90% of all patients who die from metastatic prostate cancer.[4] Various imaging modalities have been used to demonstrate skeletal metastases but none has been selected or indentified as the gold standard due to their difference in cost, sensitivity and specificity. [5] Several studies have been performed to determine the sites of skeletal metastases in patients with ca prostate using various imaging modalities. However, these studies have been conducted in other areas like in the Western countries and none has been conducted locally. Computer axial tomography (CT), plain radiography as well as Magnetic resonance imaging have been tried in assessing skeletal metastases with varying success. RNI has a high sensitivity only second to MRI in detecting skeletal metastases, though relatively cheaper.

This study will identify the most likely anatomical sites of skeletal metastases and demonstrate the efficacy of RNI in identifying metastases. The study will also help to sensitize the clinicians on the use of RNI in identifying early metastases for effective chemo or radiotherapy as bone metastases without therapeutic intervention is the major cause of death in patients with prostate cancer.[6]

CHAPTER TWO

LITERATURE REVIEW

According to the National cancer statistics of America, Prostate cancer is the most common cancer and the second most common cause of cancer related deaths in American men. The number of prostate cancer cases recorded in the United States and the United Kingdom has increased markedly in the last 15 years. This change predominantly represents an increase in the number of cancers diagnosed rather than a real increase in the number of cancers in the population. In the year 2006, 234,460 new cases were recorded in the USA while 27,350 deaths occurred in the same period. It was observed that 91% of these cases were diagnosed at the local or regional stages before metastases had occured.[7]

In sub-Saharan Africa, reports from the region have been hospital-based and very few studies have been done on indigenous general population. Initially it was alleged Africans in Africa rarely develop prostate cancer, and this was associated with a general short life expectancy, a diet high in fiber and low in fat and liver diseases which seemed to protect the rural African man from getting prostate cancer. In a study done to determine the prevalence of prostate cancer in Dibombari, a rural district in Cameroon, out of the 34 enrolled patients, three had cancer of the prostate, giving a prevalence of 8.6% and therefore, it was concluded that cancer of the prostate is a common disease with a prevalence comparable to that in the black population in the West.[8]
In Kenya a study done by Ngugi and Byakika (2007) in KNH, Nairobi hospital and Upper Hill Medical center to determine the histology of the prostate after prostatectomy and ultrasound guided needle biopsy, 108 cases were studied. The ages of the patients ranged between 48 and 83 years, 76% (82 patients) were found to have had benign prostatic hyperplasia while 26 patients (24%) had prostate cancer. It was concluded that prostate cancer is quite common in Kenyan population.[9]

Bone metastasis are very common in ca prostate and in a study done by Dreicer and others in 2007, they found more than 90% prevalence of skeletal metastases in patients with prostate ca at autopsy.[10] Bone metastases limit the patient's quality of life and life expectancy by causing reduced mobility, pain and bone weakness. Bone metastases also predispose these patients to

pathologic fractures, spinal epidural compression, and bone marrow failure thus bone metastases is the major cause of mortality in prostate cancer patients.[11]

In a retrospective study designed to examine the rate of clinical complications related to bone metastases carried out in the USA, a large group of non-randomized patients with metastatic prostate carcinoma was involved to determine predictors of theses complications. More than 50% of the patients developed pathological fractures, bone pain, paraplegia, anemia and hemorrhagic disorders from bone marrow failure among other complications. From these, 51% had more than one complication and approximately 80% of those with bone-limited metastases at the time of diagnosis developed metastases in other sites, as did 60% of those with bone and visceral metastases. The study concluded that skeletal complications were extremely common and the presence of bone disease at the time of initial presentation was predictive of disease complications. In this group of patients, the authors were unable to identify any racial subgroup with a lower rate of clinical complications.[12]

Mortality from prostate cancer has decreased in the United States since 1992.It has also been decreasing in the United Kingdom since 1995. This decrease has appropriately been associated with the early diagnosis of the cancer and its complications. However, these gains have not been recorded in the African population. This has been attributed to the more aggressive screening and advanced health care in the West unlike in developing countries .Maximum mortality is in those aged 85 years and older.[11]

Landis et al. in a study done in 1999 at California Cancer clinic to assess skeletal metastasis found that 60% of bone metastasis in men was from cancer of the prostate. Up to 90% of skeletal metastasis occurred in multiple sites affecting mostly axial skeleton starting with the vertebral pedicle.[12]

Memon et al. in a study to determine the common sites of prostatic cancer metastases to the skeleton using SPECT, ^{99M}TC MDP and MRI found that by the time of diagnosis the tumor had spread to more than one site. The lesions generally occurred in the axial skeleton (44%), shoulder joint (38%) and sacral iliac joint (28%). Other sites like the iliac crest, mandible, tibia,

femur and hip joint were found to be less affected. The axial skeleton which has residual red marrow is more affected in adults.[13]

Galasko in 1981 in a study to show the pathways in skeletal metastases, demonstrated that overall prostatic spinal metastases occur most commonly in the lumbar, sacral and thoracic vertebrae.[14] Bontoux et al. in France used ^{99M}TC MDP bone scans to determine the rate of bone metastases in patients with cancers of breast, prostate, lung, kidney, colon, bladder and ENT. The study showed that there were significant differences in involvement of 9 selected regions. Patients with ca prostate had more of pelvic metastases while breast cancer patients had more of skull involvement. Lung and kidney cancers gave more of skull involvement than prostate cancer.[15]

In a retrospective study done in Karachi between 1998 and 2005,135 patients with skeletal metastases from ca prostate were analyzed. Their bone scan reports were used to determine the most common secondary skeletal sites from ca prostate. The most common sites of involvement were the lumbar-sacral vertebra 33%, shoulder 28%, and sacral-iliac joint 21%. Other sites involved included the mandible, femur, sternum, scapula and hip joint.[16]

In a study done in the USA to compare SPECT and PET in assessing skeletal metastases and determine the pattern of bone metastases, the imaging characteristics of bone metastases detected using PET and ^{99}Tc MDP (SPECT) bone scans in the same patients were compared. Based on the final diagnosis confirmed through histopathology and also through clinical follow-up, the findings of patients with positive bone metastases were evaluated in terms of location, intensity, and patterns. When the PET scan was positive, the PET results were compared with the findings of available SPECT bone scans. PET revealed more lesions than did ^{99}Tc MDP bone scans, independent of the type of cancer or location of bone involvement. In patients who were diagnosed by PET imaging, the vertebrae were the most frequently involved bones, followed by pelvic bones, ribs, upper extremities including the scapula, sternum, and lower limbs.[17]

Schimid et al. in a study done in Zurich University concluded that CT is a technically feasible and reliable imaging technique in the detection of recurrent tumor tissue within the prostate in

patients with biochemically proved recurrent tumor. However, for distant metastases, SPECT was demonstrated to have been valuable in skeletal metastases.[18]

A study carried out by Effert and Bares to determine whether routine bone scanning is justified during the follow-up of patients with prostate carcinoma. The occurrence of bone pain was compared with the results of skeletal scanning, skeletal X-ray examinations and routine biochemical findings. The results reviewed showed that typical signs of skeletal metastases were found in bone scans in 74% of those who had bone pain. There was a statistical correlation between the number of affected skeletal parts and the absolute level of alkaline phosphatase. PET scans gave no evidence of bone metastases in some patients who had bone pains, skeletal metastases in 12% was found in those without any clinical symptoms. In conclusion the authors felt that bone scan in the postoperative control of prostate cancer is justified only after the onset of clinical symptoms and (or) if there is an abnormally raised alkaline phosphatase activity.[19]

In a study conducted in Australia, serial bone scans, radiographs and records of bone pain were reviewed in order to determine the relative contributions of these parameters in the assessment of response of bone metastases to treatment. Patients with abnormal bone scans due to metastatic cancer were studied with serial bone scans done every six months. Some of the patients showed an early temporary flare on subsequent bone scans including apparent new lesions after the initiation of treatment. Confirmation that such new lesions did not denote progressive disease was provided by subsequent improvement in symptoms and reduction in intensity and number of lesions on a follow-up bone scan. Target x-rays of the affected areas were found to be unreliable as a sole method for assessing response to therapy or disease progression. Tentative response criteria incorporating bone scan, target radiographs and symptoms were suggested. The criteria incorporated recognition of the fact that new lesions appearing on a bone scan within six months of initiation of therapy may comprise part of a healing flare-up response.[20]

In a study to assess the significance of skeletal scintigraphy in oncology practice, Kampmann and Buchelt underlined the high ranking of skeletal scintigraphy in assessing bone metastases. Among the patients studied, the rate of false negative scintigrams was less than 1%. After the study the question as to whether there were any bone metastases could be correctly answered

with a probability of about 96% by means of skeletal scintigraphy with an analogous x-ray film as a complementary examination.[21]

In 1964, Sklaroff and Charkles did a study to compare RNI and plain radiography in detecting skeletal metastasis. They were able to demonstrate excellent correlation between the two modalities and their complementary roles in assessing skeletal metastasis.[22] However, Farber and coworkers on a follow-up study concluded that bone scan is more sensitive than the skeletal radiograph in the detection of skeletal metastasis from cancer of the prostate.[23] Schaffer and Pendergrass in 1976 concluded that bone scans are the most sensitive means of detecting osseous metastasis. Patients with prostate cancer and normal radiographs were found to have abnormal scans. False negative bone scans occurred in less than 2% of the patients, but this was attributed to the presence of widespread symmetrical metastasis which was wrongly attributed to normal increase in osteoblasts activity.[24] However, Thrall et al. concluded that bone scans are relatively nonspecific and should be viewed along with bone radiographs. The bone scans should generally be performed before other radiological survey and detailed radiographic views should be obtained to evaluate areas of increased isotope uptake.[25]

CT scan has been extensively evaluated as a means of staging pelvic lymph nodes and regional metastasis (Levitt et al, 1978). However, it was found to be unable to detect microscopic metastasis. Most studies suggest that CT is only 50% sensitive in detecting metastasis and the false positive rate of the findings is approximately 10%[26].However, these conclusions were made using the older generation of CT scanners which used to collect the data axially but the current machines collect the data volumetrically.[27]

In a study done by Suderlund in 1996, it was concluded that the specific appearance of bone metastases is often useful in suggesting the nature of the underlying primary malignancy. Metastases from certain primary sites for instance renal cell or thyroid carcinomas are almost always osteolytic. Those from other sites like the prostate are predominantly sclerotic. Other malignancies associated with sclerotic metastases include breast carcinoma, colonic carcinoma, malignant melanoma, bladder carcinoma, and soft tissue sarcoma.[26]

In 2007 Frederic et al. did a study in Belgium to evaluate the diagnostic performance, cost and impact on health of MRI, target plain radiograph and technitium-99 bone scans in diagnosing prostate cancer bone metastases. A combination of bone scan and target plain radiograph had a sensitivity of 63% while whole body MRI detected almost 100% of the bone metastases. They concluded that MRI is more sensitive than the bone scans and radiography currently in use to identify bone metastases in high-risk prostate cancer patient. The economic impact was variable among countries, depending on reimbursement rates. However reality specifically in developing countries has to be considered while choosing alternatives.[28]

The bone scan is an important modality to evaluate skeletal pathological condition and is of utmost prognostic significance. The bone scan is the most frequently requested investigation for the evaluation of bone metastases from prostate cancer. Because of its sensitivity and the ability to examine the whole skeleton in a single examination, it still remains the, economic most important investigation in the evaluation of skeletal metastases from prostate cancer in clinical practice.

Pathology

Prostate cancer begins in the peripheral zone in 70% of the cases, 20% in transitional zone and 10% in central zone. Histologically; more than 90% of ca prostate are adenocarcinomas, about 5% are squamous or transitional cell neoplasms and less than 1% are sarcomas. The potential of tumor spread correlates with histological grade, tumor volume and tumor stage.[29] Clinically prostatism, hematuria and bone pain do occur. Pathological fractures, uremia and bleeding tendencies due to release of prostatic fibrinolysin are other clinical features.[30] For the patients known to have primary carcinoma, development of bone pain is considered to be highly suggestive of bone metastases according to Bailey and Love's short practice of surgery. [31] Patients with bone metastases may present with pathologic fractures where the force applied is less than that required to fracture a normal bone. Imaging is necessary to reveal the pre-existing lesion. Patients may also present with complications of bone metastases like neurologic impairment secondary to spinal epidural compression which occurs with vertebral metastases.[32]

Serology: PSA is used for early detection of prostatic cancer, staging cancer, monitoring response to therapy and detecting early relapse.[33]

PSA levels are classified as follows:

Normal-0-4ng/ml

- Intermediate-4-10ng/ml
- Abnormal-more than 10ng/ml
- PSA Density(>than 0.12 to 0.15 is abnormal)
- PSA Velocity(>than 20% rise per annum is abnormal)

Elevation of the serum alkaline phosphatase is a non-specific finding shared with Paget's disease and some metabolic bone diseases. The elevation reflects the mass of bone involvement.[34]

Prostate cancer staging: Historically, the staging of prostate cancer was based on the Jewett classification. Currently the TNM (Tumor, node, metastases.) system is widely used.
The American Joint Committee on Cancer revised the TNM staging system in 2002 and this revised system is clinically useful and more precisely stratifies newly diagnosed cancer.[32]

Bone Metastases

Carcinoma of breast and prostate are the two most common causes of skeletal metastases followed by the carcinoma of the bronchus (especially oat-cell) which has an incidence at autopsy of 30–55% of metastases.[33]

Pathophysiology

Tumor metastases to the bone may follow one or more of the following four routes: (1) direct extension, (2) retrograde venous flow, (3) seeding of tumor emboli via the blood circulation (4) invasion of the adjacent and distant organs through lymphatic drainage. Seeding occurs initially in the red marrow from the venous flow and this process accounts for the predominant distribution of metastatic lesions in the red marrow–containing areas in adults.[14]
The relationship between the osteoclastic and osteoblastic remodeling processes determines whether a predominant lytic, sclerotic, or mixed pattern will be seen on radiographs.
Levine et al. concluded that remodeling in metastases requires both the activation of osteoclasts to break down the existing bone and osteoblasts involved in bone formation. In ca prostate bone metastases are predominantly oteoblastic but markers of bone resorption are also increased in

skeletal metastases though there is no histological evidence of increase in the number of osteoclasts.[34]

Distribution

Bone metastases are often multiple at the time of diagnosis in prostate cancer patients. The lesions generally occur in the axial skeleton, shoulder joint and sacral iliac joint. Other sites like the iliac crest, mandible, tibia, femur and hip joint are also affected. The reason the axial skeleton is affected is because red marrow is ebbed centripetally in adults.[35]

Primary tumors arising from the pelvis particularly carcinoma of the prostate have a predilection for spread to the lumbosacral spine and overall, prostatic metastases spread most commonly to the lumbar and sacral vertebrae, followed by thoracic vertebrae. Retrograde venous embolization of neoplastic cells from the prostate to the vertebral bodies occurs due to the communication between prostatic venous plexus and the valveless vertebral bodies' venous plexus otherwise called Batson's plex.

IMAGING MODALITIES

Modalities used for imaging skeletal metastases include plain-radiography, Computer tomography, MRI and RNI.

Radiography

Plain radiographs are relatively insensitive in detecting bone metastases and only lesions measuring 2 cm or more are radiographically apparent. Metastases to bone become apparent on radiographs only when there is a loss or addition of more than 50% of the bone mineral content to the site of the disease. Clues to metastatic involvement include destruction of the pedicle and an associated soft-tissue mass in the vertebrae.[37]

The specific appearance of bone metastases is often useful in suggesting the nature of the underlying primary malignancy. Metastases from the prostate are predominantly sclerotic while those from other primary sites for instance renal cell or thyroid carcinomas are almost always

osteolytic. Other malignancies associated with sclerotic metastases include breast carcinoma, colonic carcinoma, malignant melanoma, bladder carcinoma, and soft tissue sarcoma.[38]

CT-SCAN

CT scans are valuable in the evaluation of suspicious focal abnormalities seen on bone scintiscans that cannot be confirmed using radiographs. CT is useful in further assessment of radiographically negative areas in patients who are symptomatic and in whom **metastases are** suggested clinically. Osteolytic, sclerotic, and mixed lesions are depicted well on CT scans. Total skeletal coverage with CT is not advisable because of its relatively high radiation dose which makes CT unsuitable as a screening tool.[38]

MRI

MRI is second in terms of sensitivity to ^{99m}Tc bone scintigraphy in detecting bone metastases. Whole-body MRI is a feasible alternative to bone scintigraphy in evaluating the entire skeleton for metastatic disease. Metastatic seeding in the bone marrow is characterized by long T1 relaxation times whereas T2 relaxation times are variable and dependent on tumor morphology. Lesions are seen as focal or diffuse areas of hypointensity on T1-weighted images and as areas of intermediate or high signal intensity on T2-weighted images. Tumor deposits typically appear hyperintense against a dark background of suppressed signal intensity within fat on STIR images. The bull's-eye or halo sign has been reported to be useful in distinguishing metastatic from benign lesions. In the vertebrae, additional criteria for malignancy include bulging of the posterior margin of the vertebral body, signal intensity changes that extend into the pedicle and paraosseous tumor spread.[39]

Scintigraphy

SPECT may reveal the presence of disease prior to the appearance of any symptoms or structural expressions of disease by providing information about the level of function within a body system unlike CT, MRI, and plain radiographs which provide structural information. PET is a newer technology and may provide additional information by identifying bone metastases at an earlier stage of spread before the osteoblasts activity starts. FDG PET depicts early malignant

bone-marrow infiltration because of the early increase in glucose metabolism by neoplastic cells. Images provided by PET are of a higher quality than those provided by SPECT but its unavailability and cost limit its use. SPECT specificity has been found to be close to that of PET in diagnosing skeletal metastases despite its lower sensitivity. SPECT compared to PET is more available and cheaper.[27]

In SPECT ^{99m}Tc methylene diphosphonate (MDP) is the most frequently used isotope for screening the whole body while assessing for bone metastases. Indium^{111} is used to assess non skeletal ca prostate metastases like spread to the abdominal organs.[24]

Isotope imaging depicts bone metastatic lesions as areas of increased tracer uptake.[40]

Bone scintigraphy is done to:

1. Assess tumor staging in asymptomatic patients.
2. Evaluate persistent pain in the presence of equivocal or negative radiographic findings in patients with ca prostate.
3. Determine the extent of bone metastases to other skeletal sites in patients with positive radiographic findings.
4. Differentiate metastatic lesions from traumatic fractures and other lesion or normal areas of increased radioisotope uptake by assessing the pattern of involvement.
5. Assess the degree of response to radiotherapy or therapeutic treatment in patients with skeletal metastases.

The gamma-camera is used as the image detector and should preferably have a low energy high resolution collimator. The whole body is imaged and the Patients should be well hydrated and asked to empty the bladder before examination.[33]

^{99m}Tc-Methylene diphosphonate (MDP) is used at the dose of 500MBq.

CHAPTER THREE

STUDY JUSTIFICATION

1. The study is important as an aid to management options of patients since RNI whole skeleton scanning plays an important role in early detection of bone metastases which can help to determine the best treatment strategy, therefore reducing the morbidity and mortality in these patients.
2. This study will sensitize the clinicians on the utilization of this imaging modality and therefore reduce the morbidity and mortality that occurs due to late diagnosis of bone metastases.
3. The study is important as a prognostic tool in patients with bone metastasis from cancer of the prostate since patients who experience recurrence after treatment at only one or two sites have a survival advantage over those with more extensive skeletal metastasis (>2sites).
4. Studies done on the subject were carried out in other populations and none has been done locally, the study will bridge the knowledge gap by relating the findings elsewhere with the findings of the study.

CHAPTER FOUR

STUDY OBJECTIVES

Main Objective

1. Evaluation of RNI in determining the pattern and distribution of bone metastases in ca prostate patients seen in MITC (Nairobi).

Specific objective

1. To describe the distribution of skeletal metastases in patients with metastatic ca prostate.
2. To determine the prevalence of bone metastases in patients with prostate cancer with no skeletal symptoms.
3. To determine the effectiveness of RNI in assessing skeletal metastases.

Hypothesis

RNI is an important diagnostic tool in determining the patterns and distribution of bone metastases in patients with prostate cancer.

CHAPTER FIVE

METHODOLOGY

Study design

Cross-sectional descriptive study.

Study area

The study was carried out at Medical Imaging and Therapeutic Centre (MITC), Nairobi.

MITC as the study center was chosen because of the number of patients attended to in the institution for the investigation of skeletal metastases secondary to ca prostate.

Study population

The study population consisted of patients with confirmed prostate cancer who had been referred for whole body radionuclide bone scanning with or without a complementary target plain radiograph.

The diagnosis of ca prostate was made by the clinician through clinical history and examinations, serological tests or through tissue biopsy.

Selection of patients

Non -randomized method was used and all patients who qualified for the study by meeting the inclusion criteria were included.

Inclusion criteria

All patients referred to MITC with a confirmed primary cancer of the prostate for radionuclide imaging to assess presence of bone metastases after giving consent to be included in the study.

Exclusion criteria

-Patients who declined participation in the study.

-Patients who had other malignancies diagnosed clinically, serologically or through biopsy, which had skeletal metastases.

Sample size determination

Prostate cancer is extremely common and frequently involves bone[9].

The prevalence of prostate cancer in Kenyan male like in other African population is 8600persons per 100, 000 or 8.6% in those between 30 and 85 years of age.[8]

Sample size was determined by following the formula by Fisher et al (1998)

$$n = \frac{z^2 p(1-p)}{d^2}$$

Where n = desired sample size

z = standard normal distribution

p = known prevalence rate for the factor of interest under study

d = the level of significant desired

When this formula is applied at d = 0.05, z = 1.96, p =0.086,

1-p= 1-0.086 =0.914

$$n=\frac{1.96 * 1.96 * 0.086 (1-0.086)}{(0.05)^2}$$

n= 120.786

n=121

Control of bias

Consecutive patients examined during the period of the study were included except those who declined participation. Only patients referred for the RNI with, histologically confirmed diagnosis of prostate cancer were included. Reporting of RNI images was done by the investigator with the help of a radiologist stationed at the RNI center while plain radiographs were reported by consultant radiologists other than the one who reported RNI. The same Diacam single head gamma camera was used on all the patients.

Materials and Procedure

Equipment

A Diacam single head gamma camera from Siemens with high resolution low energy collimator was used to acquire the images of all patients who were included in the study.

Procedure: Before the examination the patients were prepared by encouraging them to drink plenty of water and empty the urinary bladder frequently. Delayed static imaging was performed 2 or more hours after intravenous injection with 20-24mci of ^{99m}Tc-MDP. The extremities were imaged in up to 4 hours while those on dialysis or renal failure took up to 6 hours. The images taken included the anterior and the posterior views of the whole skeleton plus anterior oblique views of the thorax to separate the uptake from the spine and the sternum. For examination of the posterior ribs, scapula or shoulder, an extra posterior thorax view with arms above the head were taken to move the scapula away from the ribs. For imaging small bones and joints, magnified views were taken.

Data collection, Analysis and presentation

Data was collected by the investigator from MITC. Radionuclide skeletal survey findings were recorded using a structured data collection sheet (appendix 1). Patient's bio-data (age, serial no), clinical summary and the specialty of the referring clinician were recorded on the request forms. Possible source of error included inadequate clinical summary from the clinician and imaging parameters like patient motion during imaging.

Data Analysis

The data was then entered into the computer spread sheet and analyzed using, software programme for social science research (SPSS). The results were presented in the form of frequency distributions and descriptive statistics and then discussed. The variables analyzed included patients bio-data, reason for referral, histological diagnosis, category of referring clinician and metastatic sites.

Study limitations

1. Degenerative conditions, old fractures and bone infections may show areas of increased tracer uptake and could be mistaken for metastases.
2. Presence of other unidentified malignancies could give skeletal metastases which would be assumed to be prostatic in origin.
3. Incomplete clinical data from the primary clinician who did not clarify the exact reason of referral for bone scan which was sorted out by taking the history in department.
4. Previous treatment with chemotherapy or radiotherapy could have altered the pattern of metastases and radiographic and scintigraphic features.

Ethical Considerations

Patient's name was not recorded during the study to maintain confidentiality.

The information acquired will not be used for any other purpose other than the study.

No information or examination results shall be obtained without patient consent.

No examination was done on the patient except the one requested by the primary physician.

Before commencement of the study a request was submitted together with a copy of the proposal to the ethical and research committee at KNH and approved.

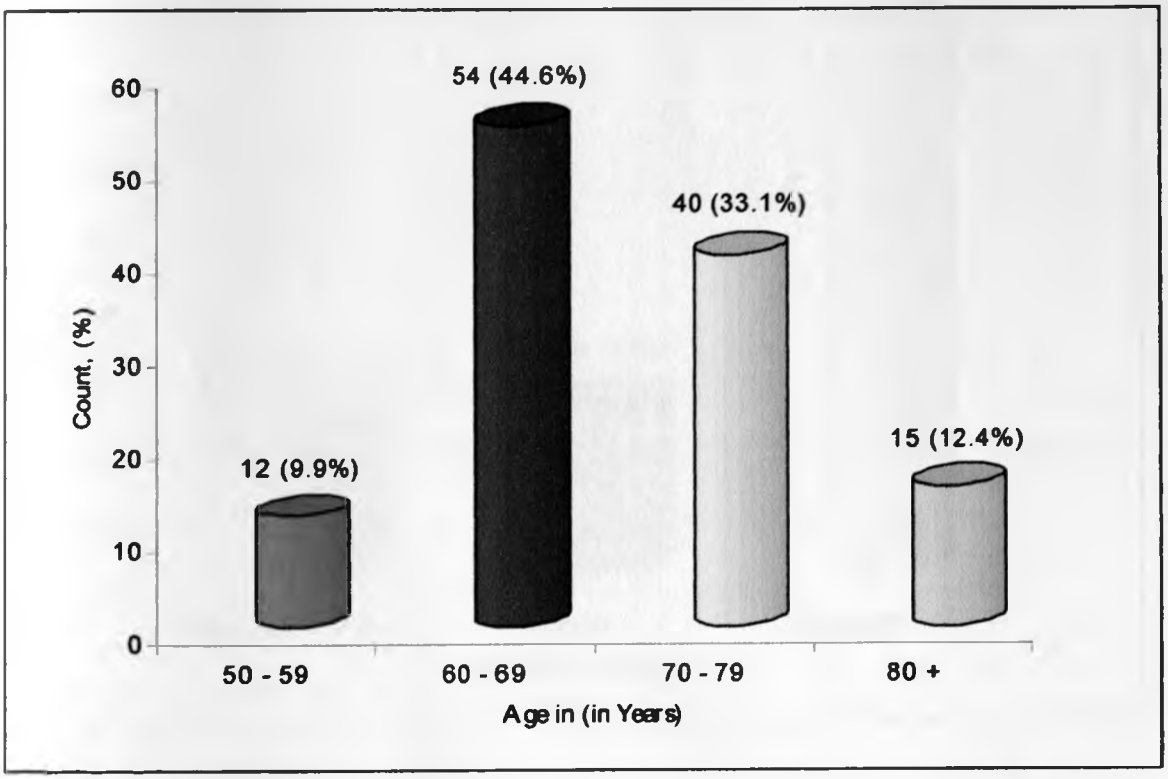
Approval to conduct the study at MITC was obtained.

CHAPTER FIVE

RESULTS

A total of 121 patients were included in the study. The age ranged between 51 to 94 years with a mean age of 68.9 years. Figure 1 shows the age distribution of the patients included in the study.

Figure 1: Distribution by Age (in years)

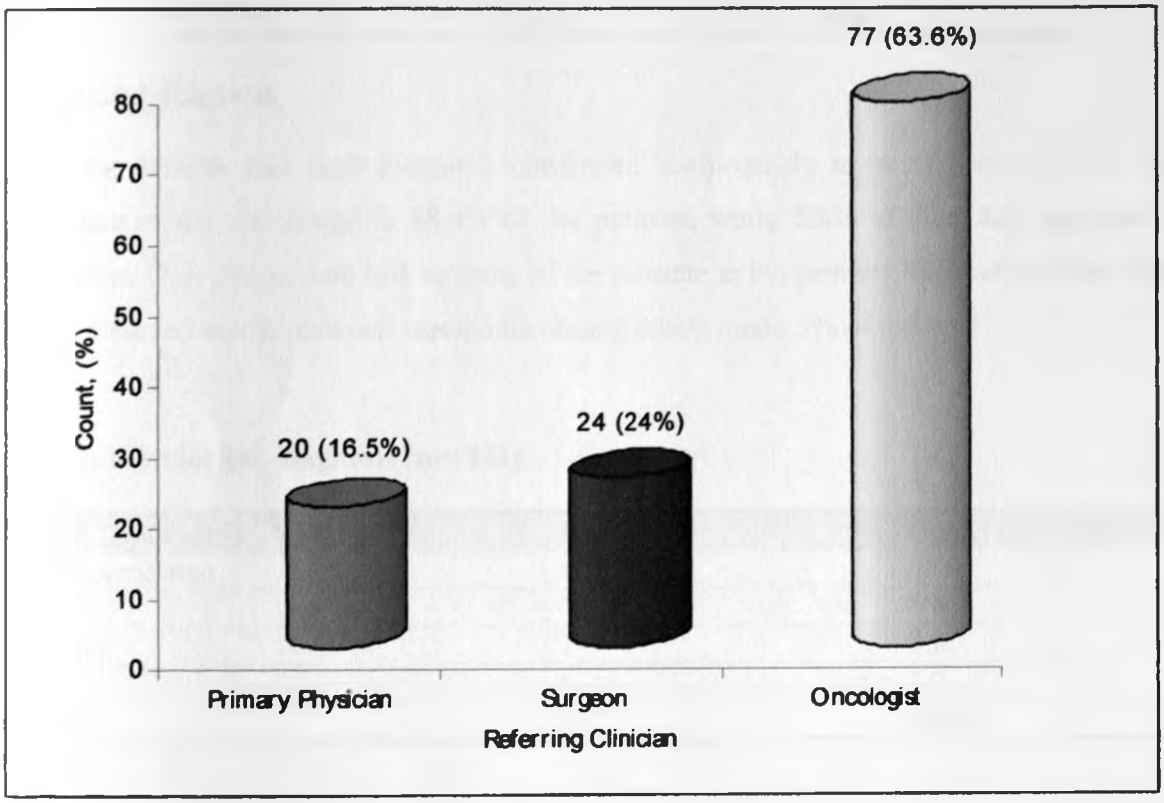


Majority of the patients 54 (44.6%) were between 60-67 years, these were followed closely by those between 70-79years who were 40 in number making 33.1%.Those above 80 years of age were only 15(12.4%).Twelve patients (9.9%) were below 60 years of age.

Referring Clinician

During the study, it was established that majority of the patients were referred by the oncologist 63.6%, surgeons 24% while primary physician who has the first and most frequent contact with the patients only referred 16.5%.

Figure 2: Distribution by Referring Clinician (n = 121)



Clinical Features at the Time of Referral

Bone pain was the most common clinical presentation given by the majority of patient before they were referred for radionuclide bone scan (72.7%). Pathological fractures were found in only 3.3%. Twenty five patients or 20.7% of all referred patients had non skeletal symptoms like urinary retention, weight loss and general body weakness. The other reasons for referral included follow-up during the course of management

Table 1: Clinical Features at the Time of Referral (n = 121)

Clinical Feature	Frequency	Percent
Bone Pain	88	72.7
Pathological Fractures	4	3.3
Others (follow-up)	4	3.3
Non-Skeletal symptoms	25	20.7
Total	**121**	**100.0**

Histological diagnosis

All of the patients had their diagnosis confirmed histologicaly as shown by the table above. Adenocarcinoma was found in 88.4% of the patients, while 5.8% of them had squamous cell carcinoma. Only one patient had sarcoma of the prostate as his primary diagnosis. Other varieties which included transitional cell carcinoma among others made 5% of the total

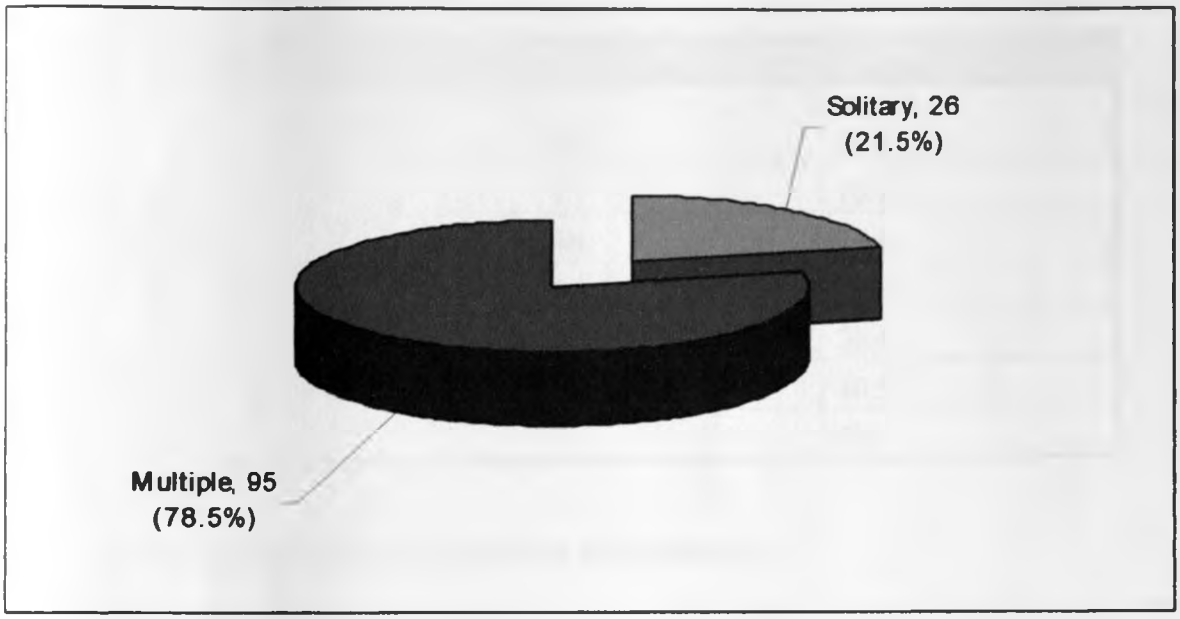
Table 2: Histological diagnosis (n = 121)

Clinical Features	Frequency	Percent
Adenocarcinoma	107	88.4
SCC	7	5.8
Sarcoma	1	0.8
Other	6	5.0
Total	**121**	**100.0**

Metastatic status at the time of referral

Through radionuclide study, it was established that 78.5% of the patients had more than one site of skeletal metastases, only 21.5% had a solitary site of skeletal metastases as demonstrated by the table below.

Figure 3: Metastatic status using radionuclide imaging



Distribution of metastases.

On the distribution of skeletal metastases axial skeleton was affected in 80.9% while metastases to the appendicular skeleton were seen in 33.4% as shown below.

Table 3: Distribution of metastases to the axial and appendicular akeleton.

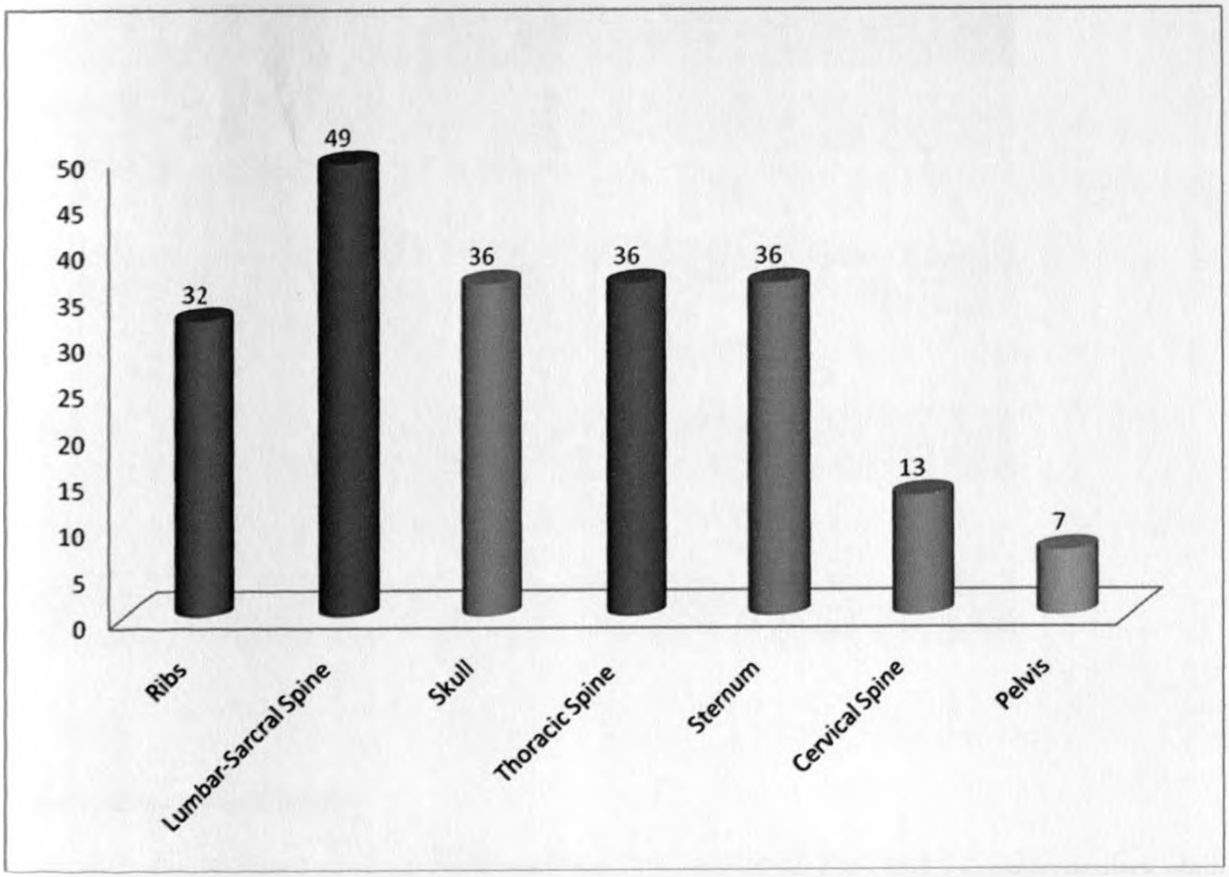
Skeletal site	Frequency	Per Cent
Axial skeleton	98	80.9
Appendicular skeleton	44	33.4

The lumbar-sacral spine was the most commonly affected site on the axial skeleton at 40.5% followed by the thoracic spine; sternum and the skull which were involved in 30.4% each. The ribs were involved in 31.3 % of the cases. The cervical spine was involved in 10.7% of the cases while the pelvis was the least involved part of the axial skeleton at 5.8% as shown on the table below.

Table 4: Distribution of metastases to the axial Skeleton.

Axial	Frequency	Percent
Skull	36	30.4
Cervical Spine	13	10.7
Thoracic Spine	36	30.4
Sternum	36	29.8
Ribs	32	26.4
Lumbar-Sacral Spine	49	40.5
Pelvis	7	5.8

Figure 4: Distribution of metastases to the axial Skeleton.



Distribution of metastases to the appendicular skeleton

The appendicular skeleton was divided into the upper limbs including the shoulder girdle and the lower limbs. On the upper limbs, the scapular was involved in 5 patients (11.5%), the clavicle 2(4.5%) and the humerus 2(4.5%). The ulnar was involved in 1(2.3% of the patients. The radius, phalanges, carpal and metarcarpal bones were not involved. On the lower limbs the femur was the most affected bone of 14(31.8% while the tibia and the fibula were both involved at 2(4. 5%) each as shown by the table below.

Table 5: Distribution of metastases to the appendicular skeleton.

Site of metatastases	Frequency	Percentage
Scapular	5	11.4%
Clavicle	2	4.5%
Humerus	2	4.5%
Ulna	1	2.3%
Femur	14	31.8%
Tibia	2	4.5%
Fibula	2	4.5%

Plain radiography findings

Only 18, of the 121 patients examined using RNI for bone metastases had a complementary plain radiograph done. The lumbar sacral spine was the most commonly involved site in the skeletal

system at (38.8%). The ribs were affected in 22.2%, the thoracic spine and pelvis in 11.1% each, while the skull, sternum and the femur were affected in 5.6 % each as shown on the table below.

Table 6: Distribution of metastases using plain radiography where it was done.

Site	Frequency	Percent
Skull	1	5.6%
Thoracic Spine	2	11.1%
Sternum	1	5.6%
Ribs	4	22.2%
Lumbar-Sacral Spine	7	38.8%
Pelvis	2	11.1%
Femur	1	5.6

Table 7: Association between histological type and site of metastases

Type of Malignancy	Scan Finding		OR (95% CI)	p-value
	Solitary, n (%)	Multiple, n (%)		
Adenocarcinoma	22 (84.6)	85 (89.5)	0.6 (0.2 – 2.3)	0.493
Sarcoma	0	1 (1.1)	-	-
SCC	2 (7.7)	5 (5.3)	1.5 (0.3 – 8.2)	0.638
Other	2 (7.7)	4 (4.2)	1.9 (0.3 – 11.0)	0.469

There was no significant association between the histological type and the status of metastases ($p>0.05$).

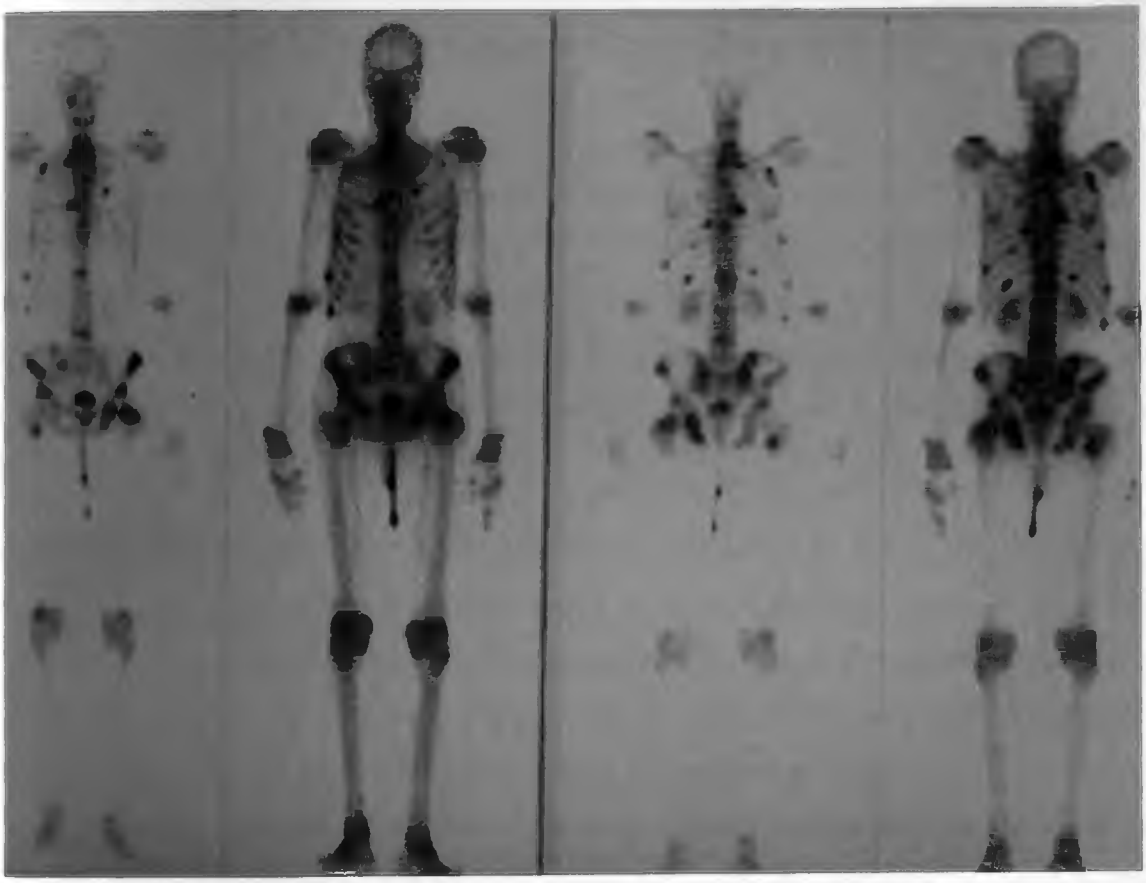
Table 8: Association between age and Status of Metastasis

Age	Status of Metastasis		P-value
	Solitary, n (%)	Multiple, n (%)	
50-59	2 (7.7)	10 (10.5)	Reference
60-69	10 (38.5)	44 (46.3)	1.000
70-79	11 (42.3)	29 (30.5)	0.706
80+	3 (11.5)	12 (12.6)	1.000

There was no significant association between the status of metastases and the age of the patient ($p>0.05$).However the most commonly involved age group also had the highest number of multiple metastases.

SELECTED IMAGES

The scintigram 1 below demonstrates areas of increased uptake of radiopharmaceutical in the cervical region, the ribs and the pelvis.



Discussion:

The nine month cross-sectional descriptive study was carried out between May 2008 and January 2009 at MITC Nairobi where 121 patients with ca prostate and skeletal metastases were assessed. Their age ranged between 51 to 94 years with a mean age of 68.9 years.

The age distribution is in keeping with the ca prostate prevalence within the general population where at 50 years of age 30% have histological evidence of ca prostate with the prevalence rising with age advancement. The low frequency for those above 80 years (12.4%) could be related to the low life expectancy which according to Kenya demographic health survey of 2003 is 51years.[41]

During the study it was established that majority of the patients were referred by the oncologist 63.6%, surgeons 24% while primary physician who has the first and most frequent contact with these patients only referred 16.5%. These findings could be explained by the fact that majority of patients were treated for advanced disease after histological diagnosis through prostatectomy or transrectal biopsy after which they were referred to the oncologist by the primary physician or surgeon for chemotherapy or radiotherapy.

Bone pain was the most common clinical presentation given by the majority of the patients before they were referred for radionuclide bone scan72.7%. Pathological fractures were found in only 3.3%. Non skeletal features like urine retention, weight loss and general body weakness was found in 25 patients (20.7%). These findings led to investigators conclusion that patients who present with skeletal clinical manifestation have a high chance of having skeletal metastases. However patients who present with non skeletal symptoms have a significant chance of having clinically silent skeletal metastases with associated morbidity and mortality.

Adenocarcinoma was found in 88.4% of the patients this in keeping with other works done previously which found adenocarcinoma to be the most prevalent histological type of prostate cancer at 90% followed by squamous cell carcinoma at 5%. In our study squamous cell carcinoma was seen in 5.8% of the patients. Only one patient had sarcoma of the prostate as his primary diagnosis. Other variety included transitional cell carcinoma among others which made 5% of the total. There was no significant association between specific histological types of prostate cancer and any skeletal site of secondary deposits

On imaging through radionuclide study, it was established that 78.5% of the patients had more than one site of skeletal metastases; only 21.5% had a solitary site of skeletal metastases. These findings correlated well with the results of a study done by Landis et al. in 1999 at California Cancer clinic. They found that up to 80% of skeletal metastasis occurred in multiple sites affecting mostly axial skeleton starting with the vertebral pedicle.[12]

On the pattern of metastases using ^{99m}Tc-MDP, axial skeleton was affected in 80.9% while metastases to the appendicular skeleton were seen in 33.4%. The most commonly affected site on the axial skeleton was the lumbar-sacral spine at 40.5% followed by the thoracic spine, sternum and the skull which were involved in 30.4% of the cases each. The ribs were affected in 31.3% of the cases. The cervical spine was affected in 10.7% of the cases while the pelvis was the least involved site of the axial skeleton at 5.8% of the cases. These findings correlate with the results in a study by Galasko CSB who concluded that primary tumors arising from the pelvis particularly carcinoma of the prostate have a predilection of spreading to the lumbar-sacrum.[6] Overall, prostatic metastases spread most commonly to the lumbar and sacral vertebrae, followed by thoracic vertebrae among the other sites in the axial skeleton. This can be explained by retrograde venous embolization of neoplastic cells from the prostate to the vertebral bodies, due to the communication between prostatic venous plexus and the vertebral venous plexus otherwise called Batson's plexus through the communicating valveless veins.[14]

The femur was the most affected bones of the appendicular skeleton at 20.6%, the scapular was involved in 12 patients (9.9%), tibia and fibula were affected in 5% each. The clavicle and humerus were each affected in 3.6% of the cases. The ulnar was involved in 1.7% of the patients. These findings correlated well with results of a study done in Karachi by Anjuman G. M. et al who concluded that skeletal metastases is less common in the appendicular skeleton compared with axial skeleton in the adults.[13]

Bone metastases occur more commonly in the axial skeleton through the blood stream after the tumor cells escape from the primary tumor. The cells enter the blood stream from where they are arrested in the vasculature of a secondary organ, before being extravasated to form new tumor cells colonies. The reason why the axial skeleton is affected more compared with the peripheral

skeleton is because the red marrow which as the main heamopoetic site is highly vascularised and it is centripetal in adults.[32]

The results show the significance of scintigraphy in the investigation of patients with prostate cancer and suspected to have skeletal metastases to improve their therapeutic care. This concurs with the findings of Lin K, et al who in 1999 during their work on the value of a baseline bone scan in patients with newly diagnosed prostate cancer, concluded that skeletal metastases is more in the axial skeleton.[42] Locally in the country there is still a shortage of the facilities as there are only three gamma cameras serving the region and thus most of the patients are referred for the investigation. Affordability is also an issue and this calls for investment in this crucial service.
The more easily available modality for detecting skeletal metastases is plain radiography. In our study only 18 out of the 121 patients examined using RNI for bone metastases had plain radiograph of one or more regions of interest done. Majority of the metastases were seen in the lumbar sacral region 38.8%. Plain radiography is relatively insensitive in detecting bone metastases and only lesions measuring 2 cm or more are radiographically apparent. Metastases to the bone become apparent on radiographs only when there is a loss or addition of more than 50% of the bone mineral content to the site of the disease.[32] However; it is inconclusive to use the above number of patients to make a conclusion on the behavior of the malignancy.

CONCLUSION

Prostate cancer with skeletal metastases is a common condition and affects men between 51 to 94 years with a mean age of 68.9 years. The most common histological type is adenocarcinoma. Mostly these patients present with bone pain. Axial skeleton compared with appendicular skeleton is the most common site of bone metastases. The lumbar sacrum followed by the thoracic spine, sternum and the skull were the most affected sites.

Referral of prostate cancer patients for skeletal survey was mainly from oncologist despite their limited number in the country followed by the surgeons. Majority of the patients with skeletal disease secondary to ca prostate present with skeletal signs and symptoms, however a significant fraction of patients with skeletal metastases present with non skeletal symptoms. Radionuclide imaging is a sensitive modality and should be integrated in the initial workup of the patients with ca prostate as bone metastases is the main cause of death in patients with prostate cancer.[42]

RECCOMENDATION

1. The primary health care providers should be sensitized on the importance of whole skeleton scintigraphy in the management of prostate cancer.
2. Resources should be made available to acquire gamma cameras and other facilities needed in the provision of radionuclide imaging. More personnel should be trained to operate these facilities.
3. A local large scale study should be done to compare RNI and other modalities of skeletal survey like computer tomography or magnetic resonance imaging in terms of cost and efficiency in detecting and management of skeletal metastases.

APPENDIX A

A: DATA COLLECTION FORM

1.PATIENT SERIAL NUMBER: .....

PATIENT X-RAY NUMBER----------

2. AGE: .....

3. **REFERRING CLINICIAN**

3.1 PRIMARY PHYSICIAN

3.2 SURGEON

3.3 ONCOLOGIST

3.4 OTHERS

4. INDICATIONS FOR REFFERAL

4.1 STAGING

4.2 FOLLOW UP

4.3 COMPLICATIONS

4.4 OTHERS

5. TYPE OF PRIMARY MALIGNANCY.

5.1 ADENOCARCINOMA

5.2 SQUAMOUS CELL CARCINOMA

5.3 SARCOMA

5.4 OTHERS

6. CLINICAL FEATURES AT THE TIME OF REFFERAL

6.1 BONE PAIN

6.2 PATHOLOGICAL FRACTURE

6.3 NEUROLOGIC IMPAIREMENT

6.4 OTHERS

6.4 NON-SKELETAL SYMPTOMS

7. BONE SCAN FINDINGS

7.1 PRESENCE OF METASTASES

7.11 Solitary

7.12 Multiple

7.2 ABSENCE OF METASTASES

8 METASTATIC SITES

8.1 AXIAL SKELETON

8.11 SKULL

8.12 CERVICAL SPINE

8.13 THORACIC SPINE

8.14 STERNUM
8.15 RIBS
8.16 LUMBAR-SACRAL SPINE
8.17 PELVIS

APPENDICULAR SKELETON
8.1 UPPER LIMB AND SHOULDER GIRDLE
8.11 SCAPULAR
8.12 CLAVICLE
8.13 HUMERUS
8.14 RADIUS
8.15 ULNA
8.16 CARPAL BONES
8.17 METARCARPALS AND PHALANGES
8.2 LOWER LIMB
8.21 FEMUR
8.22 TIBIA
8.23 FIBULA
8.24 PATELLA AND TARSAL BONES
8.25 METATARSALS AND PHALANGES

9. **PLAIN RADIOGRAPH** **DONE---------- NOT DONE----------**

IF DONE SITES OF METASTASES

9.1 AXIAL SKELETON
9.12 SKULL
9.13 CERVICAL SPINE
9.14 THORACIC SPINE
9.15 STERNUM
9.16 RIBS
9.17 LUMBAR-SACRAL SPINE
9.18 PELVIS

9.2 APPENDICULAR SKELETON
9.21 SCAPULAR
9.22 CLAVICLE
9.23 HUMERUS
9.24 RADIUS
9.25 ULNA

9.26 CARPAL BONES

9.27 METARCARPALS AND PHALANGES

9.3 LOWER LIMB

9.31 FEMUR

9.32 TIBIA

9.33 FIBULA

9.34 PATELLA AND TARSAL BONES

9.35 METATARSALS AND PHALANGES

9.4 NO METASTASES SEEN

APPENDIX B

Patient consent form

My name is Dr Joseph Muigai Mburu a master of medicine student in the department of Diagnostic Imaging and Radiation Medicine at the University of Nairobi. I am doing a study on the pattern of bone metastases and I would wish to recruit you as a participant. The information obtained from you and the findings of your investigation will be handled with utmost confidentiality.

This examination will involve intravenous injection of a radiopharmaceutical into your arm and will be taken up by your bones. The agent to be used during your investigation is a special substance which when injected in your body it's taken up by the bones but more intensely by diseased bone compared to normal bones. From your bones the agent produces a form of energy which is going to be detected using a special camera which enables us to know whether you have any spread of the cancer to the bones. Please note that no extra examination will be carried out on you for the purpose of the study except the one requested by your doctor but we are only going to use the examination findings for the study.

Your name will not be included, except the serial number. The results of the study will be used to improve the diagnosis and management of patients with prostate malignancies. Please note that you are not obliged to participate and you have a right to decline or withdraw from the study at any stage.

If you accept please sign below

Signature: _____

Date: _____

I certify that the patient has understood and consented participation in the study

DR JOSEPH MUIGAI MBURU

Signature: _____

Date: _____

APPENDIX C

KIBALI CHA MGONJWA

Jina langu ni Daktari Joseph Muigai Mburu. Mimi ni daktari na pia mwanafunzi katika chuo kikuu cha Nairobi. Ninafanya uchunguzi zaidi kuhusu ugonjwa wa saratani. Kwa maana wewe uko hapa kupigwa picha ya mifupa, ningeomba ruhusa yako ili niyatumie majibu yako katika uchunguzi wangu.

Picha ya mifupa yako itachukuliwa na mtambo maalum na itaweza kutujulisha hali ya mifupa yako na kama saratani imeenea humo.

Majibu yoyote ambayo tutapokea kutoka kwa uchunguzi wako ni ya siri. Jina lako halitawekwa kwenye uchunguzi wetu ila nambari ya fomu tu. Majibu ya huu uchunguzi wako na ya wengine yatasaidia kuboresha matibabu ya magonjwa ya saratani humu nchini.

Tafadhali elewa kuwa siyo lazima wewe kuhusika kama hiyo siyo hisia yako.

Ukikubali kuhusika, tafadhali weka sahihi hapa chini

Sahihi_____

Tarehe_____

Mimi Daktari Mburu Muigai Joseph ninakiri kwamba mgonjwa ameelewa na amekubali kuhusishwa katika huu uchunguzi

Sahihi_____

Tarehe_____

REFERENCES

1. Hsing AW, Tsao L, Devesa SS. International trends and patterns of prostate cancer incidence and mortality. *Int J Cancer* 2000; **85**:60-67.
2. Jensen HD. The history of the theory of the structure of atomic nucleus. Science 1962; **147**:1419-1425.
3. Yu KK, Scheidler J, Hricak H et al. Prostate cancer: prediction of extra-capsular extension with endorectal MR spectroscopy imaging. Radiology 1997; **203**: 653-659.
4. Brawer M K, Deering R E, Brown M S et al. Predictors of the pathological stage in prostate carcinoma metastases. *Cancer* 1994; **173**:601-606.
5. Edelstein GA, Gillespie PJ, Grebbel FS. The radiological demonstration of osseous metastases. *Clin Radio*1967; 18:158.
6. Galasko C S B. The anatomy and pathways of skeletal metastases. *Bone metastases* 1981; 46-63
7. Ross R K, Herderson B D. The epidemiology of prostate cancer family and preventive medicine. *J preventive medicine* 2006; 3-9.
8. F Angwafo, A Zaher. The National Health Survey of Cameroon. *Prostate Cancer and Prostatic Diseases* 2003; **10**: 34–38.
9. Ngugi PM and Byikika B. The histology of prostate in prostatectomy done for BPH and prostate needle biopsy for raised PSA. *East African medical journal* 2007; **84**:363-366.
10. Robert Dreicer.MRI vis-à-vis plain radiograph and bone scan in detection of bone metastases. *J. Clin Oncol* 2007; **25**:3281-3285
11. Stephenson R.A Stanford JL. Population based prostate cancer trends in the United States. *world journal of urology* 1997; **15**:331-335
12. Landis SH, Bolden S. Skeletal metastases. *Cancer J* 1999; **15**: 48-31
13. Anjuman G M, Anina Jaleel, Jaweed A. Sites of prostatic cancer bone metastases using SPECT. *Pakistan journal of Radiology* 2006; **22**:157-160
14. Galasko C S B. The anatomy and pathways of skeletal metastases. *Bone metastases* 1981; 46-63

15. Bontoux D, Plazanet F, Azais I. Scintigraphy study on the distribution of bone metastases of cancers. *J Urology* 1998; **182:**1008-1009

16. . Memon, Anina , Jaweed Aftab. Pattern of prostatic carcinoma metastases. *Pakistan journal of medical sciences* 2003; **18**:116-118.

17. Nakamoto Y, Osman M, Wahl RL. Prevalence and patterns of bone metastases detected using PET. *Clin Nucl Med* 2003; **28**:302-307.

18. Daniel T Schimid, Hubert John et al. Imaging prostate cancer with 11C-choline PET/CT. *J Nucl Med* Aug 2006;**47(8):**1249-1254.

19. Effert PJ, Bares R Handt, S Wolf .Metabolic imaging prostate cancer by positron emission tomography with 18flourine-labbled deoxyglucose .*J urology* 1999;**19**:994-998.

20. Schuster R, Lenzhofer R, Pirich K, Dudzak R. Is routine bone scanning justified during the aftercare for prostate cancer*? Dtsch Med Wochenschr* 1984; **109(43):**1639-1642.

21. Gold RH, Bassett L W 1981 Radionuclide evaluation of skeletal metastases, practical considerations. *Skeletal Radiol* 1981; **15**:1-9.

22. Sklaroff and Charkles. Comparing RNI and plain radiography in imaging prostate ca skeletal metastases. *American journal of oncology* 1964; **5**:301-304.

23. Farber D, Wahman G. E et al. An evaluation of RNI and plain radiographs for the detection and localization of bone metastasis. *J. urol* 1993; **5**: 96-526.

24. Sherry MM, Greco FA, Johnson DH. Metastatic prostate cancer confined to the skeletal system. *Am J Med* 1986**; 81(3):**381-638.

25. Thrall J H, Ghaed G E, Pisky et al. Pyrophosphate skeletal imaging. *Radium Ther. Nucl. Med* 1974; **121**: 739-745.

26. Suderlund V. Radiological diagnosis of skeletal metastases. *Eur Radiol* 1996; **6:** 587–595.

27. Levitt R, Sagel S, Stanely R. Computed tomography of the pelvis. *Roentgenol* 1978; **13**: 193-197.

28. Frédéric E L, Geukens, Annabelle S et al. MRI, Plain radiography and SPECT in assessing skeletal metastases. *Journal of Clinical Oncology* 2007;**22**: 3281-3287.

29. McNeal J E. The prostate gland. Morphology and pathology. *Monogr Urol* 1983; **4**:5-13.

30. Roddie M.N.MacSween. Muir's Text book of pathology. Published by Edward Arnold, London 1992; 13th edition: 1789-1790.
31. Mann C V, Russsels R C. Bailey and Love short practice of surgery. Published by Chapman and Hall, London 1992; 21st edition: 141-1433.
32. Domchek SM, Younger J,et al. Predictors of skeletal complications in patients with metastatic prostate Cancer. *j. American Urology* 2000; **89(2):**363-370.
33. Libson E, Bloom R A, Husband J E et al. Metastatic tumors of bones. *Skeletal Radio* 1987; **14**: 10-19.
34. Schweitzer M E, Levine C, Mitchell D G. Useful MR discriminators of osseous metastases. *Radiology* 1993; **188**: 249-252.
35. Reidy J F. Osteoblastic metastases from a hypernephroma. *Br J Radiol* 1975; **48**:225-227.
36. Lisbon E, bloom RA, Husband JE. Metastatic tumors of the bone to the hand and foot. *Skeletal radiology* 1987;**16**:387-392.
37. Huggins C, Bear R S. The course of prostatic ducts and the anatomy, chemical and x-ray diffraction analysis of prostatic calculi. *J Urol* 1944; **51**:37-47.
38. Scott, JR Mutchnik et al .Carcinoma of the prostate in elderly men. *J.urol* 1969; **101**:607-700.
39. Rosenthal D I. Radiological imaging for the diagnosis of bone metastases. *Q J Nucl Med* 2001; **45**:53-54.
40. Schaffer D L, Pendergrass H P. Comparison of enzyme, clinical, radiological and RNI methods of detecting bone metastasis from prostate cancer. *Radiology* 1980; **121**: 700-709.
41. Kenya demographic survey: 2003.
42. Lin K, Szabo Z, Chin BB, Civelek AC. The value of a baseline bone scan in patients with newly diagnosed prostate cancer. *Clin Nucl Med* 1999; **24**(8): 579-82.