COLLEGE OF HEALTH SCIENCES, SCHOOL OF MEDICINE

DEPARTMENT OF INTERNAL MEDICINE,

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Assessment of indications and clinical significance of bone scintigraphy among patients referred to Nuclear Medicine Unit, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia.

By: Solome Yemaneberhan (MD,NMR3)

February, 2023

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Abbreviations

AAU	Addis Ababa University
BS	Bone Scintigraphy
CRPS	Chronic Regional Pain Syndrome
DPD	2,3- dicarboxypropane-1,1-diphosphonate
^{67}Ga	Gallium-67
HDP	Hydroxyethylelne diphosphonate
^{111}In	Indium-111
MDP	Methylene diphosphonate
MRI	Magnetic Resonance Imaging
PSA	Prostate Specific Antigen
SPECT	Single Photon Emission Tomography
SPSS	Statistical Package for Social Science
TASH	Tikur Anbessa Specialized Hospital
^{99m}Tc	Technetium-99m
TPBS	Three-phase bone scintigraphy
WBC	White blood cells

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Abstract

Background: Bone scintigraphy is a very sensitive diagnostic nuclear medicine imaging technique that uses a radiotracer to assess the distribution of active bone growth in the skeleton in relation to malignant and benign disease as well as a physiologic process. The general indications for bone scintigraphy are to investigate for particular bone disease, unexplained symptoms and prior to therapy for metabolic evaluation. There is no baseline study to assess the indications and clinical significance in TASH.

Objective: The aim of this study was to evaluate the clinical indication and significance of bone scintigraphy in patients who were referred to Tikur Anbessa Specialized Hospital.

Methods: A hospital-based retrospective cross-sectional study was conducted using secondary data from a record of a bone scintigraphy from 2007 to 2012 at the Nuclear Medicine Unit at Tikur Anbessa Hospital. SPSS version 22 was used to examine and analyze the gathered data using descriptive and inferential statistics.

Result: In this investigation, 110 Planar and SPECT scan record of patients was used. Out of which 76 (69.1%) were female and 34 (30.9%) were male. The most common indications was the evaluation of metastatic breast cancer at 59 (53.6%), followed by prostatic cancer 22 (20%), Using a binary logistic regression analysis there was a significant correlation between female patients and positive outcome of scans p=0.06 and OR=4. Those aged between 40-49 years had a significant correlation with outcome of the scan compared to their oldest counterpart (>70yr) p=0.03, OR=11.

Conclusion: In this study, 94.5% of indications were for oncologic work up. Breast cancer metastatic workup is the most common indication. Positive results were four times more likely to be seen in female patients than males. People between the ages of 40 and 49 had an eleven fold higher likelihood of obtaining positive scans than the oldest age group (>70 years).

Keywords: *Bone Scintigraphy, SPECT, Planar, Malignant, Benign.*

1. Introduction

1.1 Background

Bone scintigraphy is a highly sensitive diagnostic nuclear medicine imaging technique, uses a radiotracer to evaluate the distribution of active bone formation in the skeleton related to malignant and benign disease as well as a physiologic process. It is a highly sensitive, most frequently performed procedure [1].

The radiotracers used are ^{99m}Tc (99- Meta Stable Technetium) labelled biphosphonates: methylene diphosphonate (MDP), hydroxyethylene diphosphonate (HDP), and 2,3- dicarboxypropane-1,1-diphosphonate (DPD) [1,2].

Biphosphonates have high skeletal uptake and rapid soft tissue clearance. It is believed to be adsorbed to the mineral phase of bone. Binding is not specific for a particular disease process. Degree of binding of bisphosphonates depends on local blood flow, extraction efficiency, vitamin D, parathyroid hormone, corticosteroids, intraosseous tissue pressure, capillary permeability, acid-base balance and sympathetic tone [1].

Bone scan is not specific, therefore we use the tracer ^{111}In (Indium 111) and ^{67}Ga (Gallium 67) to boost their specificity., ^{67}Gallium is one of the most commonly used radioisotopes in tumor imaging, as well as in the imaging of infection and inflammation [2, 3].

^{111}In (Indium 111) and ^{99m}Tc labeled hexamethylpropylene amine oxime (^{99m}Tc-HMPAO) are commonly used for radiolabeling of leukocytes to localize musculoskeletal infection. ^{111}In–labeled white blood cell (WBC) scintigraphy is used in the diagnostic evaluation of occult infections when other imaging modalities are either contraindicated or uninformative [3].

Bone scintigraphy can be performed as a). Spot view or limited bone scintigraphy (planar image of selected portion of skeleton) b). Whole body bone scintigraphy (planar image of the entire skeleton in the anterior and posterior view), c) Single

photon emission computed tomography (SPECT) (image of a portion of the skeleton and d) multiple phase scintigraphy (immediate and delayed images to study) [1, 4].

In oncology the standard is whole body bone scintigraphy. Spot view are only required for clarification when a specific problem is detected on whole body imaging. Multiphase image includes blood flow images, immediate images and delayed images. Blood flow (Vascular) images are dynamic sequence of planar images of areas of greatest interest simultaneously as the tracer is injected. Immediate (blood pool or soft tissue phase) includes one or more static planar image of area of interest immediately after the flow portion of the study, completed within 10 min. Delayed images may be limited to the area of interest or may include the whole body, may be planar or tomographic, acquired 2-5 hrs after injection. Additional delayed image can be obtained up to 24hr after tracer injection as needed [1, 5].

SPECT is more sensitivity compared to planar imaging. SPECT-CT increases the diagnostic confidence in both oncologic and non-oncologic conditions, it aids in the accurate assessment of the site, shape and structure of the abnormalities [1, 6, 7].

The indications for bone scintigraphy are vast but it can be sized down into 3 clinical scenarios: (1) when a specific bone disease is present or suspected, (2) to explore unexplained symptoms, and (3) for the metabolic assessment prior to the start of therapy [1, 4].

SPECT accuracy is 88%, SPECT-CT accuracy is 92%, and conventional bone scans are 80% accurate. The full skeleton can be assessed with a bone scan, which is also widely available, reasonably priced, and offers a minimal radiation dose.

1.2. Statement of the problem

Bone scintigraphy is the backbone of skeletal nuclear medicine imaging [1]. The identification of occult metastasis is the most common indication. Bone pain is the common presenting symptom for Bone metastasis. It is highly sensitive in detecting osteoblastic metastasis from primary cancers of breast, prostate, lung, renal cancers etc. It can also be used to follow the progress of treatment of certain condition. For evaluation of presumed bone pain, to detect occult fractures, infections[1].

In Ethiopia, breast cancer is the leading cause of cancer among adult women, accounting for one-third of all female cancer cases and one in five cases overall. It is estimated 16,133 new breast cancer cases and 9061 breast cancer deaths are reported annually. Majority of cases presentation is at an advanced clinical stage [8]. In this patient categories, bone scintigraphy can be utilized to identify bone metastases. In addition, it can be used to exclude bone metastases in patient with early stage breast cancer that can benefit from curative therapies.

Prostate cancer according to National cancer Institute of America of 2022 is the second most common cancer [9]. Prostate cancer has the highest age standardized death rate in Ethiopia [10]. Early bone metastasis detection will aid in the early intervention to avoid the associated possible complications.

Primary bone tumors are uncommon malignancy but important cause of morbidity and mortality. The commonest primary malignant tumor was osteosarcoma and osteochondroma was the most common benign bone tumor. Most age group affected by primary bone tumors were 10-29 yrs at TASH (Tikur Anbessa Specialized Hospital) [11]. Early detection help in the decision making about management of the patient.

1.71 billion People worldwide suffer from musculoskeletal conditions. Back and neck pain, osteoarthritis, rheumatoid arthritis and fractures are among the most disabling musculoskeletal disorders. It can lead to chronic morbidity and disability accounting for 1.7%-3.4% of global disease burden.

Musculoskeletal disorder ranked second in the East Mediterranean and third in Africa in prevalence of chronic disorders [12]. In a study in Northwest Ethiopia about magnitude of musculoskeletal disorders, was found the magnitude to be 40.1% [13]. Bone Scan can promote early diagnosis and treatment for the betterment of outcome.

No published research on the subject of study has been conducted since the establishment of the nuclear medicine center in our country. Knowing what bone pathology is regarded as prudent by referral doctors and the pattern of bone pathology in the clinical setting will allow one to address any ambiguities in the justification of the indication for referrals and have a baseline study that is clinically pertinent with regard to our demographics.

1.3. Significance of the study

Ethiopia with a population of 110 million had only one functioning Nuclear Medicine up until recently. Change in the demography and epidemiology is leading to rise in non-communicable disease, making it an emerging public health issue. Even though the growth of the field is slow with multiple barriers, it appropriate utilization will aid in the reduction of patients who undergo unnecessary invasive procedures, reduction in the cost of diagnostic tests and accurate and timely diagnosis.

This study will shine a light on pattern of patients that had bone scan in TASH in the study period, which pathology was more prevalent. It will help in educating physicians regarding the justified indication for bone scans. It will function as a baseline research in the event the need to scale up clinical service is desired. It might help in planning bridging the gap between where we are now and where we would like to be in the near future. Conducting new research has been shown to facilitate the adoption of new techniques in small-scale initiatives.

2. Literature Review

Bone scan is the cornerstone for skeletal nuclear medicine imaging. Its application ranges from oncologic to benign disease process [3].

Bone metastasis are most common malignant bone tumors, skeletal involvement occurs in 30-70% of all cancer patients, with breast cancer leading in women and prostate cancer in men followed by lung cancer[14]. About 30-75% of the bone mineral content must be lost before a metastasis is evident on a radiograph. In contrast, as little as a 5-10% change in the ratio of the lesion to normal bone is required to detect an abnormality on bone scan [15]

The osteoblastic component of the metastasis represents reaction of normal bone to the metastatic process. Rapidly growing aggressive metastases tend to be lytic, whereas sclerosis is considered to indicate a slower tumor growth rate [9].

Sensitivity rates of bone scintigraphy in detecting bone metastases vary between 62% and 100% with a specificity of 78%–100% [15]. Bone scan is 50 to 80% more sensitive than radiographs in detecting skeletal metastases [16]. SPECT-CT can further improve accuracy by improving anatomic localization and by permitting better evaluation for underlying bone pathology [17].

In SPECT images, abnormalities that extend beyond the vertebral body are invariably due to osteophytes. Uptake confined only to the articular facets is nearly always benign. Tracer uptake involving both the vertebral body and pedicles is usually indicative of metastatic disease. SPECT imaging results in overall improved sensitivity with the detection of 20-50% more lesions in the spine when compared to planar images [18-20].

Bone metastases of breast cancer are lytic, sclerotic, or mixed in their radiographic appearance [14,21]. The risk for bone involvement, as assessed by bone scintigraphy, depends on the stage of the disease and varies between 4% (0-18%) for Stage I and 7% (0-32%) for Stage II disease. In patients with Stage III disease, the yield may be as high as 14 to 28%.

In stage IV disease, bone metastases can be found in up to 40.5% of patients. Recommendation for a baseline bone scan is for all patients with Stage II-IV Breast cancer [21].

Following initiation of therapy, up to 75% of patients with breast cancer show increased activity or new lesions due to bone repair at responding sites of metastatic disease called Flare Phenomenon [21].

In a meta-analysis of prostate cancer, bone scan/SPECT had a per patient combined sensitivity of 79% and a specificity of 82% for the detection of metastatic disease. The per lesion sensitivity and specificity were 59% and 75%, respectively for planar imaging, and 90% and 85%, respectively for SPECT imaging [22].

Guidelines vary, but in general, bone scan should be limited to patients for initial staging with a T-stage greater than 2, elevated PSA (greater than 10 or 20 ng/mL), high Gleason scores (8-10), locally advanced disease, elevated alkaline phosphatase, or bone symptoms [23,24,25].

The most frequent primary bone cancer in children, although being an uncommon lesion, is osteosarcoma. Skeletal metastasis are only seen in 3% of patients at the time of presentation, whereas pulmonary metastasis can be found in 20% (planar imaging) to 40% (SPECT imaging) of patients. A baseline bone scintigraphy is usually recommended [26]. To detect pulmonary metastasis scintigraphy is much less sensitive than CT [27].

There are conflicting views regarding the use of further bone scan to find metastatic lesion in osteosarcoma. According to some experts, skeletal metastasis do not develop in the absence of lung metastasis, hence repeat bone scans are not necessary unless subsequent CT scanning reveals new pulmonary lesions [28]. Others believe bone metastasis may be detected before lung metastasis, possibly as a result of alteration in the malignancy's normal course in response to severe chemotherapeutic treatment [29].

For lymphoma Ga-67 Citrate scintigraphy is a sensitive imaging modality in detecting bone involvement of lymphoma, mainly with the administration of high doses of ^{67}Ga and the use of SPECT. Both lytic and sclerotic lesions were reported to be ^{67}Ga avid [30-31]. ^{67}Ga has a lymphoma seeking property rather than bone [30].

Bone scintigraphy can detect osteomyelitis 1 to 2 weeks before radiologic changes are manifested (bone scans imaging are often rapidly positive within 24-48 hours of the onset of symptoms [32,33]. A 5% change in bone turnover can be detected at bone scintigraphy [33].

The 3 phase bone scan has a reported sensitivity of 90-100% and a specificity of 70-95% for identification of osteomyelitis in non-violated bone. Specificity drops to about 35% in complicating bone conditions. In an adult a negative bone scan essentially rules out infection [33,34]. Bone scans may remain positive on delayed images for up to 1 to 2 years following successful treatment of osteomyelitis due to continued remodeling.

To assess treatment response of osteomyelitis ^{67}Ga imaging is a better technique.^{67}Ga scan at the initiation of therapy is most useful. Return of the ^{67}Ga activity to normal or very near normal signifies a complete response to antibiotic therapy based on studies in the rabbit model [35-36].

It is important to perform whole body imaging in children [34]. In a child, hyperemia may be absent, even when there is a clear abnormality on delayed images [35]. False negative exams are unusual, but they may occur in the transition period from decreased to increased tracer localization. Thus in children, even if the bone scan is normal, if there is sufficient clinical suspicion, a repeat exam should be performed in 2 to 3 days, or a gallium exam may be performed. As the condition evolves into the subacute phase, hyperemia rather than ischemia becomes the dominant finding [35].

^{111}In-labeled WBC's has a higher sensitivity and specificity for the diagnosis of acute osteomyelitis than combined bone/Gallium imaging. ^{111}In WBC imaging to have a sensitivity of between 90-95% in acute osteomyelitis for all bones in the body (overall sensitivity from various studies ranges from 80 to 100% [35,36].

Nuclear medicine imaging is a crucial imaging technique for patients with low back pain, chronic regional pain syndrome (CRPS), and extremities pain. Physicians encounter low back pain frequently; prevalence ranges from 49% to 70% [37]. For the examination of lower back pain, particularly when a bone abnormality is suspected, bone scintigraphy and single photon emission computed tomography (SPECT) may be used [38].

When the anatomic location of enhanced uptake is precisely identified, different patterns of tracer activity can be seen and used to assess bones and joints. Lesions centered about the disk space and vertebral body include spondylodiskitis, metastatic disease, vertebral body fracture, and degenerative disease (disk disease, spondylosis deformans) [38].

Complex regional pain syndrome (CRPS) is a painful condition that affects the extremities and is characterized by sensory, autonomic, vasomotor, and trophic abnormalities. Three-phase bone scintigraphy (TPBS) is regarded to be superior to other modalities for aiding in the diagnosis of CRPS, and because of its high specificity, it could be used to rule out CRPS [39]. TPBS in CRPS has a sensitivity between 14% and 100% and a specificity between 50% and 100% [40]. False positive TPBS might be due to other clinical conditions mimicking similar biological processes such as post traumatic or post-operative bone affections [41].

Bone scintigraphy is highly sensitive in detecting acute fractures. 80% of bone scans will show increased activity at a site of fracture by 24 hours, and 95% by 72 hours, older (over 75 y) and debilitated patients may not show activity for several days to as much as 2 weeks [42].

An Israel study in 310 military recruits with bone scan that had a gradual onset bone pain showed that bone scan much more sensitive than plain film for diagnosing stress fractures [42]. More than 80% of stress fractures will not be evident on initial radiographs, while the sensitivity of bone scan for the diagnosis of stress fracture approaches 100% [43].

In spondylolysis, when initial radiographs are negative, bone scintigraphy may serve to initiate more specialized anatomic imaging for diagnosis. In addition to planar imaging, SPECT of the thoraco-lumbar spine is mandatory [44].

Bone scan in metabolic bone disease is most widely used to detect complication like fractures in osteoporosis and pseudofractures in osteomalacia and to evaluate Paget's disease. It can result in is diffusely increased skeletal activity, with decreased renal activity producing a "super scan" appearance [45]

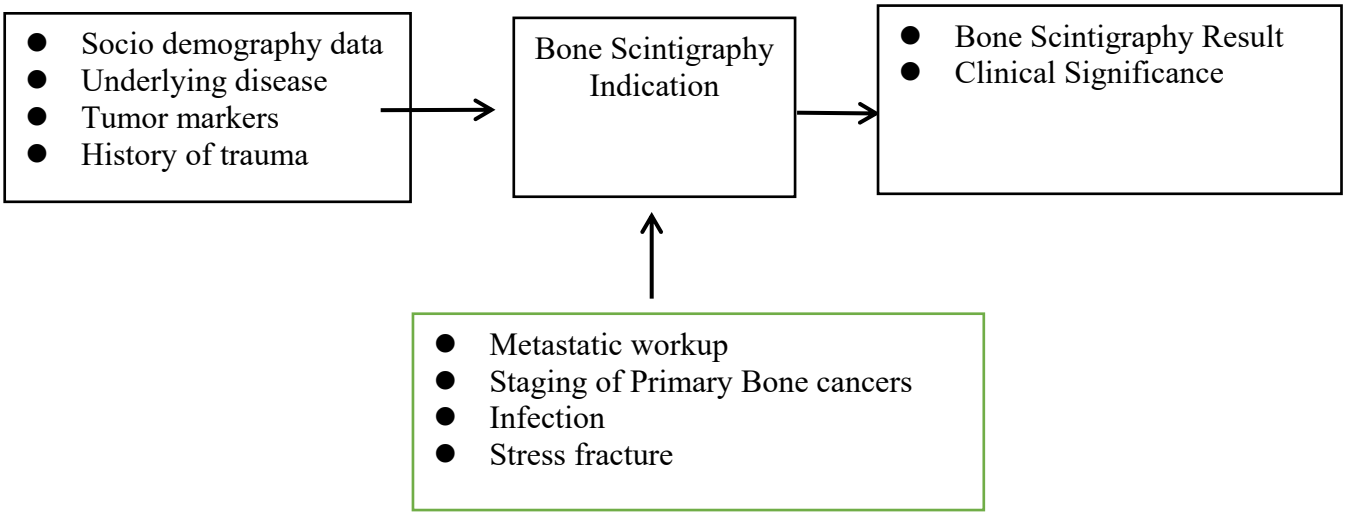
.

Study in Sudan [46], Tanzania [47] and Nigeria [48] corroborate with the studies done in other countries in that, they suggested bone scintigraphy in patients with prostatic cancer for those with preoperative PSA>20ng/ml and/or bony symptoms provided the Gleason score is <7 [46-48].

A South African study [49] illustrated the value of bone scintigraphy in localizing and monitoring benign bone tumors.

In Ethiopia, no literature on the subject could be found.

2.1. Conceptual framework



3. Objectives

3.1 General objective

- To assess the indication and clinical significance of bone scintigraphy among patients referred to Nuclear Medicine Unit, Tikur Anbessa Specialized Hospital

3.2. Specific objectives

- To determine the indications of bone scan among patients referred to Tikur Anbessa Hospital.
- To evaluate the clinical significance of the bone scan results
- To evaluate the prevalence of the bone pathologies among patients with bone scintigraphy in TASH during the study period.

4. Methodology

4.1. Study area and study period

4.1.1. Study area

The study was conducted at Tikur Anbessa Specialized Hospital (TASH), located in Addis Ababa, Ethiopia. It is one of the oldest and largest referral hospital in the country. It gives specialized care for some clinical specialties rendered unavailable in other hospitals.

4.1.2. Study period

The study period was from November 10, 2022- Feburary10, 2023.

4.2. Study design

Hospital based retrospective cross-sectional study was conducted to assess bone scintigraphy indications and clinical significance among patients referred for bone scintigraphy at Tikur Anbessa Specialized Hospital.

4.3. Source population

Bone scintigraphy scans at Tikur Anbessa Specialized Hospital's Nuclear Medicine unit served as the study's source population.

4.4. Study population

Bone scintigraphy scans at TASH done between 2007-2012 that fulfill the inclusion criteria.

4.5. Eligibility Criteria

4.5.1. Inclusion Criteria

Patients who took part in bone scintigraphy procedure and whose data is complete was included.

4.5.2. Exclusion Criteria

Data which is incomplete/ missing was excluded from the study.

4.6. Sampling Technique and size determination

4.6.1. Sample size determination

The representative sample size was calculated using the single population proportion formula for the cross sectional study design, taking into account incomplete records of 10%, a margin of sampling error acceptable of 5%, and a proportion of bone scintigraphy of 50%.

$$n=\frac{(z\alpha/2)^2 p(1-p)}{d^2} = \frac{(1.96)^2 0.5(1-0.5)}{(0.05)^2} = 384$$

Where p=50%

q =1 –p

d = margin of sampling error tolerated (0.05)

n = the required sample size.

Total population of the study is 160; the minimum sample size (n') was obtained by:

n'=n/ (1+n/N), Where;

n' = Corrected (minimum) sample size

n= determined sample size = 384

N=total number of Bone scan performed from from 2007 to 2012 = 160.

n'=n/ (1+n/N)= 384/(1+384/160)= 113+10% incomplete record,

Final n = 113+11.3 = 124

4.6.2. Sampling technique

Convenience non-random sampling technique was used. After applying the exclusion criteria, the cleaned data was finally 110.

4.7. Data collection and screening techniques

4.7.1. Data collection instrument

Data collecting questionnaire containing a socio-demographic part, clinical indication and results. The source of data was patient's hospital record.

4.7.2. Data collection method

All medical records of those who underwent bone scintigraphy examination was retrieved. All the necessary data from the chart was extracted using semi structured questionnaires.

4.7.3. Data collector

Data was retrieved by principal investigator.

4.8. Study variables

4.8.1. Dependent variable

- Clinical indication
- Clinical significance
- Bone Scintigraphy result

4.8.2. Independent variables

- Age
- Sex
- Tumor Markers
- Underlying disease
- Medications

4.9. Operational Definition

Gleason score used to help evaluate the prognosis of men with prostate cancer using samples from prostate biopsy.

Flare Phenomenon- as bone-scan findings that show disease progression after treatment despite indications of a good therapeutic response in terms of clinical symptoms or decreased tumor size on computed tomography (CT) scans.

Lower Back Pain-It is usually defined as pain, muscle tension, or stiffness localized below the costal margin and above the inferior gluteal folds, with or without leg pain (sciatica).

Metastatic- spread of cancer from the site of origin to other part of the body

Malignant- cell that grows uncontrollably and can spread locally and distant

Osteomyelitis - infection in the bone.

Pedicle - The pedicles help encase the spinal cord and act as a bridge between the vertebral body and the rest of the vertebra

Spondylolysis- a condition caused by a defect in the pars interarticularis of a vertebra, causing back pain

4.10. Data Processing and Analysis

After the confirmation of the completeness of the data, the data was cleaned, coded and analyzed using SPSS version 22.0 and the findings was summarized using descriptive statistics inferential statistics. .

4.11. Data Quality Assurance

Completeness of the data was reviewed by the principal investigator, incomplete data's were discarded. When problems arose at any time during the data collection or the analysis part, it was discussed with the advisors and come to a solution. To control the quality of data, it was edited and cleaned before entry and analysis.

4.12. Ethical considerations

Ethical clearance was obtained from the Department of Internal Medicine to conduct the study. After acquiring the clearance letter, patient's health records was coded and kept confidential. The data collected was and will not be disclosed for reasons other than the specified objectives.

4.13. Dissemination plan

The results of this study will be submitted to Nuclear Medicine unit, department of Internal medicine, college of health science, Addis Ababa University. Publication of the study findings will be considered on the reputable peer-reviewed national, regional and international journals.

5. Result

The data included in this study came from a total of 110 patients.76 women and 34 men (69.1% and 30.9%, respectively) were among the total (Table 1).

The mean and standard deviation of age of patients with bone scintigraphy record were 51.29 ± 14.13, with range of age between 11 and 86 years.

Table 1. Sex ratio of bone scntigraphy at TASH, nuclear medicine unit , 2007-2012

		Frequency	Percent	Cumulative Percent
	Female	76	69.1	69.1
	Male	34	30.9	100.0
	Total	110	100.0	

Table 2- Age frequency table bone scintigraphy at TASH , nuclear medicine unit , 2007-2012

Age	Frequency	Percent %	Valid Percent	Cumulative Percent
11-30	8	7.3	7.3	7.3
31-39	15	13.6	13.6	20.9
40-49	25	22.7	22.7	43.6
50-59	32	29.1	29.1	72.7
60-69	17	15.5	15.5	88.2
>70	13	11.8	11.8	100.0
Total	110	100.0	100.0	

5.1. Procedure

The patients in our study underwent scintigraphy using either planar or SPECT imaging, with ^{99m}Tc-MDP being the preferred radiopharmaceutical. In the examination of patients with acute osteomyelitis 3-phase bone scans was performed and a whole body scan for known and suspected oncologic patients.

5.2. Indications

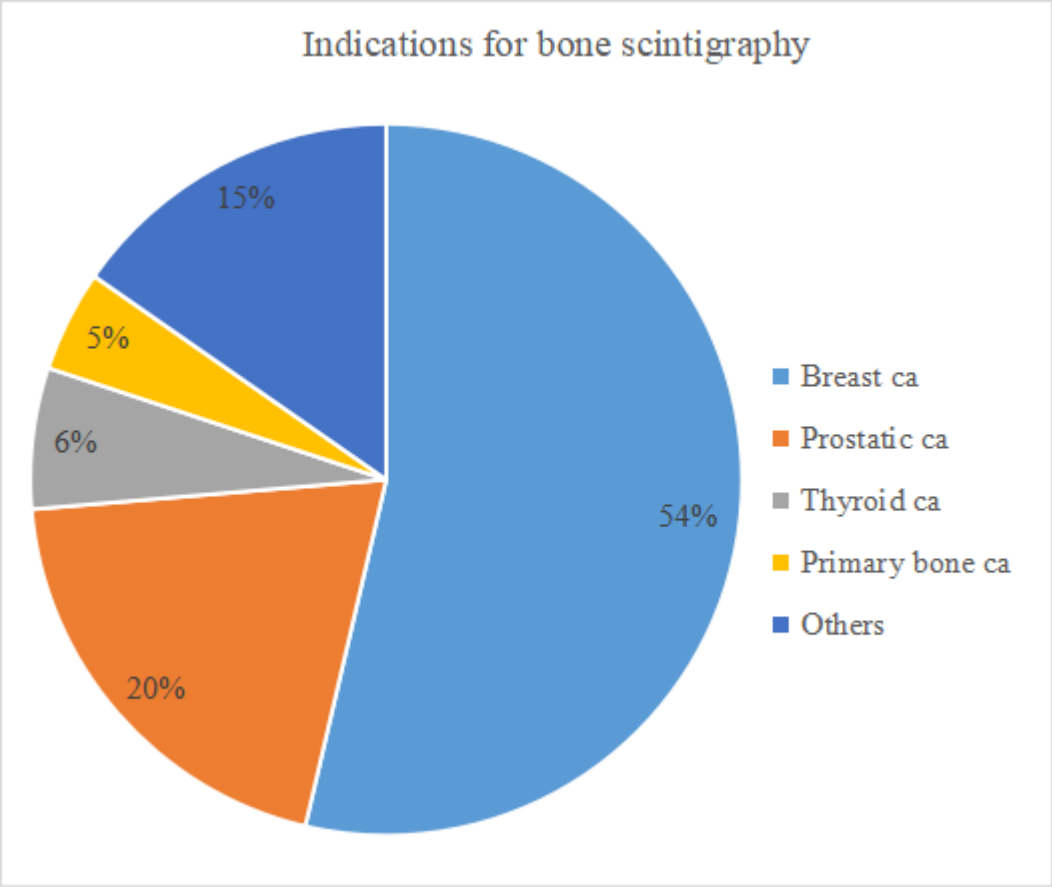
According to the data gathered, the majority of indications were oncologic cases 94.5%, followed by cases involving osteomyelitis and 3 cases involving back pain evaluation and one case of stress fracture (Table 3).

Table 3. Indication frequency of bone scintigraphy in TASH , nuclear medicine unit, 2007-2012

Indication of bone scintigraphy	Frequency	Percent %	Cumulative Percent
Prostatic cancer	22	20.0	20.0
Breast cancer	59	53.6	73.6
Multiple myeloma	4	3.6	77.3
Thyroid cancer	7	6.4	83.6
Osteomyelitis	2	1.8	85.5
Primary bone tumor	5	4.6	90.0
Lung cancer	1	0.9	90.9
Cervical cancer	3	2.7	93.6
Evaluation of back pain	3	2.7	96.4
Ovarian cancer	1	0.9	97.3
Colonic cancer	2	1.8	99.1
Stress fracture	1	0.9	100.0
Total	110	100.0	

The most common indications was in the evaluating of metastatic disease in breast cancer 59 (53.6%), followed by prostate cancer 22 (20%) , thyroid cancer 7 (6.4%) and primary bone tumor at 5 (4.5%,) respectively (figure 2).

Figure 2- Indications of bone scintigraphy in TASH, nuclear medicine unit, 2007-2012



Breast cancer patients data, 57 (96.6%) were females and 2 (3.4%) males. The mean and the standard deviation of age record were 48±11.8 years, with range of age between 24 and 76 years (Table 4). Outcome of the scan resulted in 32 (54%) positive and 27 (45.7%) negative cases.

Second most common indication is metastatic work up of prostatic cancer, has a mean and standard deviation of age of 63.7± 10.23years, with range of age between 43-78 yrs (Table 4). The scans had 19 (86.4%) positive outcomes and 3 (13.6%) negative outcomes. Most cases were above 60 years of age.

Table 4. Age characteristics of bone scintigraphy of patients with breast and prostate cancer at TASH, nuclear medicine unit, 2007-2012

	Age category	N	Percent%
Breast cancer	24 - 30	4	6.8
	31 - 39	12	20.3
	40 - 49	15	25.4
	50 - 59	19	32.2
	> 60	9	15.3
	Total	59	100
Prostate cancer	40-49	3	13.6
	50-59	4	18
	60-69	7	32
	>70	8	36.4
	Total	22	100

Thyroid cancer third most common indication 7 (6.4%) with female to male ratio of 2.5:1 with median age of 53 and range of age between 38-81years. It had 4 positive yields and 3 negative.

Three of the five reported cases of primary bone tumors were known osteosarcoma patients between the ages of 11 and 26; the other two cases were referred to help with the diagnostic workup of patients who were believed to have primary bone tumors (Table 5).

Table 5. Results of Primary bone tumors in TASH, nuclear medicine unit,2007-2012 *mets,metastasis

Cases	Age	Sex	Result
Osteosarcoma	11	M	Mets* to Proximal humerus
	22	F	Rt hip pathologic uptake
	26	F	Normal bone scan
R/o Osteiod osteoma	48	F	Normal bone scan
R/o Primary bone tumor	40	M	Parietal bone expansile lesion, vertebrae mets

62.7% of the 110 bone scintigraphy scans yielded positive results, whereas 37.3% had negative results (Table 6). With each case's sex ratio listed in (Table 7).

Table 6. Outcome of bone scintigraphy scans seen in TASH, nuclear medicine unit, 2007-2012

	Results		
	Frequency	Percent	Cumulative Percent
Positive	69	62.7	62.7
Negative	41	37.3	100.0
Total	110	100.0	

Table 7. Sex ratio of each bone scintigraphy indication in TASH, nuclear medicine unit, 2007-2012

	Male	Female
Breast cancer	2	57
Multiple myeloma	2	2
Thyroid cancer	2	5
Osteomyelitis	1	1
Primary bone tumor	2	3
Lung cancer	1	0
Evaluation of back pain	1	2
Colonic cancer	1	1
Stress fracture	0	1
Total	12	72

Most often occurring locations for metastatic spread in analysis of oncologic patients included vertebrae, ribs, and pelvic bone (Table 8).

Table 8. Frequency of metastatic sites in % of bone scintigraphy indications at TASH, nuclear medicine unit, 2007-2012

	Rib%	Vertebr	Pelvic	Clavicle	Sternum	Femur
Breast cancer	32.2	49.1	15.2	5	15.3	13.6
Prostatic cancer	50	77.3	27.3	13.6	4.5	36.4
Thyroid cancer	14.2	57.1	14.2	----	28.6	28.6
Multiple myeloma	25	75	25	25	25	25
Cervical cancer	33	33	33	33	---	33
Lung cancer	100	---	100	--	100	--
Colonic cancer	100	100	100	--	--	100

The non-oncologic indications 6 (4.45%) included assessment of acute osteomyelitis, stress fracture, and lower back pain. The bone scintigraphy performed have 50% positive yield in the acute osteomyelitis diagnosis. Scintigraphy for back pain evaluation resulted in normal bone scans and a positive scan for the diagnosis of stress fracture.

Bone scintigraphy scans that were included in this study were only initial scans. Follow up scans to assess therapeutic response were very few in number and incomplete to be included in this study.

The Binary logistic regression analysis of our data demonstrated that females and those aged between 40-49 years had a significant association with positive outcome of the scans. The likelihood of a positive scan was four times higher in females than in males (Table 9). When compared to the oldest age group, those between the ages of 40 and 49 had an 11-fold higher likelihood of having positive scans P=0.031, OR= 11 (Table 10).

Table 9. Binary logistic regression analysis of Sex and outcome

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
sex(1)	1.382	.505	7.482	1	.006	3.984	1.480	10.725
Constant	-1.540	.450	11.725	1	.001	.214		

Table 10. Binary logistic regression analysis of Age and outcome

	B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
							Lower	Upper
age			4.747	5	.447			
11-30	1.974	1.271	2.411	1	.121	7.200	.596	87.020
31-39	2.079	1.167	3.177	1	.075	8.000	.813	78.733
40-49	2.405	1.115	4.651	1	.031	11.077	1.245	98.548
50-59	1.974	1.103	3.203	1	.074	7.200	.829	62.550
60-69	2.128	1.152	3.415	1	.065	8.400	.879	80.265
>70	-2.485	1.041	5.700	1	.017	.083		

There was no correlation between the age and outcome in breast and prostatic cancer.

6. Discussion

In this study, we used 110 patients bone scintigraphy data for analysis. The mean and standard deviation of age of patients were 51.29 ± 14.13, with range of age between 11 and 86 years. Females made up 76 (69.1%) of the 110 bone scintigraphy scans, with a female to male ratio of 2.24:1.

Oncologic cases were the most common indications 104 (94.5%), metastatic work up of breast cancer ranked first 59 (53.6%). In metastatic workup of breast cancer, 27 (45.8%) were within the age range of 31-49 years, with female predominance of 57 (96.6%). Given that breast cancer is the most common malignancy among women in the nation [8] with 33% of cancer in women and 23% of all cancers identified from Addis Ababa cancer registery [50], this result is not unexpected. The 45.7% negative result could be due to early stage of the disease, failure to detect osteolytc process by bone scintigraphy or it could be a true negative.

The second most frequent indication is prostate cancer, which has the highest age standardized death in Ethiopia [9,10]. 22 (20%) cases recorded with a mean and standard deviation of age of 63.7± 10.23years. The positive yield is 86.3% for this study. In a systematic review of yield of bone scintigraphy in treatment naive prostate cancer [51], it uses serum PSA level and Gleason score to analyze outcome [23,24]. The variables are absent from our study, and a future investigation into the relationship between blood PSA level, Gleason score and bone scan yield is required. Additionally, it will aid in avoiding pointless imaging when staging low risk prostate tumors.

Thyroid cancer metastatic work up is the third most frequent indication, 7 (6.4%). In our result mean age is 58yr with female to male ratio of 2.5:1. The study in TASH showed that thyroid cancer had a predilection to occur in a younger age with a mean age of 37, female to male ratio of 1.7:1 [52]. The difference from our result could be due to the small number of patients with thyroid cancer in our sample.

Osseous metastasis occurs in 4% of all thyroid cancer patients. Most commonly seen in Follicular and Medullary thyroid cancer. It is poorly studied but associated with high mortality. Thyroid cancer osseous metastasis are predominantly osteolytic so bone scintigraphy is relatively less sensitive. ^{131}I WBS are helpful among radioiodine avid thyroid tumors [53].

This variation in frequency or percentage of indication may be brought on by variations in the accessibility and availability of the scintigraphy modality, as well as in the expertise of the referring physician.

In addition to the most frequent indication for bone scans, less common oncologic indications were observed in cases of cervical, ovarian, and colon cancer.

Two cases of colonic cancers were recorded (1.8%) of all the cases. Both patients had metastasis to the ribs, vertebrae and femur, only one had metastasis to the pelvis. Bone metastasis in patients with colorectal cancer (CRC) is very rare, and data are extremely lacking. The prognosis of patients with bone metastasis from colorectal cancer is very poor [54].

3 patients (2.7%) with cervical cancer were found in this review. With rib, vertebral, pelvic, and femoral metastases in two of the patients. The small number of cases seen despite being the second most prevalent and second most lethal cancer in Ethiopia [55], can be due to the fact that bone metastasis in cervical cancer is rare. The result is in line with studies done in India [56] and South Africa [57]. Despite the rarity of bone metastasis, bone scan should be the study of choice in symptomatic patients at any stage of the disease [57, 58].

Only one case of ovarian cancer indication was recorded in this study. Ovarian cancer is third commonest cancer in women according to Addis Ababa city cancer registry and seven most common in the world. The frequency of the cases seen is consistent with the rarity of malignancy related bone metastases, hence the bone scan indication. Vertebrae, pelvic bones, and the skull were the most often affected areas. The osteolytic lesions were the most prevalent radiologically [59, 60] and herald poor

prognosis. The negative scintigraphic outcome in our study can be true negative or as result of osteolytic predominance in the ovarian cancer.

Acute osteomyelitis, stress fractures, and the examination of back pain were the non-oncologic indications observed.

Bone scans sometimes show multiple abnormal uptake areas, but both benign and malignant lesions coexist, and it is not possible to clearly distinguish between benign and malignant specific lesions. Multiple uptakes were seen in the joint space areas.

7. Limitations and Strength of the study

7.1. Strength of the study

This research can serve as a baseline study because it is the first of its kind in the nation. The sample size is relatively adequate. It is inclusive of various indications.

7.2. Limitation

This study was limited by its retrospective, non-randomized design, as well as selection bias and performance at a single institute. Most of the data were incomplete limiting our analytic potential.

8. Conclusion and Recommendation

8.1. Conclusion

Oncologic work up was the most frequent reason for bone scintigraphy in TASH over the specified study period. Breast cancer metastatic workup is the most common indication followed by prostatic cancer. Positive results were four times more likely to be seen in female patients than males. In comparison to the oldest age group (>70yrs), people between 40 to 49 had an 11-fold higher likelihood of having positive scans. Bone scintigraphy is not routinely used in colonic, cervical and ovarian cancers. The result data demonstrates the applicability beyond the obvious indications and the necessity for more research.

8.2. Recommendation

Bone scintigraphy is recommended in evaluation of malignancies like breast cancer and prostate cancer The clinical circumstances and specific cases should be taken into consideration while choosing bone scintigraphy for different tumors.

There are some missing data points. Relevant patient information needs to be accurately recorded and placed. Prospective investigations in the future are strongly advised.

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Annexes

Semi-structured data collecting format

1. Patients card number

2. Age (years)

3. Sex

A. Male B. Female

4. Type of Procedure

A. Spot View bone Scintigraphy C. Whole body bone scintigraphy

B. Three phase scintigraphy D. SPECT

5. Radiopharmaceutical used

A. ^{99m}Tc MDP C. ^{99m}Tc DPD

B. ^{99m}Tc HDP D. Others

6. Indication

A. Oncologic primary staging C. Bone Pain evaluation

B. Osteomyelitis D. Fracture

E. Others

7. Most common metastatic cancer indicated

A. Prostatic ca. B. Lung E. Other

B. Breast ca. D. Thyroid cancer

8. Common primary Bone tumor indicated

A. Osteosarcoma C. Chondrosarcoma

B. Ewing Sarcoma D, Primary non-Hodgkin Lymphoma of the bone

9. Underlying Disease

10. Initial clinical stage

11. Tumor marker

12. Medication

13. Results of Bone scan

DECLARATION

I, the undersigned, declare that this thesis is my original work, has not been presented for a degree in Addis Ababa University or any other universities. I also declare that all sources of materials for the thesis have been duly acknowledged.

Name of the candidate: Dr. Solome Yemaneberhan Tadesse

Signature: _____

Place: Addis Ababa University, Addis Ababa, Ethiopia

Date of Submission: _____

The thesis has been submitted for examination with my approval as University Advisors.

	Name	Signature	Date
1.	_____	_____	_____
2.	_____	_____	_____

ADDIS ABABA UNIVERSITY COLLEGE OF HEALTH SCIENCES
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Department Review Board

ANNEX3

IRB's Decision

Meeting No: 45/22
Protocol number: 45/22

Meeting Date: 01/12/2022

Protocol Title: **"Assessment of indications and Clinical significance of Bone Scinitigraphy among patients referred to the Nuclear Medicine Unit, Tikur Anbessa Specialized Hospital, Addis Ababa, Ethiopia"**		
Principal Investigator:	**Dr. Solome Yemaneberhan Tadesse**	
Institute:	College of Health Sciences, AAU Department of Internal Medicine	
Elements Reviewed		√ Attached ☐ Not attached
Review of Revised Application ☐ Yes ☐ No		Date of Previous review:
Decision of the meeting:	√ Approved ☐ Approved with Recommendation ☐ Resubmission ☐ Disapproved	

I. Elements approved
1. Protocol Version No: 2
2. Protocol Version Date:
3. Informed consent Version No. 2
4. Informed Consent Version Date:

II. Obligations of the PI
1. Should comply with the standard international & national scientific and ethical guidelines
2. All amendments and changes made in protocol and consent form needs IRB approval
3. The PI should report SAE within 10 days of the event
4. End of the study, including manuscripts and thesis works should be reported to the IRB
5. The PI should report non-compliance and unanticipated events

III. To NERC ☐

Institution Review Board (IRB) Approval: Period from: Decemeber 1, 2022 – December 31, 2022

Follow up report expected in Not applicable

3 Months √ 4 Months ____ 1 Year ____ 10 years ____

Chairperson, IRB
Dr. Addisu Melkie

Signature ____
Date: 01/12/2022

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Department of Internal Medicine
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