CORRELATION OF PLAIN RADIOGRAPHY AND RADIONUCLIDE SCAN FINDINGS IN BREAST CANCER PATIENTS WITH SUSPECTED BONE METASTASIS IN KENYATTA NATIONAL HOSPITAL AND AGAKHAN UNIVERSITY HOSPITAL.

A DISSERTATION SUBMITTED IN PART FULFILLMENT FOR THE DEGREE OF MASTERS OF MEDICINE IN DIAGNOSTIC RADIOLOGY OF THE UNIVERSITY OF NAIROBI.

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H58/63421/1
DECLARATION

This dissertation is my original work and has not been presented for a degree in any other university.

Signed:..................................... Date: 12/9/2014

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APPRECIATION

I am eternally thankful to God Almighty for strength and guidance throughout my life and career.

My heartfelt gratitude to my facilitator DrM.N.Wambugu for the support, advice and guidance throughout the proposal drafting, data acquisition and finally the drafting of the research results.

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My husband Lemayian, loving sons Lekishon and Koinet, you indeed are pillars in my life.
TABLE OF CONTENTS

Title Page
Declaration.............................................................ii
Appreciation ..........................................................iii
Table of Contents...................................................iv
Abbreviations used..................................................v
Abstract........................................................................1
1. Literature review....................................................2
   Global burden of breast cancer.................................2
   Efficacy of WBBS and PR in bone metastasis.............15
2. Justification of study.............................................24
3. Objectives and specific objectives..........................25
4. Problem statement...............................................25
5. Study design and methodology................................26
6. Ethical considerations...........................................30
7. Results....................................................................31
8. Discussion.............................................................45
9. Conclusion and recommendations.........................48
10. Reference............................................................50
Appendix i: data collection form.................................53
Appendix ii: consent explanation form..........................56
Appendix iii: consent form.........................................57
Project budget..........................................................58
ABBREVIATIONS USED

KNH.............Kenyatta National Hospital
AKUH............AgaKhan University Hospital
ALP..............Alkaline Phosphatase
ANOVA.........Analysis of variance
ASCO.............American Society of Clinical Oncology
BIRADS.........Breast Imaging, Reporting and Data System (BI-RADS®)
BS................Bone scans
BM................Bone metastasis
Bq................Becquerel
Ca................Cancer
Ci...............Curie
CI..............Confidence Interval
CT................Computerised Tomography
DXT.............Radiotherapy
EGFR...........Epidermal growth factor receptor
ESMO............European Society of Medical Oncology
FDA..............Food and Drug Administration
FDG..............Fluo-2-deoxy-D-Glucose
Fig...............Figure
HER2.............Human epidermal growth factor receptor 2
ICS.............Intercostal Space
IQR.............Interquartile range
MBD.............Metastatic Bone Disease
MDP.............Methylene Diphosphonate
MRI.............Magnetic Resonance Imaging
NCI.............National Cancer Institute
NDAé é é ...National Drug Administration

NIHé é é é ..National Institute of Health

\( ^{99\text{m}}\text{TcO}_4^- \)..........Technetium 99-metastable pertechnetate

PET..................Positron emitted tomography

PR..................Plain Radiography

RNI...............Radionuclide Imaging

RTC............Radiotherapy Clinic

RNI.................Radionuclide imaging

SD..................Standard deviation

SPECT.............Single photon emission computed tomography

Tc-MDP............Technetium 99\textsuperscript{m}Methylene Diphosphonate

UoN.................University of Nairobi

WBBS..............Whole Body Bone Scans
ABSTRACT

Introduction

The presence of bone metastasis in patients with breast cancer impacts on the management options. The diagnosis of metastatic bone disease is important in staging, managing, follow-up and predicting prognosis in these patients. Whole body bone scans (WBBS) has long been considered the gold standard for imaging the bones in breast cancer patients presenting with bone pain, in order to exclude metastatic bone disease as the causative factor. It however provides a diagnostic dilemma when equivocal findings are noted.

This study aims to correlate the findings of WBBS and Plain Radiography (PR) in the detection of Metastatic Bone Disease (MBD). It also aims to rule out MBD from other types of bone pain like degenerative changes, referred pain, and soft tissue pain in order to obviate the need for aggressive imaging and reduce the radiation burden to patients.

Methods

The findings of 125 patients with breast cancer who were suspected to have metastatic bone disease were compared. Recruited patients complained of pain that was periodically resolving with analgesics. Patients with acute onset of sharp pain, referred pain, radicular pain and swelling around bone were required to undergo radiological investigations. All these patients were suspected to have MBD and as such were investigated further to exclude the same.

This was a seven-month prospective descriptive study from June 2013 to December 2013 undertaken at the Kenyatta National Hospital (K.N.H) Nuclear Medicine Unit, AgaKhan University Hospital Radiology Department and University of Nairobi Radiology Unit.

Conclusions

In most patients there was no evidence of bone metastasis on PR or WBBS. WBBS had higher sensitivity in detection of metastatic bone disease than PR. When used as an adjunctive diagnostic tool, PR assists in detecting the presence or absence of metastatic lesions with high level of confidence.

The study emphasizes the role of PR and WBBS as baseline investigations in suspected bone metastasis in breast cancer patients. Overall there was significant difference in the detection rate of bone metastasis between the two modalities. Normal PR findings do not exclude bone metastasis but helps in diagnosis of degenerative disease which is not accurately detected by WBBS.
LITERATURE REVIEW

GLOBAL BURDEN OF BREAST CANCER.

Breast cancer is common, affecting 1 in 9 females and causing deaths in Kenya annually, with an annual incidence of 25,000 new cases according to Kenya Breast Health Program (1). Data from the National cancer registry 2002 showed that breast cancer constituted 23.3% of all cancers detected (1). This statistics showed that of all the cancers registered, breast cancer accounted for 23.3%, while cervical cancer was the second leading cause in women at 20%. It is estimated that 60% of Patients diagnosed with breast cancer die within 5 years from the disease. Late diagnosis has been the main reason for a high mortality with an estimation of 80 to 90% of breast cancer patients going for consultations when they are in stage III and stage IV of the disease. Up to 95% of women in Kenya have never had a clinical breast examination due to scarcity in screening mammography in the country. For most of them, their immediate fear is the fate of their families, career prospects and dealing with the stigma of living with cancer (1).

The incidence of breast cancer is predicted to increase in developing countries due to lifestyle changes, increased awareness about the disease, increased use of hormone replacement therapy and probably higher rate of early diagnosis. There is need for Government to set up screening programs, research centers and training institutes to deal with cancer due to the high morbidity and mortality associated with breast cancer. The course of the disease is exemplary if diagnosed in early stages before the disease has spread beyond the breast. Several studies have revealed that the 5 year survival rate of stage 1 breast cancer approaches 100% while diagnosis at a late stage reduces the survival rate to a dismal 22%. Currently there are only 4 radiation centers in the country all in Nairobi. The treatment cost is high and out of reach for many Kenyans. Many patients diagnosed with breast cancer take on average 9months before radiotherapy can be instituted in public hospitals. The National Cancer Control Strategy established in 2012 and projected to be implemented within 4 years aims to reduce the overall burden of the disease (2). These include education on monthly breast self examination, medical examination every 1 or 2 years and screening mammography which should be free at the point of delivery. Mammography is able to detect small impalpable lesions and also guides in image guided needle biopsy. Concern for radiation induced cancer from widespread screening mammography exists but the benefits outweigh the risks. Currently, a cancer awareness month that occurs every October and run by the government is empowered to facilitate free medical check-ups in every government hospital in an attempt to diagnose and combat the disease at an earlier stage. Information on causative factors for breast cancer discussed later in the text and how to avoid them is also needed. Many more cancer centers should be established to exclude the need for prolonged wait in starting radio chemotherapy.

Although there is a higher incidence of breast cancer in the USA, there is a lower mortality due to efficient health systems programs. These include widespread screening of patients, adequate treatment and radiotherapy centers resulting in prompt and proper management of these patients.
Estimated new cases and deaths from breast cancer in the United States in 2012:(3).

New cases- 226,870 (female); 2,190(male)
Deaths -39,510 (female); 410(male)

More than 70% of those with operable disease will be alive and well 5 years after diagnosis (3, 4). Therefore, patients should be educated to recognise early signs of breast disease and to get medical advice without delay. This is postulated to improve cure rates eventually to 100% (5).

The pattern of survival in metastatic disease is variable. Metastatic disease is the common presenting symptom at the time of diagnosis in Kenya. It may follow primary treatment of an earlier operable tumour. In the developed countries due to effective screening programmes, earlier detection of breast cancer is the norm. Presence of 1 to 3 positive lymph nodes is more likely to die from the disease as compared to those with negative nodes. Women with estrogen receptor negative are also more at risk of earlier mortality than the estrogen receptor positive counterparts. Generally metastatic breast cancer is not curable but systemic therapy exists in order to prolong and improve the quality of life. Cancers expressing human epidermal growth factor (HER) 2 respond to herceptin therapy and are associated with longevity. In our setting this cell typing is not widely available and it is quite expensive.

ANATOMY AND PATHOPHYSIOLOGY

The breast is conical, round or hemispherical in shape. It is a modified sweat gland located in the fatty superficial fascia and has 15-20 lobes each encased in fascia sheath defined by anterior mammary fascia and posterior mammary fascia. It extends from the 2nd/3rd intercostal space (ICS) to the 6th/7th rib inferiorly, its lateral border is the anterior axillary fold and medial border is the lateral sternum. It overlies the pectoralis muscles. An axillary tail of Spence extends to the axilla. The nipple is at the 4th ICS mid clavicular line. The areola is the pigmented skin around the nipple. It contains the glandular and stromal elements (6).

The breast is an accessory organ of the reproductive system whose main function is nourishment of the infant.
Breast cancer is the malignant proliferation of epithelial cells lining the ducts or lobules of the breast. It is the most common cancer occurring in females in Kenya followed by cancer of the cervix (1). Triple negative breast cancer has low expression of estrogen, progesterone and HER 2. This is seen in basal-like breast cancer. These tumours are associated with large tumours, positive nodes and fulminant course with recurrence. Many of these tumours also amplify the endothelial growth factor (EGFR). Tumours in women with BRCA 1 gene mutations have similarities to basal-like breast cancer. These tumours have been shown to respond to agents such as cisplatin. Recent improvements in breast cancer management including the availability of treatment targeted against HER 2 with herceptin and anti EGRF helps to relieve cancer associated symptoms. To date these studies are limited by small sample sizes and limited follow up times. They also require immunohistochemical studies for diagnosis and this is not widely available.
Factors predisposing to the disease are (7);

1. Ageing. The incidence is about 1 in 10 in females < 45 years and 1 in 4 >55 years.

2. Inherited genetic susceptibility. The presumed aetiology of breast cancer is DNA damage. 25% have TP53 mutations, 10% have BRCA1 on chromosome 17 & and 40% have BRCA 2 mutations at chromosome13, HER, P53 (27), CHEK2. If a 1st degree relative had cancer before 50 years the risk is twice more. Triple negative breast cancers which exhibit EGRF and have negative estrogen, progesterone and HER 2. They are associated with relatively rapid progression and poor outcome. The rate of recurrence after 8 years however was dismal in comparison with women with other types of breast cancer.

3. Breast exposure to high doses of radiation during breast development such as radiotherapy for lymphoma.

4. Atypical hyperplasia or lobular neoplasia found on a breast biopsy.

5. Other family history of breast cancer (first-degree relative). Personal history of breast cancer in one breast has a 4 fold increase in the same or contra lateral breast.

6. Early menarche and late menopause
7. Nulliparity

8. Late age at first full-term pregnancy >30 years is two times the risk of cancer than a woman whose 1st pregnancy is less than 20 years. More pregnancies before 20 years further reduces the risk.

9. Geographic variations and lifestyle.

10. Race and Ethnicity.

11. Hormone Replacement Therapy.

12. Further studies are on-going regarding other causative factors.

**Staging of breast cancer (8).**

Stage 0 (carcinoma in situ).

In stage I, < 2 cm and has not spread outside the breast.

In stage IIA, the cancer is either:

- < 2 cm but has spread to the axillary lymph nodes (the lymph nodes under the arm);
- or between 2 and 5 cm but has not spread to the axillary lymph nodes

Stage IIB the cancer is either:

- between 2 and 5 cm and has spread to the axillary lymph nodes
- or larger than 5 cm but has not spread to the axillary lymph nodes

In stage IIIA, the cancer is either:

- < 5 cm and has spread to the axillary lymph nodes which attached to each other or to other structures;
- or > 5 cm and has spread to the axillary lymph nodes and the lymph nodes may be attached to each other or to other structures

In stage IIIB, the cancer has either:

- spread to tissues near the breast
- spread to lymph nodes inside the chest wall
In stage IV, the cancer has either:

- spread to other organs of the body,
- spread to the lymph nodes in the neck,
- Recurrent cancer
- Inflammatory breast cancer

**SCREENING**

Early screening campaigns have led to the detection of 75% of malignancies in stage 0 (in situ) or stage 1. All palpable lesions should be referred for ultrasound in patients under 35 years or mammogram in over 35 years. Earlier mammograms in patients under 35 years can be done in inherited high risk women. More than 88% of cancers are detected by mammogram. 10% of cancers are palpable but not detected on mammogram. Almost 20% cancers are detected by physical examination. 20% of cancers that appear within 1 year of negative screen are missed by combination of mammogram and physical exam. Radiation risk of screening is higher in young females under 35 years and lactating mothers. It is negligible after 40 years.

- Screening programmes following ACR recommendations include;
- Monthly breast self-examination to begin at age 20.
- Medical examination every three years between 20 and 40 years (yearly after 40)
- No mammography screening before age of 35 unless inherited risk suspected.

**Breast Imaging, Reporting and Data System (BI-RADS®).** Breast radiological reports are organised by a short description of breast architecture, location and consistency of any lesion, any interval change in follow up cases and overall diagnosis. Recommendations are also furnished to the clinician. In mammography a detailed description including the breast symmetry, density, type of calcification if any, any skin or subcutaneous lesion and lymph node involvement must be included.

This is a quality assurance tool developed by American College of Radiologists to enable fairly consistent reporting on breast pathology. The system was initially developed for mammography but has been expanded for use in Ultrasound and MRI. It is based on the worst features detected (8).

- BI-RADS 0- incomplete exam; further imaging required
- BI-RADS 1- negative exam
- BI-RADS 2- benign finding (s)
BI-RADS 3- probably benign (2% risk of malignancy); initial short interval follow-up is suggested (3-6 months)

BI-RADS 4- suspicious abnormality (2-95% risk of malignancy) hence biopsy is recommended.

- 4A Low suspicion
- 4B Intermediate suspicion
- 4C Moderate suspicion

BI-RADS 5- probably malignant (>95% risk of malignancy) appropriate action should be taken.

BI-RADS 6- known biopsy proven malignancy

Some faults on this system include:

- The 6 month follow up recommendation whereby some lesions will not change in size over a short period. The rare exception is hematoma which will regress during such interval.

- Heterogeneously dense breasts lower sensitivity of mammograms and a short statement to this effect must be included in the report.

- The BI-RADS system is not suitable in male subjects generally.

Pathophysiology of metastatic bone disease

The bone is a common site of metastasis from breast cancer. How does cancer generally spread from an organ spread to bone? Two main theories are still entertained. In 1889, Sir James Paget, an English surgeon, developed his "seed and soil" theory by studying the medical records of 735 patients with breast cancer. The majority of metastases were noted to occur in the liver and brain. Dr. Paget realized that there was a discrepancy between the blood supply and the frequency of metastasis in various organs. He then determined that local organ factors must favour implantation in specific sites. He did not think that metastasis was related to the blood supply of a particular organ, as skeletal muscle and the spleen have a rich blood supply but are not frequent targets for metastasis. Dr. Paget felt that it was not simply that the cancer cells had the ability to survive and spread to a new site (the seed), but that the local environment had to be nurturing of further tumour growth (the soil). Only with both of these factors could successful metastatic spread occur (9).

In contrast, James Ewing, M.D., an American pathologist, proposed his circulation theory in 1928. He proposed that tumors colonized particular organs due to the routes of blood flow carrying tumor cells away from the primary site. He thought organs were passive receptacles for tumour cells but did not explain targeting to specific sites (9).
Modern day scientists still accept these two theories as contributory but they are neither fully exhaustive nor mutually exclusive. The blood flow may help dictate the course of tumor cell travel, but inherent properties of the tumor cells and hostile environment of the site of spread may facilitate or inhibit metastatic growth (9). Bone cancer spreads to bone in 70 to 80% of patients with advanced breast cancer. Breast cancer spread to bone relies on interactions among tumor cells, osteoclasts and bone regenerating cells the osteoblasts. A signaling protein called jagged 1 sends destructive instructions that activate a group of molecules that work together, one molecule activating the next in the ‘notch signal pathway’ in the bone cells. Notch signaling stimulates the bone degrading activity of osteoblasts releasing tumor growth factors from the bone matrix. Meanwhile, notch signaling in bone building osteoclasts increases secretion of another protein IL-6 which feeds back to tumour cells to promote their growth, forming a vicious cycle in bone metastasis.

These recent studies by Nilay et al. suggest that a jagged 1 molecule found in Tumor Growth Factor-1 plays a crucial role by binding to Notch 1 receptor molecules in osteoclasts. This incites a tumor response leading to metastatic lesions (10). There are many such signaling pathways. But in the case of metastatic breast cancer, a disruptive pathway is formed. The signaling molecule the ligand, connects with the receptor molecule on certain bone cells and activates a cellular pathway that ultimately disrupts healthy bone renewal. This activates the ‘notch pathway’ resulting in upregulation of growth and reduced apoptosis.

Predictors of Tumour invasiveness and metastatic potential include: (11)

- TNM staging
- Axillary lymph node status
- Histological subtypes
- Angiogenesis markers
- Markers of cell proliferation
- Oncogenic growth receptor expression
- Protease expression

Symptoms of metastatic breast cancer include:

- Bone pain (possible indication of bone metastases).
- Shortness of breath (possible indication of lung metastases).
- Lack of appetite (possible indication of liver metastases).
- Weight loss (possible indication of liver metastases).
- Neurological pain or weakness, headaches (possible indications of neurological metastases).
These symptoms are sometimes but not always associated with metastatic breast cancer and having one or more of these symptoms do not necessarily mean that a woman has metastatic breast cancer. Most women whose breast cancer has metastasized do not show symptoms until the disease is extensive.

**Evaluation of skeletal metastasis and metastatic bone pain**

This is the most common site of secondary breast cancer with ¾ of patients with advanced cancer having bone metastasis (12). Approximately 75% of spine metastasis and 60% of femoral metastasis in women are from breast ca (13). 60-84% of patients with metastatic disease have bony involvement with 70% of these patients suffering from bone pain as a result of their disease (13). Cancer cells have spread past the breast and axillary lymph nodes to other areas of the body where they continue to grow and multiply. Breast cancer has the potential to spread to almost any region of the body particularly the lungs and liver. These organs have a rich network of vessels thus supporting the earlier theories mentioned (9).

In older women who are commonly affected by breast cancer and osteoporosis, it is important to distinguish the two etiologies as the management and prognosis differs. In osteoporosis, cortical bone maybe preserved whereas cortical bone destruction is common in metastasis (10).

Patients with Metastatic Bone Disease may have marked pain in the spine, pelvis or extremities, decreased activity, and potentially severe problems such as fractures because the bone is weakened by the tumour. This pain can be relieved with radiation treatments, pain medication or newer, minimally invasive surgical techniques such as radiofrequency ablation (14).

Other complications that can arise from bone metastases include those involving surgical treatment for fractures, hypercalcemia, and spinal cord compression which can impair quality of life (14, 15).

Any bone can be afflicted, however there is preference of bones with greatest blood supply containing red bone marrow, hence the axial skeleton is affected more commonly than the appendicular skeleton in adults, that is, vertebrae (basivertebral plexus before extending to pedicle and posterior elements), pelvis, proximal femora and humeri, skull, and ribs.

On radiography, most metastatic lesions are osteolytic (60%). Osteoblastic (15%) and mixed lesions (25%) can also occur. Cortical metastasis identical to those from lung cancer can also occur (16).

Osteolytic lesions result when the tumour produces substances that can directly elicit bone resorption (vitamin D-like steroids, prostaglandins, or parathyroid hormone-related peptide) or cytokines that induce the formation of osteoclasts (interleukin 1 and tumour necrosis
factor). Osteoblastic lesions result when the tumour produces cytokines that activate osteoblasts (11). In general, purely osteolytic lesions are best detected by plain radiography but they may not be apparent until they are >1cm. These lesions are more commonly associated with hypercalcemia and with the excretion of hydroxyproline-containing peptides, indicative of matrix destruction. When osteoblastic activity is prominent the lesions may be readily detected using WBBS (which is sensitive to new bone formation), and the radiographic appearance may show increased bone density or sclerosis. Osteoblastic lesions are associated with high levels of ALP, and if extensive may produce hypocalcaemia.

Cells with a cancer stem cell phenotype which disseminate early in the course of primary cancer, often remain dormant in their new location for a long time and become active only if their new microenvironment favours growth of the metastatic cancer cells. If the primary cancer is large, it can not only be a source of metastasizing cells, but also of biologically active mediators that promote development of favourable premetastatic niches, where colonization by dormant or newly arrived metastatic cells will be supported (18).

Radiographs are recommended to evaluate indeterminate or non-specific tracer uptake on WBBS. At least 30% of the bone must be destroyed for lytic metastases to be identified on radiography, and overlapping structures can further limit the sensitivity of radiography for BM (19). When visible, abnormalities are typically diagnosed with high confidence and in addition radiographs are relatively inexpensive. In patients with one or few sites of skeletal pain, targeted radiographs may be used for initial imaging (20, 21), and if radiography shows metastasis, the remainder of the skeleton can then be examined with WBBS (22).

A further diagnostic challenge arises when the tumour infiltrates the marrow rather than causing bone destruction per se. Such disease can be best detected by Magnetic Resonance Imaging (MRI) or Computed Tomography (CT). Single Photon Emission Computed Tomography (SPECT) has been reported to identify more metastases than planar WBBS by virtue of its cross-sectional nature (23), and its accuracy is enhanced by the fused CT, but SPECT/CT is not widely available and is costly.

MRI may be used when the initial bone imaging is non-diagnostic (22). The high soft tissue resolution of MRI can allow the medullary cavity of bone, where most bone metastasis (BM) arise, to be more clearly discerned than can X-ray-based technologies (PR and CT), which have lower soft tissue resolution. MRI has been reported to detect more BM than radiography, CT, or BS (23) but is relatively expensive (19). The limitations of Conventional MRI are that it is carried out on a limited portion of the body, requires longer imaging duration, thereby predisposing to motion artefacts. Currently, diagnostic-quality whole-body MRI is now clinically feasible (23). However, MRI is estimated to cost 2-3 times as much as WBBS and the most expensive modality (18F) 2-fluoro-2-deoxy-D-glucose (FDG) scanning costs 8 times as much.

Where PR, WBBS and MRI yield equivocal results, metabolic evaluation with Positron Emission Tomography (PET) or fused PET and CT (PET/CT) has been recommended
FDG, the most commonly used PET tracer, is a glucose analogue whose phosphorylated molecular structure delays metabolism by the cell; FDG accumulation can, therefore, be detected in highly metabolic tissues, such as malignancies (23). PET can be used to investigate bone lesions, however, PET alone may lack anatomic detail; this problem can be overcome by fusion of PET/CT images which potentially improves its diagnostic capability for metastatic disease. As with Bone Scans (BS), PET can give false-positive results due to various common benign bone processes, and PET is more sensitive for detecting lytic than blastic BM (19). There is some evidence of enhanced incremental accuracy for some of the above-mentioned tests when used concurrently as opposed to one imaging modality (22).

The different components of bone which are cortical, trabecular and marrow elements, can be involved in MBD. Each modality visualizes different aspects of tissue. CT scan and PR visualize cortical bone, while MRI is invaluable for imaging the marrow. SPECT and WBBS reveal bone metabolism while FDG PET shows tumors metabolism before cortical destruction is visible (12). MRI is less sensitive for cortical bone which has no mobile protons therefore producing dark signal on all sequences.

Breast cancer management requires a multidisciplinary approach with surgeons, pathologist, radiologists and radio-oncologists. Once there is tumor recurrence, physicians will order a variety of other tests to determine whether the cancer has metastasized to distant organs. These tests include: Bone scan, ultrasound. Chest radiograph, CT or MRI. Blood tests are usually non specific and seldom useful in determining metastatic disease.

Most tumours can metastasize to bone, but breast, prostate, lung, kidney and thyroid do so particularly frequently. However, some metastases are not detectable by radionuclide bone examination, because of their failure to excite sufficient osteoblastic response as seen in Fig. 3 below (10).

Fig.3.

A) Technetium-99m MDP scan. There is a focal absence of isotope uptake in the left ninth rib. At the margins of the "cold" area, slight increased uptake is visible. Very destructive lesions may produce focal cold areas as
the result of complete bone destruction in the affected area. Increased uptake in the marginal, less destroyed bone is not unusual.
B) An oblique radiograph of the chest demonstrates complete absence of the posterior ninth rib.

**Restaging of symptomatic patients**

Once a patient has been diagnosed with breast malignancy and considered free of disease after appropriate therapy, presence or recurrent bone pain becomes an important element of their medical history. Any prolonged or persistent complaint of pain will usually precipitate an aggressive search for recurrence of disease.

Lethargy, fatigue and weight loss are frequent symptoms. The imaging modality of choice should be sensitive to the suspected organ of involvement when there are localizing symptoms such as abdominal pain or distension, dyspnoea, bone pain, or a neurological event. The choice of investigation should be directed appropriately, for example, patients with abdominal pain should first be investigated with an ultrasound examination of the abdomen. Knowledge of the pattern of disease spread will assist choice and interpretation of investigations. With a history of breast cancer, acute bone pain from metastatic disease is likely, whereas for instance ovarian tumors are more likely to disseminate through the peritoneal cavity, causing poorly localized abdominal pain and ascites. In breast cancer 7% of patients with a normal skeletal scintigram have MBD on MRI (24). See Fig 4.
Fig 4. Patient previously diagnosed with breast cancer presenting with back pain. (A) Skeletal Scintigram. There are no focal areas of abnormal uptake in the skeleton. (B) T1-weighted Sagittal MRI study of spine demonstrating multiple areas of low signal in the vertebral bodies consistent with bony metastases. Mechanical cord compression is threatened in the upper thoracic area. MRI was performed a week after scintigraphy (24).
EFFICACY OF WBBS AND PR IN DETECTION OF MBD

Although the skeleton is the commonest site of metastasis, radiographic methods of detecting metastasis are not very sensitive. Eldestyn and his colleagues (1967) found that at least 50% of the bone, in the beam axis must be destroyed before the lesion is seen radiographically. Some authors (see table below) have also tried to compare the accuracy of scintigraphy and PR in detection of MBD. It is worth noting that on autopsy more lesions are seen compared to those detected on radiographs (25).

WBBS has decreased specificity and higher false positive than PR. This is because it detects metabolic reaction of bone due to several disease processes including trauma, inflammation (26, 27).

Table 1. Accuracy of scintigraphy versus plain films in detection of bone metastasis (25).

<table>
<thead>
<tr>
<th>Authors</th>
<th>No. of investigations</th>
<th>Scintigram more accurate</th>
<th>X-ray more accurate</th>
<th>No difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Charkes and sklaroff (1965)</td>
<td>156</td>
<td>34</td>
<td>5</td>
<td>117</td>
</tr>
<tr>
<td>Simpson and Orange (1965)</td>
<td>62</td>
<td>34</td>
<td>3</td>
<td>25</td>
</tr>
<tr>
<td>Briggs (1967)</td>
<td>83</td>
<td>29</td>
<td>1</td>
<td>53</td>
</tr>
<tr>
<td>French and McCready (1967)</td>
<td>57</td>
<td>12</td>
<td>4</td>
<td>41</td>
</tr>
<tr>
<td>Hammer et al. (1969)</td>
<td>159</td>
<td>49</td>
<td>6</td>
<td>104</td>
</tr>
<tr>
<td>Milner et al. (1971)</td>
<td>100</td>
<td>17</td>
<td>9</td>
<td>74</td>
</tr>
<tr>
<td>Galasko (1972)</td>
<td>50</td>
<td>36</td>
<td>0</td>
<td>14</td>
</tr>
<tr>
<td>Gnekow et al. (1972)</td>
<td>359</td>
<td>32</td>
<td>11</td>
<td>316</td>
</tr>
<tr>
<td>Shearer et al. (1974)</td>
<td>314</td>
<td>32</td>
<td>18</td>
<td>264</td>
</tr>
</tbody>
</table>

A more crucial question would be the accuracy of radiography and scintigraphy in detecting early disease by ruling out skeletal metastasis. Studies have shown that at least 26% of patients with initial negative scintigram develop recurrence and dissemination of disease. In addition 21% of these patients die from the disease despite being detected at an early stage (25).
Table 2. The 5 year follow-up in 50 patients subjected to skeletal scintigraphy at the time of presenting with apparently ‘early’ mammary carcinoma (25).

<table>
<thead>
<tr>
<th>No. of patients</th>
<th>Scintigram +ve 12</th>
<th>Scintigram –ve 38</th>
<th>Total 50</th>
</tr>
</thead>
<tbody>
<tr>
<td>Developed advanced disease</td>
<td>12 (100%)</td>
<td>10 (26%)</td>
<td>22 (44%)</td>
</tr>
<tr>
<td>Died from cancer</td>
<td>10 (83%)</td>
<td>8 (21%)</td>
<td>18 (36%)</td>
</tr>
<tr>
<td>Died from other causes</td>
<td>0</td>
<td>3 (8%)</td>
<td>3 (6%)</td>
</tr>
<tr>
<td>Alive 5 years</td>
<td>2 (17%)</td>
<td>27 (71%)</td>
<td>29 (58%)</td>
</tr>
<tr>
<td>Alive with metastatic disease</td>
<td>2 (17%)</td>
<td>2 (5%)</td>
<td>4 (8%)</td>
</tr>
<tr>
<td>Alive with no evidence of recurrence</td>
<td>0</td>
<td>25 (66%)</td>
<td>25 (50%)</td>
</tr>
</tbody>
</table>

It has been shown that the prevalence of detectable metastatic disease in the population of patients at the first diagnosis of breast cancer is exceedingly low and increases from stage I to stage III. In a systematic review, Myers et al. reported percentages of patients with positive Bone Scans (BS) at baseline varying across studies from 0.9% to 40% (all stages) with the lowest prevalence observed in stage I patients (0.5%, 95% confidence interval (CI) 0.1–0.9) and the highest in stage III patients (8.3%, 95% CI 6.7–9.9) (21).

Confusion exists in the literature as to whether bone pain is primarily related to metastatic bone cancer or to other causes like arthritis which is common among the women in this similar age group who are commonly affected by breast cancer. Bone scans are non-specific in differentiating arthritic changes from metastatic deposits especially in the spine, while plain radiographs are not sensitive in detecting early bone destruction.

Breast cancer relapse often spreads to bone. Approximately 18-20% of the patients diagnosed with early breast cancer have relapse after 10 years (28). Among these 70% have cancer that has spread to bone.
Clinical Condition: Metastatic Bone Disease

Table 3. Variant 1: Stage 1 carcinoma of the breast. Initial presentation, asymptomatic.

<table>
<thead>
<tr>
<th>Radiologic Procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>RRL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>X-ray radiographic survey whole body</td>
<td>1</td>
<td></td>
<td>☢☢☢</td>
</tr>
<tr>
<td>Percutaneous biopsy area of interest</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI area of interest without contrast</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>MRI area of interest without and with contrast</td>
<td>1</td>
<td>0</td>
<td></td>
</tr>
<tr>
<td>Tc-99m bone scan whole body</td>
<td>1</td>
<td></td>
<td>☢☢☢</td>
</tr>
<tr>
<td>FDG-PET/CT skull base to mid-thigh</td>
<td>1</td>
<td></td>
<td>☢☢☢</td>
</tr>
</tbody>
</table>

Rating Scale: 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

Table 4. Variant 2: Stage 2 carcinoma of the breast. Initial presentation, with back and hip pain.

<table>
<thead>
<tr>
<th>Radiologic Procedure</th>
<th>Rating</th>
<th>Comments</th>
<th>RRL*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tc-99m bone scan whole body</td>
<td>9</td>
<td>To be done first to evaluate for presence of lesions suspicious for metastatic disease.</td>
<td>☢☢☢☢</td>
</tr>
<tr>
<td>X-ray spine and hip</td>
<td>9</td>
<td>Radiographs obtained after bone scan if needed for further lesion characterization</td>
<td>☢☢☢</td>
</tr>
<tr>
<td>FDG-PET/CT skull base to mid-thigh</td>
<td>5</td>
<td>If bone scan is negative and the results of the PET examination will influence the use of systemic treatment.</td>
<td>☢☢☢☢</td>
</tr>
<tr>
<td>Tc-99m bone scan whole body with</td>
<td>1</td>
<td></td>
<td>☢☢☢</td>
</tr>
<tr>
<td>Radiologic Procedure</td>
<td>Rating</td>
<td>Comments</td>
<td>RRL*</td>
</tr>
<tr>
<td>----------------------------------------------------------</td>
<td>--------</td>
<td>---------------------------------------------------------------------------</td>
<td>---------------</td>
</tr>
<tr>
<td>Tc-99m bone scan whole body</td>
<td>9</td>
<td></td>
<td></td>
</tr>
<tr>
<td>FDG-PET/CT skull base to mid-thigh</td>
<td>5</td>
<td>If bone scan is negative and the results of the PET examination will influence the use of systemic treatment</td>
<td></td>
</tr>
<tr>
<td>SPECT femur</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-ray radiographic survey whole body</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CT femur without and with contrast</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>MRI femur without and with contrast</td>
<td>1</td>
<td></td>
<td></td>
</tr>
<tr>
<td>X-ray femur</td>
<td>1</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Rating Scale:** 1,2,3 Usually not appropriate; 4,5,6 May be appropriate; 7,8,9 Usually appropriate

Table 5. Variant 3: Patient with known bone metastatic disease (carcinoma of the breast). Presenting with pathological fracture of a femur on radiography.

In summary, Radionuclide bone scanning is the most widely used primary imaging examination for detecting osseous metastasis. After an abnormality has been detected, radiographs should be obtained to make sure the abnormality does not represent a benign process. If radiography is not diagnostic, additional lesion workup with MRI, CT, SPECT, or
FDG-PET/CT is highly variable and should be based on the clinical situation and lesion location.

**Fig 5 comparison of various imaging modalities in MBD (10).**

A. Plain radiograph showing lytic suspicious lesion in the right proximal femur

B. T1+C axial showing increased uptake with disruption of cortex

C. Coronal T1W image showing corresponding low signal lesion

D. WBBS showing increased focal uptake in the right proximal femur
RADIONUCLIDE IMAGING (RNI).

Many historians consider the discovery of artificially produced radionuclides by Frédéric Joliot-Curie and Irène Joliot-Curie in 1934 as the most significant milestone in nuclear medicine. In February 1934, they reported the first artificial production of radioactive material in the journal Nature after discovering radioactivity in aluminium foil that was irradiated with a polonium preparation. Their work built upon earlier discoveries by Wilhelm Konrad Roentgen for X-ray, Henri Becquerel for radioactive uranium salts, and Marie Curie for radioactive thorium, polonium and coining the term "radioactivity." Taro Takemi studied the application of nuclear physics to medicine in the 1930s. The history of nuclear medicine will not be complete without mentioning these early pioneers (29).

The first description of bone scintigraphy was by Flemming and colleagues in 1961 using 85 strontium as radiotracer, but radiolabeled diphosphonates are currently the most widely used substances. These are labelled with $^{99m}$Tc a convenient radiotracer. Other radiopharmaceutical tracers are available for more specific situations for instance $^{131}$I iodine for differentiated thyroid cancer metastasis, $^{123}$I metaiodobenzylguanide (MIBG) for neuroblastoma (29).

Naturally occurring radionuclides are unsuitable for use due to their shortage, long half life, type of particles emitted and their energy states. Radionuclide generators facilitate generation of short half life radionuclides from their long-lived parents (29, 30).

Bone scintigraphy with $^{99m}$Tc remains the most widely used method for diagnosis and surveillance of bone metastases. Because both Mo-99 and $^{99m}$Tc have fairly short half-lives (66 hours and 6 hours, respectively), these drugs cannot be stockpiled. $^{99m}$Tc is derived from an isotope called molybdenum-99 (Mo-99), which is made mostly in highly enriched uranium nuclear reactors (29,30).

The FDA has approved a new drug application from the National Cancer Institute (NCI), part of the National Institutes of Health, for a new strength of a previously approved drug, Sodium Fluoride$^{18}$F, for use in bone scans (31).

In contrast to $^{99m}$Tc which had been the only approved radioactive tracer for bone scans, Sodium Fluoride $^{18}$F is not subject to the supply problems that have led to recent nationwide shortages of $^{99m}$Tc. $^{18}$F was approved in 1972 but withdrawn in 1975, when the less expensive tracer $^{99m}$Tc became available (31).

Positron Emission Tomography previously regarded as a research tool is now used in cancer staging on specially adapted gamma cameras and dedicated PET scanners. A number of single photon tumour specific tracers exist, like $^{201}$Thallium, an analogue of potassium and $^{99m}$Tc sestamibi.

Pharmacophysiology
Uptake of diphosphonates depends both on local blood flow and osteoblastic activity. The actual mechanism of uptake is still not fully understood, but diphosphonates are probably incorporated into the hydroxyapatite crystal on the bone surface. $^{99m}$Tc-methylene
diphosphonates (MDP) is the most widely used bone agent giving optimal contrast between normal and diseased bone though other diphosphonates tracers exist. The PET tracer $^{18}$F is up-taken in a similar manner. $^{201}$Thallium is up-taken by sodium potassium Adenosine Triphosphatase (ATPase) pump while sestamibi relies on mitochondrial activity. Bone scanning is done by multiheaded gamma cameras that are able to provide high resolution whole body images with a rapid scan time acquiring both anterior and posterior projections spontaneously. More recent cameras have the ability to perform topographic images or single photon emission computed tomography (SPECT). These facilitates three dimensional data acquisition and increases sensitivity because of increased contrast resolution as structure superimposition is avoided (29).

The success of these tracers depends on the fact that bone destruction by metastasis is nearly always accompanied by a degree of osteoblastic response. Even predominantly lytic lesions are usually associated with an attempt at bone repair and, therefore, appear as areas of increased radiotracer uptake. Purely lytic lesions that do not excite an osteoblastic response or aggressive tumours where bone is unable to mount sufficient response as seen in some breast carcinoma appear as cold spots. These photopenic lesions may pose diagnostic difficulties (32, 33).

**Limitations of scintigraphy**

1. Apart from the photopenic lesions, increasing hot lesions on follow up scans or previously invisible lesions being detected does not always correspond to progressive disease. This can be subsequent to the flare response seen following successful systemic chemotherapy indicating a healing osteoblastic response. Hence a history of recent therapy should be obtained and scans delayed for 2-3 months (32).

2. Rarely when bone metastases are extensive, a bone scan may appear normal due to the confluent nature of the lesions. This “superscan” however, has distinguishing features. The soft tissues and kidneys maybe inconspicuous due to the increased ratio between skeletal and soft tissue accumulation (5).

3. Normal variants of increased uptake exist in the manubriosternal junction and clues such as asymmetry or lack of linearity should raise suspicion.

4. Other variants are the confluence of sutures at the pterion, deltoid muscle insertion and tip of scapulae. The latter can be distinguished from a rib lesion by further view with arms raised to exclude the overlying scapula from the ribs.

5. A single lesion with known malignancy may turn out to be malignant in 41% of patients. In the vertebrae diagnostic difficulties of a solitary lesion exists due to frequency of degenerative diseases. Baxter et al found out that just over half (57%) of the cases turned out as benign disease on clinical and imaging follow-up (32).
6. Pseudofracture of osteomalacia, hypercalcemia and renal dystrophy features maybe difficult to distinguish and the often co-exist in patients with breast cancer.

7. Bone scintiscans have the disadvantages of poor spatial and contrast resolution. In many patients, further imaging is required to characterize regions of disseminated abnormality.

8. There are various differential diagnoses of multiple scintigraphic abnormalities including metabolic problems (e.g., Cushing syndrome), osteomalacia, trauma, arthritis, osteomyelitis, Paget disease, and infarctions.

**PLAIN RADIOGRAPHY**

A heterogeneous beam of X-rays is produced by an X-ray generator and is projected toward an object. According to the density and composition of the different areas of the object a proportion of X-rays are absorbed by the object. The X-rays that pass through are then captured behind the object by a detector (film sensitive to X-rays or a digital detector) which gives a 2D representation of all the structures superimposed on each other.

It is true that of the various structures of the human body, bone is well imaged by radiography allowing fine spatial resolution. This usually allows a proper differential diagnosis (specificity) though its sensitivity raises significant problems as only relatively late in the pathological process can bone pathology be detected (29). Accurate diagnosis depends partly on location. For instance, metastases to dense cortical bone are easier to detect than those involving trabecular (medullary) bone. In the axial skeleton, medullary metastases may not be detectable until 50% of the trabecular bone has been destroyed (34). Among the advantages of radiography is the fact that certain features may help to distinguish metastases from other conditions and aid in identification of the primary tumor. Radiography may be used to assess the risk of pathological fracture, which is said to be high if 50% of the cortex is destroyed by a lesion. Whereas bone scans define an active process involving bone incorporating nuclide with quantities as little as 10^13gm, radiography requires destruction or accretion of bones in amounts measured in grams (5).

**Limitations of plain radiography**

1. Osteolytic destruction of a vertebral body, which is primarily composed of trabecular bone, can be very difficult or impossible to detect by radiograph, some visible only when upto 70% of the vertebral body is destroyed (33). On the other hand destruction of the pedicle composed of cortical bone is readily detected and manifests as absence of one or both "eyes" on frontal views. Therefore, a small pedicle lesion can foretell a large undetectable lesion by CT or MRI (33).

2. Vertebral compression fracture can be due to osteoporosis or metastasis. Upto one third of patients with pathological fractures will have a benign cause (35). Fractures that produce a focal angulation of all or part of the end plate have characteristics of
malignancy, while those producing a more concave pattern of end-plate deformation are more frequently associated with benign disease (36). Skull metastasis maybe difficult to detect due to curved calvarium and tangential views maybe required. Skull base osteosclerotic metastasis may mimic fibrous dysplasia or Meningiomas (36). Sacral metastasis though uncommon maybe difficult to visualise due to overlying soft tissues.

3. Radiography, though excellent in structural detail, remains inadequate in investigation of function therefore becoming difficult to distinguish between old and new events, metabolically active and functionally neutral pathology, and assessment of healing and response to therapy (32).

4. Skeletal surveys are time consuming and may just reveal subtle changes in trabecular pattern which may be difficult to interpret, and events of ionising radiation in skeletal survey also introduce a drawback.

5. In a patient more than 45 years of age with an area of osteolytic lesion, the possible diagnoses include MBD, myeloma or lymphoma hence drawing a limitation in the specificity of PR.
STUDY JUSTIFICATION

Although bone scans are frequently used for evaluation of MBD, they are associated with higher costs and higher radiation in comparison to PR. They are also not as widely available as PR. WBBS is recommended for evaluation of patients with multiple sites of bone pain or for staging of patients at high risk of having metastases. However, it may not be justifiable for patients with bone pain affecting a single area. The recently recommended radiotracers remain widely unavailable and require cyclotron production.

The usefulness of PR increases if there is suspected polyostotic involvement, or where the scan does not provide a definitive diagnosis.

PR is even more rewarding when it follows the bone scan and investigates lesions picked up by the scanning procedure (36). This is especially so when the bone scans pick a solitary lesion or a few lesions in a pattern for which a non-metastatic explanation cannot be found.

These tests should remain mandatory as baseline workup in suspected MBD in breast cancer patients. Furthermore, no official guidelines on this topic have been set out to date by the leading professional societies, such as the American Society of Clinical Oncology (ASCO) or the European Society of Medical Oncology (ESMO). Instead, ASCO clinical guidelines for breast cancer surveillance do not recommend serial imaging tests following primary intervention (11, 18).

A review from Hamaoka et al. (19) has highlighted that imaging modalities visualise different aspects of osseous tissues (cortex or marrow) in terms of density, water content, vascularity, or metabolism. Hence, the appearance of osteolytic, osteoblastic, or mixed osteolytic/osteoblastic lesions may differ considerably depending on the imaging modality used, leading to variable detection capability for different imaging tests. These should, therefore, prompt the clinician to recommend either modality with confidence and the limitations should be availability or affordability not the reliability of these tests.

This study therefore examines both PR and WBBS and evaluates their accuracy in detection of MBD.
OBJECTIVES

To establish the accuracy of WBBS and PR in detection of skeletal metastasis in breast cancer patients seen in K.N.H and AKUH.

Research question

Does PR and WBBS have a role in detecting MBD and what are the limitations of either modalities.

Hypothesis

Both PR and WBBS are invaluable in diagnosis of MBD.

SPECIFIC OBJECTIVES

1. To establish the frequency of positive bone scans in the setting of normal PR findings.
2. To evaluate the prevalence of MBD in breast cancer patients.
3. To establish sensitivity of WBBS and PR in detection of early metastatic disease.
4. To determine the pick-up rate of targeted plain radiography in establishing diagnosis after detection of a solitary lesion on scintigraphy with indeterminate diagnosis.

Problem statement

The Gamma machine breakdown that persists to date at KNH greatly limited follow up of patients recruited for the study. 15 patients referred for WBBS to Agakhan university hospital could not afford its more than double cost at AKUH. They had to be dropped out of the study. The machine is currently still not working.
No problems were encountered in acquiring PR.
STUDY DESIGN AND METHODOLOGY

Study area

This was done at K.N.H Radio Nuclear Medicine Unit, Radiology Department and Radiotherapy clinic from May 2013 to July 2013 and subsequent to gamma camera malfunction, further data acquisition was done at AKUH nuclear medicine unit.

Study population

Due to frequency of complains of bone pains in premenopausal and post menopausal females, there is need to categorize the aetiology of such pains. A high index of suspicion is required if the patient is a known breast cancer case as this prompts the clinician to request further investigation. The need for staging and assessment of prognosis is also vital for the patient and the clinician.

An average of 70 patients are referred and booked for bone scans per month. A further 40 patients have had a prior plain radiograph taken for complains of athralgia.

Study design

This is a prospective cross sectional study.

Sampling method

All consecutive patients sent to K.N.H and AKUH for WBBS within the period of study and who met the inclusion criteria below were included in the study.

Inclusion criteria

This included patients with breast cancers who consented and were referred for plain radiography and WBBS. These patients presented with complaints of bone pain and the primary clinician requested investigations to exclude MBD during the study period. This included 99 patients who had undergone WBBS within 3 months of the radiographs. 6 had undergone prior MRI for persistent back aches in addition to PR and found to have evidence of bone metastasis. A WBBS was therefore requested for to assess the dissemination of metastatic lesions. A further 20 had a WBBS prior to PR. The rationale for using radiographs acquired 3 months prior is that even WBBS done after 3 months from the earlier study did not result in any significant change in radiological findings. Further patients with earlier radiographs taken within a time span of 6 months to the current PR had no interval increase in disease progression.
Exclusion criteria

Patients who declined to consent were not included. Other exclusions were mainly due to language barrier and 3 patients who were markedly debilitated by disease requiring admission. 7 patients were excluded as their medical records could not be traced.

8 patients were excluded as they did not present for PR after WBBS was done.

15 patients were excluded as they did not present for WBBS at AKUH after machine in KNH broke down. However the total number of patients studied were 125.

WBBS Exam

Patient referred by the clinicians were booked by the technologist after confirming the appropriateness of the examination for the indication given.

Patient availed all previous films, radiographs or scintigrams on the day of the examination.

No special instructions were given prior to imaging.

Patient clinical summary and indication for referral were included in the study.

A form with the patients name and date of examination was given to the patient (or guardian) with a summary of how the examination is carried out. A consent explanation form was also issued prior to imaging.

On the day of examination the standard method as outlined in the earlier section on literature review was carried out.

PR Exam

Patient availed the request form and the examination carried out without any preparations or special instructions.

Information about other radiologic investigations was also obtained by reviewing the patients previous investigations as archived in the Picture Archiving and Communicating Systems (PACS). This was in order to assess the morbidity associated with the disease.
Sample size determination

To obtain 95% confidence interval for a precision of 5% the required minimum sample $n$ was obtained using the Fisher's formula below:

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

where: $n$ is the sample size

$p$, the prevalence of metastatic breast disease in the general population is 9%

$z$, is 1.96, the confidence that error does not exceed 0.05

d, is 0.05, the tolerable error

Calculated sample size was 126.

Control of bias

All examinations done during this period were reported by qualified and widely experienced Nuclear Medicine consultant in Radio nuclear Unit in collaboration with consultant Radiologist in Radiology Department. The same gamma camera machine was used and good quality radiographs chosen to minimize technical inaccuracies and inter observer bias. The reporting consultant Radiologist was not blinded to the findings on WBBS or to the patient's disease process.

Limitations of study

The study had several variables. Firstly, the PR requested was for a single body part (and not the entire skeleton) that was in pain, the findings were positive on WBBS which effectively searched for whole body bony deposits including rib deposits. This resulted in a positive WBBS and negative PR exam due to differential imaged body parts. Secondly, the sample was biased since it was based on patients treated in two referral hospitals. These hospitals receive known biopsy proven cases of breast cancer. In addition these hospitals have adequate facilities for detection of bone metastasis. In contradistinction peripheral hospitals have limited mammography machines and are referred to these hospitals where they are immediately recruited into their clinics thereby skewing the population of breast cancer patients managed and treated in the periphery.
**Data collection, analysis and presentation.**

Data collection was done by the Radionuclide Technician, Nuclear Physician and the principle investigator using a structured data collection sheet (Appendix 1).

Findings on WBBS were all reviewed by the resident nuclear physician at AKUH and KNH. PR films were reported by highly skilled radiologists with vast radiological experience.

The information obtained was entered in the data collection form (Appendix I) by the principle investigator.

At the end of the study all this information was analysed with the help of a statistician to establish the pattern of findings as seen on PR and WBBS. Where other radiological modalities were employed, note was made of them.

This information is represented in the section on results with the aid of images, tables, graphs and charts.

A time frame for research and data acquisition is summarised in the table 5 below.

**Table 6.Gantt chart**

Timeline for research study

<table>
<thead>
<tr>
<th>Activity</th>
<th>From</th>
<th>To</th>
<th>Duration weeks</th>
<th>% completion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Question development and literature research</td>
<td>15/10/2012</td>
<td>15/01/2013</td>
<td>12</td>
<td>100</td>
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<tr>
<td>Drafting proposal</td>
<td>16/01/2013</td>
<td>1/03/2013</td>
<td>6</td>
<td>100</td>
</tr>
<tr>
<td>Approval by supervisor</td>
<td>2/03/2013</td>
<td>2/04/2013</td>
<td>4</td>
<td>100</td>
</tr>
<tr>
<td>ERC review and approval</td>
<td>2/04/2013</td>
<td>15/06/2013</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>Data collection at KNH</td>
<td>15/06/2013</td>
<td>14/08/2013</td>
<td>9</td>
<td>100</td>
</tr>
<tr>
<td>Gamma camera breakdown at KNH</td>
<td>14/08/2013</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Re-approval by AKUH research committee</td>
<td>30/08/2013</td>
<td>16/09/2013</td>
<td>2</td>
<td>100</td>
</tr>
<tr>
<td>Data collection at AKUH</td>
<td>16/09/2013</td>
<td>22/12/2013</td>
<td>14</td>
<td>100</td>
</tr>
<tr>
<td>Statistical analysis and draft report</td>
<td>06/01/2014</td>
<td>27/02/2014</td>
<td>8</td>
<td>100</td>
</tr>
<tr>
<td>Approval by supervisor</td>
<td>03/03/2014</td>
<td>12/04/2014</td>
<td>5</td>
<td>100</td>
</tr>
</tbody>
</table>
ETHICAL CONSIDERATIONS

The research protocol was subjected to the K.N.H ethical committee for approval. The AKUH ethical committee also approved data collection at their facility.

Only patients who gave informed consent were included in the study.

Only patients referred for both PR and WBBS were recruited.

No extra costs were incurred by the patient as only the examination requested by the clinician was carried out.

A serious adverse event was defined as any incident causing hospital admission, death, threat to life, or permanent impairment. If any radiograph was required and was not requested by the clinician, in order to facilitate comparison, the principle investigator bore the additional costs. Routine chest radiographs were not carried out so as to avoid unnecessary radiation.

All patients were managed with utmost professional care by qualified radiologists and technologists.

Radiology equipment was comparable to the recommended standard specifications in order to ensure accurate diagnosis of disease patterns.

No name or personal identification was included in the study.

Only identification was the Bone scan serial number and age.

Data base was secured to ensure only the principal investigator had access to it.

The raw data was the exported to the statistician for analysis.

All statistical tests were interpreted as significant only if p value was <0.05.

Upon completion all raw data were destroyed by burning.

All DICOM and JPEG images were also deleted to avoid retrieval.
RESULTS

Overview of recruited patients

The study recruited a total of 125 patients sent by the referring clinician primarily the oncologists, surgeon and even radiologists who had a high index of suspicion of metastatic bone disease. These patients were suspected to have MBD. The patients were aged between 21 and 112 years with radiographically and biopsy proven breast malignancy undergoing WBBS at KNH and AKUH between May and December 2013. All the 125 patients underwent WBBS within 12 weeks of plain radiography and most (60, 48%) were referred for investigations by oncologists. The proportion of cases referred by oncologists 48% (95% Confidence Interval-CI 40-57.1) did not differ significantly from referrals by other clinicians 36% (95% CI 27.6-45), Figure 9.1. This confirms the multidisciplinary approach in management of breast cancer patients. This has led to significant strides in the reduction of breast cancer incidence and mortality (36).
Figure 7: Proportion of patients referred to radiology unit for WBBS by oncologists, surgeons, and Others.

**Age at presentation**

The mean age of patients was 51.3 years (SD 12.8) and most were aged 41-50 years (41.9%) or 51-70 years (34.7%). As shown in Table 9.2 the proportion of patients aged 41-50 years and 51-70 years were significantly higher than proportions in the age categories 30 years and below or 70 years or above.
Table 7. Age distribution of breast cancer patients referred for WBBS following plain radiography at KNH and AKUH.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Frequency (n = 125)</th>
<th>Percent (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age group</td>
<td></td>
<td></td>
</tr>
<tr>
<td>21-30 years</td>
<td>3</td>
<td>2.4(0.1-5.1)</td>
</tr>
<tr>
<td>31-40 years</td>
<td>16</td>
<td>12.8(6.9-18.7)</td>
</tr>
<tr>
<td>41-50 years</td>
<td>52</td>
<td>41.6(32.8-50.4)</td>
</tr>
<tr>
<td>51-70 years</td>
<td>44</td>
<td>35.2(26.7-43.7)</td>
</tr>
<tr>
<td>71-112 years</td>
<td>10</td>
<td>8.0(3.2-12.8)</td>
</tr>
</tbody>
</table>

The difference was not statistically significant as shown on Figure 8. The median age (IQR) of patient with positive, negative and unequivocal scans was 51 (46-51), 48 (44-53.5) and 53 (48-54) years, respectively (Kruskal Wallis ANOVA, p value = 0.32).
Indications for referral for WBBS

The four main indications for WBBS investigation following plain radiography were: bone pain in 97 cases (77.6%, 95% CI 69.3-84.6), indeterminate PR findings (where the reporting clinician detected a lesion but did not feel it was definitely malignant or otherwise this is mainly to avoid litigation), bone metastasis 12 (9.6, 95% CI 5.1-16.2), referral for staging of cancer 3 (2.4%, 95% CI 0.5-6.9) and other indications including paraplegia, follow up, 12 (9.6, 95% CI 5.1-16.2). Median age for the patients with these different indications were 49.5 (IQR 44-56), 48 (42-51.5), and 49.5 (46-53) years for bone pain, suspected metastasis and
other indications like suspected recurrence, respectively. Figure 9 shows that there was no statistically significant association between patient age and indications for referral for WBBS investigation (Kruskal Wallis ANOVA p = 0.39).

Figure 9: Indication for plain radiograph and WBBS investigations in breast cancer patients at KNH according to age
Note is made of two patients who were referred by a renown herbalists where the indications was to rule out MBD. The duo had florid metastasis throughout the axial and appendicular skeleton.

Fig 10.

WBBS from two patients referred by a herbalist demonstrating widespread skeletal metastasis (arrows). This was the finding in the two patients who were on herbal therapy.
Other pertinent clinical history

Two patients presented with acute hip pain. PR clearly revealed presence of right hip and superior pubic ramus pathological fractures.

One patient had a tibial fracture and had been managed by internal fixation device. She was referred by the surgeon for PR and WBBS scan to assess the possibility of a pathological fracture. Despite the instrumentation both modalities suggested trauma as the aetiology rather than metastatic deposit.

Four patients in this study group were diagnosed with breast cancer on screening mammography whose programme runs in October at AKUH, (see Fig 11). The results for metastatic spread were negative in these patients. This highlights the importance of screening for breast cancer in detecting early breast cancer thereby reducing morbidity associated with the disease.

Fig 11. Mammograms showing a definite speculated left breast mass that was a malignancy. The WBBS, CXR and abdominopelvic scan were negative for malignancy
Correlation of WBBS and plain radiography

The frequency of negative findings on bone scans was 76 (60.8%), 7 (5.6%) scans were equivocal and the remaining 42 (33.6%) were positive. Bone scan findings did not show statistically significant associations with the referring clinician (p = 0.30) but scan findings were significantly associated with indication for referral (p = 0.04), Table 8. Of the two main indications for WBBS, 58% of suspected metastasis had positive bone scans compared to 27% of patients referred with bone pain. Table 8 shows that 56% of patients with other indications also had positive bone scans.

Table 8: Bone scan findings according to indications for referral and referring clinician

<table>
<thead>
<tr>
<th>Bone scan findings</th>
<th>Chi</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>65</td>
<td>67</td>
</tr>
<tr>
<td>Positive</td>
<td>33</td>
<td>39</td>
</tr>
<tr>
<td>Equivocal</td>
<td>7</td>
<td>44</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Indication</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Bone pain</td>
<td>14</td>
<td>70</td>
</tr>
<tr>
<td>Suspected metastasis</td>
<td>39</td>
<td>65</td>
</tr>
<tr>
<td>Other indication</td>
<td>23</td>
<td>51</td>
</tr>
</tbody>
</table>

Referring clinician

Oncologist

Surgeon

Other
Fig 12 a: Bone scans of a patient showing disseminated metastasis throughout the axial and appendicular skeleton.
On PR, particular challenge was identification of metastatic lesions involving the sternum, iliac wing, scapula and sacroiliac joints. Lesions of the ribs were also difficult to detect on PR.
particularly because most of the patients had associated thoracic pathology like malignant effusion that silhouettes the ribs. See Fig 13b.

**Fig 13 a-c**

A) Axial CT scan of the pelvis showing fracture of the right inferior pubic ramus which was poorly visualised on PR.

B) The patient also had rib metastasis that were barely discernible on CXR labelled b due to pleural effusion.
Fig 13c. In these bone scan images, there is right inferior pubic ramus fracture in addition to multiple rib metastasis and vertebral deposits.
Radiographs of a 42-year-old showing:

a) The CXR image shows a right malignant pleural effusion (dark arrow).

b) Inferior pubic ramus pathological fracture shown on this pelvic radiograph. (curved)

c) Lumbosacral spine showed mixed lytic and blastic lesions. Degenerative changes are noted (arrowheads).
The positivity of both WBBS and PR in detecting early metastatic bone disease is shown in Table 9. The findings of the two investigations showed a correlation in 91 (72.8%, 95% CI 64.1-80.4) patients. Both investigations were positive in 21 (16.8%, 95% CI 10.7-24.5%) patients and negative in 70 (56%, 95% CI 46.8-64.9) patients. Findings for 19 patients were discordant where one modality was positive while the other was not. 8 had equivocal PR this was mainly due to platyspondyl and diffuse osteoporosis and MBD was not entirely excluded as the cause they were positive on bone scans. 7 patients had equivocal WBBS findings. In these studies increased uptake was noted and the radiologist could not commit whether it was due to degeneration or inflammation (especially adjacent to the ribs). A recommendation of a repeat WBBS was made within 3-6 months. Unfortunately these results are not available to the investigation due to limited duration of study. This explains in part the limited specificity of WBBS and medicolegal implications associated with an incorrect report.

WBBS findings were used as the gold-standard for diagnosis of MBD in these breast cancer patients. (Table 9). PR was positive in 21 out of the 35 patients with WBBS diagnosed MBD (sensitivity 60%) and correctly identified 70 of the 75 cases that did not have evidence of MBD based on WBBS findings yielding a specificity of 93.3%. The positive predictive value of PR for MBD was 80.8% (21 out of 26) and the negative predictive value was 83.3% (70 out of 84). Five negative bone scans had been classified as positive by PR yielding a false positive rate of 6.7 % for PR in diagnosing MBD.

Table 9: Findings of bone scans and correlation with plain radiograph findings in breast cancer patients with bone pain in KNH and AKUH.

<table>
<thead>
<tr>
<th>Plain radiograph findings</th>
<th>Bone scan findings</th>
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</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Positive</td>
<td>Negative</td>
</tr>
<tr>
<td>Positive</td>
<td>21</td>
<td>5</td>
</tr>
<tr>
<td>Negative</td>
<td>14</td>
<td>70</td>
</tr>
<tr>
<td>Equivocal</td>
<td></td>
<td>15</td>
</tr>
<tr>
<td>Total</td>
<td>35</td>
<td>75</td>
</tr>
</tbody>
</table>
Discussion

The correlation of radiographic and scintigraphy findings in MBD have been described in various studies. Many studies support WBBS in screening of MBD due to its high sensitivity compared to PR. (38,39,40).

A study published in the Journal of National Cancer Institute showed that age-specific incidence of breast cancer varies with race. It showed a Black-White crossover in breast cancer diagnosis where breast cancer occurs more often in Black than White women before the age of 40, but more often in White women than Black women after age of 40 (41). In this study, there was a slightly higher proportion of women under 50 years with bone metastasis as opposed to those over 50 years. There seemed to be higher incidence of bone metastasis in the younger age group than in patients over 50 years. This agrees with a study by Chang et.al, which showed that the younger patients had higher incidence of metastatic bone disease. The prognosis of the older patients was worse since they seemed unwilling to compromise quality of life through chemotherapy and radiotherapy as compared to the young (41).

Two patients had synchronous tumor involving the colon and endometrium respectively. Interestingly enough none of them had any MBD despite complains of severe bone aches.

It was not clear if the endometrial tumor and the colon tumor were primary or secondary. It is well known that tamoxifen increases risk of endometrial cancer. The importance of delineating if tumor is metastatic or primary lies in the treatment options. In a study by Lamovec J et.al, the incidence of infiltrating lobular carcinoma metastasis to endometrium is 2-4 times higher in patients who have received tamoxifen than those who did not (42).

Colonic metastasis though rare has also been observed and invasive lobular carcinoma is most commonly the cause according to a study by Harris M et.al (43, 44).

A further two patients had synchronous bilateral breast cancer. However, the duo had disseminated skeletal metastasis as well. Vichapat V et.al studied 8472 females with breast cancer at Guys and St.ThomasôNHS foundation trust for over twenty years and found that women with contra lateral breast cancer within 5 years had a higher incidence of metastasis
in all organs compared with patients with unilateral breast cancer (45). These findings confirm the poor prognosis in females with contra lateral breast carcinoma. It further suggests that such aggressive tumors have established systemic micrometastasis despite early detection of the primary tumor.

A single patient aged 37 years was being investigated for suspected recurrence of cancer. She had been declared cured of cancer but presented with right hand pain and swelling 13 years after surgery and chemotherapy. The WBBS was negative for metastasis. A PR showed soft tissue swelling consistent with cellulitis. An ultrasound study would have been valuable to exclude lymph oedema.

Despite usage of dual radiological modalities 3 cases had unconfirmed findings on whether the lesions were metastatic or due to infection. These involved a patient with increased uptake in the costochondral junction on WBBS and a normal CXR, and two patients with lesions in the thoraco-lumbar spine. These lesions showed uptake in both sides of a single vertebra on WBBS while radiographic findings were normal. No further imaging recommendation was advised by the reporting radiologists.

A further two patients had incidental findings of sclerosis at T5 vertebra on CT scans of the chest on bone windows. The indications for the CT scans were not availed. However on WBBS and PR the lesions proved to be metastatic deposits. The patients were both known cases of ca breast. This highlights the importance of high index of suspicion for bone avid metastasis in patients with occult malignancies when a solitary lytic bone lesion is detected incidentally.

There were two patients with solitary rib lesions for which a repeat WBBS was recommended by the reporting radiologist in 3 months. PR was normal. Although the findings of the repeat WBBS were not available to the investigator, it is likely that static imaging findings will be present. A study by Chenn et.al showed that it takes average of two years to develop radiological and scintigraphic changes in patients with 1 or 2 rib lesions (42). This delay in diagnosis makes clinical decision making difficulty. The study recommends regular follow up of 2 years interval after detection of solitary rib lesions (46).
In 20 (16%) patients, an additional imaging modality was recommended to improve diagnostic accuracy of findings after PR and WBBS investigations. The recommended additional investigations included abdomino-pelvic ultrasound (n = 4), CT scan chest (n = 3), MRI (n = 12) and repeat RNI (n = 1), the time range was between 3 to 6 months. The Chest CT was to rule out pulmonary nodules less than 5mm, not detectable on plain CXR. The abdomino-pelvic ultrasound were mainly recommended to rule out abdominal metastasis and for staging. The repeat RNI was recommended to confirm presence of a solitary lumbar lesion that was likely metastatic, or lesions that were not well defined on earlier RNI. Unfortunately, all the results were not available to the investigator due to the short duration of the study.

A study conducted by Kravalis et.al in two academic centres over 20 years found that metastatic breast carcinoma confined to bone remained confined to bone for 50 months. They showed that metastatic disease confined to bone had an indolent clinical course. This should alleviate the need for aggressive follow up and puts into question aggressive therapeutic approaches employed in managing these patients (47).
Conclusion

WBBS remains an important tool in diagnosing skeletal metastasis. PR is invaluable in demonstrating pathological fractures in patients presenting with acute bone pain. It is valuable as a baseline for bone disease, is low in cost and easily acceptable to the patient. PR is less sensitive in detecting early MBD. The WBBS remains invaluable but should not be considered diagnostic when the results are equivocal due to a solitary focus of increased tracer uptake. It also has higher false positives associated with degenerative changes and costochondral trauma as shown in this study.

These two imaging modalities will continue being widely used in breast cancer staging. However, most patients with bone pain have normal radiological findings rather than metastasis. This supports a longer interval in subsequent investigations of breast cancer patients with bone pains. Additional imaging modalities like MRI should not be routinely used where PR and WBBS show negative results excluding metastasis, as the cause of bone pain.

Recommendations

1. Since bone is the commonest site of breast metastasis, a high index of suspicion and low threshold for radiological investigations is a mandatory requirement for the clinician.

2. PR should be routinely used as a baseline in breast cancer patients with bone pain. If symptoms clinically subside, further work up using bone scans is not cost effective to the patient. Later progression of bone pain warrants aggressive workup with PR and WBBS.

3. A standard method of investigating tumour response in MBD should be evaluated as currently no standardised universally acceptable method exists.

4. As shown on table 7, whereby the peak age group is 41-70 years corresponding to degenerative bone disease onset, the likelihood of multiple concurrent pathologies must be considered.
REFERENCES


APPENDIX I: DATA COLLECTION FORM

1. SERIAL NUMBER:............................

2. AGE: ...........................

3. REFERRING CLINICIAN

3.1.1 PRIMARY PHYSICIAN
    3.1.2 SURGEON
    3.1.3 ONCOLOGIST
    3.1.4 OTHER..............................

4. INDICATION FOR REFERRAL
    4.1.1 BONE PAIN
    4.1.2 RULE OUT BONE METASTASIS
    4.1.3 STAGING
    4.1.4 SUSPECTED RECURRENT
    4.1.5 OTHER..............................................

5. PREVIOUS RADIOLOGIC INVESTIGATIONS

5.1.1 PLAIN RADIOGRAPHS

5.1.2 OTHERS.............................................

6. PRIOR RADIOGRAPHY IMAGING DIAGNOSIS

6.1.1 SUSPECTED METASTASIS

6.1.2 DEGENERATIVE DISEASE

6.1.3 PATHOLOGICAL FRACTURE

6.1.4 NORMAL FINDINGS

6.1.5 OTHERS.............................................

7. BONE SCAN FINDINGS

    7.1.1 NEGATIVE

    7.1.2 POSITIVE

    7.1.3 EQUIVOCAL
8. CORRELATION WITH PR FINDINGS

8.1.1 YES

8.1.2 NO

8.1.3 OTHER EXPLANATION

9. RECOMMENDATION FOR OTHER IMAGING MODALITY

9.1.1 YES (WHICH ONE)

9.1.2 NO

10. IMPROVED DIAGNOSTIC ACCUMEN OF THE CLINICIAN

10.1.1 YES

10.1.2 NO
APPENDIX II: CONSENT EXPLANATION FORM.

Name…………………………………………………………

Date of examination……………………………………

You will be required to report at 8 am. The examination requested by your clinician will be
done by injecting a radiotracer specific to bone and images will be acquired 3 hours later. The
radiation is acceptable and is necessary for management of the disease. No further costs or
health detriments will be incurred by your participation in the study. Kindly sign the consent
form if you wish to participate in the study.

Utahitajika kujiwasilisha tarehe ulioambiwa saa mbili asubuhi . Picha inayohitajika na
daktari wako inastahili udungwe dawa itakayoenda kwa mifupa na baada ya masaa matatu
picha itanaswa kwa camera. Hakuna madhara yoyote inayotarajiwa na kiwango cha xrei
hakitabadilika ukihuishiwa katika utafitihuu . Gharama utakayopata haitaonegezeka nautafiti
huu utasaidia zaidi kuchunguza ugonjwa wa saratani. Utapiga sahihi kibali iliniweze
kuhuhusisha katika utafiti huu.
APPENDIX III: PATIENT CONSENT FORM

My name is Dr Grace Gatete, pursuing a master’s degree in Diagnostic Radiology and I am doing a study correlating radiologic findings and Whole Body Bone Scans in patients with suspected metastatic breast disease and I wish to recruit you to participate. Information will be handled with utmost confidentiality.

The examination is done with a special gamma camera and x-rays. A small volume (400M bq) of bone tracer named Technetium Methylene Diphosphonate will be injected in your arms and then you will lie on the couch for image acquisition after 3 hours. The only discomfort expected will be pain during injection otherwise it is a safe procedure with an acceptable radiation dose. Imaging procedure will be around half an hour. For the plain radiograph images will be acquired of the site specified by your doctor.

Your name will not be included in the study. The results of the study will be used to improve diagnosis and management of metastatic breast disease.

It is not a must that you participate and you have the right to decline or withdraw from the study without any prejudice.

If you accept to participate please sign below:

Sign....................................
Date....................................                     (Name)....................................

I certify that patient has fully accepted and has granted me informed consent.

Sign. ....................................
Date....................................                    (Name)...........................

........................................
KIBALI CHA KUHUSIKA KATIKA UTAFITI

Jina langu ni Daktari Grace Gatete, mwanafunzi katika chuo cha udaktari, chuo kikuu cha Nairobi. Ninafanya utafiti kuhusu udhabiti wa picha ya xrei na "scintigraphy" kwa kuchunguza ugonjwa wa mifupa kwa wanaoungua saratani ya matiti.

Jina lako na habari itakayopatikana kukuhusu, itakuwa ni siri na kutumika tu kwa kuboresha matibabu ya wanaoungua ugonjwa huu.

Utahitajika kudungwa dawa kiwango cha (400MBq) iitwayo `Technetium Methylene Diphosphonate itakayoenda kwa mifupa na baada ya takriban masaa matatu kisha utalazwa kwa meza ili picha inaswe na kamera.Dawa hii haina madhara makuu kwa mwili ila uchungu utakaohisi ukidungwa sindano hiyo. Mpangilio huu utachukua kama nusu saa. Xrei itafanywa kama ambavyo daktari wako aliyoagiza na hakuna garama zaidi itaongezewa.

Kwa kuweka sahihi inamaanisha kuwa nimepewa nafasi ya kuendelea na utafiti huu. Elewa yakwamba waweza kubadili na kukataa kwendelea na utafiti huu bila kushurutishwa na yeote yule. Kama unaku bali kushiriki, tafadhali weka sahihi yako hapa chini:

Sahihi........................................ (Jina)é é é é é é é é é é é é é

Tarehe...................................

Ninathibitisha kwamba mhusika ameelewa na amekubali kushiriki katika utafiti huu.

Sahihi................................. (Jina)........................................

Tarehe....................................
PROJECT BUDGET

ACTIVITY ESTIMATED AMOUNT (Kshs)

1. Literature research, reference materials 15,000
2. Computer and stationary 30,000
3. Printing and typing 40,000
4. Internet costs 15,000
5. Incidental costs 20,000
6. Ethics fees 2,000

TOTAL 97,000
Dear Dr. Gatete,

RESEARCH PROPOSAL: CORRELATION OF PLAIN RADIOGRAPHY AND RADIONUCLIDE SCAN FINDINGS IN BREAST CANCER PATIENTS WITH BONE PAIN IN KENYATTA NATIONAL HOSPITAL (P640/11/2012)

This is to inform you that the KNH/UoN-Ethics & Research Committee (KNH/UoN-ERC) has reviewed and approved your above revised proposal. The approval periods are 4th June 2013 to 3rd June 2014.

This approval is subject to compliance with the following requirements:

a) Only approved documents (informed consents, study instruments, advertising materials etc) will be used.

b) All changes (amendments, deviations, violations etc) are submitted for review and approval by KNH/UoN ERC before implementation.

c) Death and life threatening problems and severe adverse events (SAEs) or unexpected adverse events whether related or unrelated to the study must be reported to the KNH/UoN ERC within 72 hours of notification.

d) Any changes, anticipated or otherwise that may increase the risks or affect safety or welfare of study participants and others or affect the integrity of the research must be reported to KNH/UoN ERC within 72 hours.

e) Submission of a request for renewal of approval at least 60 days prior to expiry of the approval period. (Attach a comprehensive progress report to support the renewal).

f) Clearance for export of biological specimens must be obtained from KNH/UoN-Ethics & Research Committee for each batch of shipment.

g) Submission of an executive summary report within 90 days upon completion of the study

This information will form part of the data base that will be consulted in future when processing related research studies so as to minimize chances of study duplication and/or plagiarism.
For more details consult the KNH/UoN ERC website www.uonbi.ac.ke/activities/KNHUoN.

Yours sincerely

[Signature]

PROF. M. CHINDIA
SECRETARY, KNHUON-ERC

c.c. Prof. A.N. Guantai, Chairperson, KNH/UoN-ERC
The Deputy Director CS, KNH
The Principal, College of Health Sciences, UoN
The HOD, Records, KNH
Supervisor: Dr. Milcah N. Wambugu