COLLEGE OF HEALTH SCIENCE, DEPARTMENT OF ORTHOPEDICS AND TRAUMA SURGERY

Profile of Metastatic Bone Disease among Oncologic Patients at Tikur Anbessa Specialized Hospital from July 2022 – June 2024

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A thesis to be submitted to the department of Orthopedics and Trauma surgery, College of Health Sciences, Addis Ababa University in partial fulfillment of the requirements for a specialty certificate in Orthopedics and Trauma Surgery

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ADVISOR'S APPROVAL SHEET

This is to certify that the thesis entitled **"profiles of metastatic bone disease (MBD) among oncologic patients at Tikur Anbessa specialized hospital (TASH) from July 2022 – June 2024, a retrospective study** "is submitted in partial fulfillment of the requirements for the Specialization Certificate in Orthopedic surgery to the department of orthopedic surgery, Addis Ababa University college of health science and has been carried out by Ayenew Mulualem under my supervision. Therefore, I recommend that the student has fulfilled the requirements and hence hereby can submit the Thesis to the Department.

Ermias Gizaw (MD,orthopedic tumor surgeon) ___

Name of Major Advisor **Signature** **Date**

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Abbreviation/Acronyms

- TASH-Tikur Anbessa Specialized Hospital
- SRE-Skeletal related events
- MBD-Metastatic bone disease
- GI-gastrointestinal

- QOL-Quality of life
- ECOG-Eastern Cooperative Oncology Group
- CT-computed tomography
- PET scan-positron emission tomography

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Abstract

Background: Most cancer deaths are not due to primary tumors rather as a result of the metastatic events. Patients with bone metastasis may experience skeletal complications, such as pathological fractures, hypercalcaemia, neurologic symptoms and uncontrolled pain requiring bone surgery and/or radiotherapy, which are collectively called skeletal-related events (SREs). These skeletal related events seriously affect patient's quality of life and contribute to the poor prognosis of patients. The purpose of this study was to assess the profiles of metastatic bone disease among patients with systemic malignancies and the determinant factors which affect patient's quality of life.

Methods: This retrospective cohort study included patients diagnosed with skeletal metastasis between July 2022 and June 2024 in Oncology and Orthopedics departments of TASH. During the 2 years period, 222 patients were diagnosed with skeletal metastasis of which only 144 patients were selected for the study based on the inclusion and exclusion criteria. Data were collected from patient's charts using structured questionnaire. Data collected included patient demographics and clinical data. The performance status of patients at the initial presentation was assessed using

ECOG grading system. Collected data were computed to SPSS statistics version 27.
Descriptive analysis was done and categorical variables were expressed in numbers and percentages, continuous variables were expressed in mean and standard deviations. P value of less than 0.05 was considered statistically significant in multivariate analysis. Ethical approval was obtained from the Addis Ababa University Orthopedics and Clinical Oncology Department ethical review board.

Results: This study analyzed data from 144 patients diagnosed with metastatic bone disease over a two-year period. These patients were selected from an initial group of 222 due to having complete medical records. The study population consisted of more women (65.28%) than men (34.72%), with a mean age of 50.8 years (± 1.1 years)**.** Breast cancer accounts nearly half of the primary cancer (49.3 %), followed by prostate cancer (18.1%), lung cancer (12.5%), GI cancer (6.94%) and thyroid cancer (6.25%). Most of the skeletal metastasis were osteolytic and predominantly involves the vertebrae, pelvic girdle, proximal femur, shoulder girdle and proximal humerus. Majority of patients got multimodal treatment where as 38.6% of patients did not get any form of treatment to the skeletal metastasis. The presence of visceral metastasis and metastatic bone disease from prostate and GI origin significantly affects the patient's performance status.

Conclusion: In summary, metastatic bone disease could occur even in young patients and clinical suspicion is paramount important. Within this study, breast and prostate carcinomas were found to be the most frequent primary sources of metastatic bone disease. Our study findings were consistent with other similar studies but prospective study with larger sample size is recommended.

Keywords: Metastatic bone disease, skeletal related events, visceral metastasis, ECOG

1. Introduction

1.1. Background Information

Cancer is a leading cause of death in the U.S., responsible for almost 25% of fatalities, second only to cardiac disease. Most cancer deaths are not due to primary tumors but rather secondary metastatic disease. Bone is the most common site for these metastases, often occurring after spread to the lung and liver. The American Cancer Society reports roughly 400,000 new cases of malignant bone metastasis annually. Bone metastasis occurs in 30-75% of advanced malignant tumors, with especially high rates in advanced prostate and breast cancer. According to Global Cancer Observatory and International Agency of Research on Cancer, the incidence of new cancer cases in Ethiopia was estimated to be more than 80,334 per year. Breast, prostate, cervical, colorectal and thyroid cancers were the most common malignances diagnosed every year in Ethiopia. Due to the advent of advanced diagnostic tools and improved oncologic services, patients with malignancy have an increasing life expectancy but also an increased risk of metastatic bone disease. Treatment for bone metastasis focuses on alleviating symptoms and preventing skeletal-related events (SREs), while also employing specific anti-cancer therapies to reduce tumor burden in both bone and other sites. In Ethiopia, metastatic bone disease accounts for nearly 13% of patients who took palliative radiotherapy which is next only to locally advanced cervical cancer.[1-6]

1.2. Statement of the problem

Metastatic bone disease has become a major public health problem worldwide. Due to the poor health seeking behavior of our people, malignancies are usually diagnosed late in its advanced stage with visceral and bone metastasis. Individuals with bone metastasis may suffer from a range of skeletal complications, such as pathological fractures, hypercalcemia, spinal cord injury, and severe pain that necessitates bone surgery and/or radiotherapy. These complications are commonly grouped together as skeletal-related events (SREs). These skeletal related events seriously affect patient's quality of life (social, economic and psychological wellbeing) and

contribute to the poor prognosis of patients. There is only a single musculoskeletal oncology and reconstruction surgeon in the nation and only few cancer centers which give oncologic services in the country despite increased incidence of advanced malignancies with skeletal metastasis. Besides, having only four radiotherapy centers serving more than 120 million populations makes getting palliative radiotherapy treatment a luxury. It also has a great impact on the health cost of the country.

While bone metastases have a wide-ranging impact on cancer patients, there is a lack of local studies investigating the disease's profile and the determinants of patients' quality of life. This study was done to fill this scientific knowledge gap.[4, 7]

1.3. Significance of the study

This study would help health policy makers to know the burden of the disease, its impact on the patients' morbidity and devise strategies accordingly to provide improved care to patients with metastatic bone disease at the right time and the right place.

2. Literature review

In adults, bone is the preferential target site for metastases from primary cancers of prostate, breast, lung, thyroid, renal and other malignancies. Bone metastases pose a significant threat to cancer patients, substantially increasing their risk of serious skeletal-related events (SREs) like pathological fractures, pain, hypercalcemia, and spinal cord compression, which impair quality of life. These metastases also contribute to increased mortality and morbidity, with approximately 350,000 deaths per year in the United States. While breast and prostate cancers are leading contributors to bone metastases and SREs, lower rates occur with lung, kidney, thyroid, and other cancers. Among those with metastatic disease, bone metastases occur most often in patients with prostate cancer (88.74%), breast cancer (53.71%), and renal cancer (38.65%).[1]

Metastatic bone disease affects both gender groups nearly equally and breast cancer was the most common primary cancer in females, while lung and prostate cancers were most prevalent in males. Bone metastases were more frequently located in the axial skeleton than the appendicular skeleton and pain was the primary presenting symptom, with bone metastasis pain being the most common reason patients seek treatment. In metastatic bone disease, long bone fractures and spinal cord

tumor extension result in the most severe disabilities. Pathological fractures are more common in breast cancer, which often presents with osteolytic lesions, whereas they are less frequent in lung and prostate cancers due to shorter survival (lung) and primarily osteoblastic lesions (prostate).The prognosis was better for prostate and thyroid cancer, worse for lung cancer and worst for gastric cancer in terms of survival. Cancer of unknown origin accounted for 3-5% of all malignancies. The presence of visceral metastases and the primary cancer type were significant predictors of survival.[2]

Successful management of bone metastases is essential for reducing the skeletal complications and for maximizing patients' quality of life (QOL).[8] The number of skeletal metastasis and the presence of visceral metastasis significantly affect the prognosis of breast cancer patients with metastatic bone disease. Patients with solitary bone metastasis or those with bone metastases limited to the skeleton, without spread to other organs, generally have a more favorable prognosis. Bone marker levels were predictive of negative clinical outcomes in patients with bone metastases secondary to prostate cancer and non-small cell lung cancer and other solid tumors. A normalized level of N-telopeptide within three months after treatment, as compared with a persistently elevated level, was associated with reduced risks of skeletal complications, the need for palliative radiation therapy or surgery to bone and death.[9-11]

A Swiss study found that, upon initial diagnosis of bone metastases, the primary cancer origin was unclear in nearly 30% of cases. These patients, predominantly male, exhibited higher rates of spinal metastases, spinal cord compression, and pathological fractures, and also had significantly shorter survival times compared to those with a known primary cancer. Later investigation, often post-mortem, identified the primary site in two third of cases, with lung cancer being the most frequently identified (52%). These findings suggest that the presence of bone metastases with an unknown primary should strongly raise suspicion for lung carcinoma.[12]

In sub-Saharan Africa, the cancer burden is growing due to a transition from communicable to non-communicable diseases and most cancer patients present with advanced-stage disease, making curative treatment challenging or impossible. A retrospective analysis of cases admitted to the Rheumatology department of the University Teaching Hospital of Lomé, Togo, revealed that bone metastasis was diagnosed due to inflammatory bone pain, pathological fracture, or bone swelling. The patients had a 2.2:1 male-to-female ratio, with a mean age of 56.6 years (± 12.6) and an age

range spanning 21 to 82 years. Prostate cancer was the most frequent primary malignancy (57.1%), followed by breast cancer (15.6%). Pain in the spine was the most frequent complaint, affecting approximately two-thirds of patients. The lesions were primarily osteoblastic (48.1%) or osteolytic (40.3%), while mixed lesions were less common (11.6%).[13]

A retrospective study in Ethiopia showed that palliative radiotherapy was most commonly used for advanced cervical cancer (33% of cases) and bone metastases (13%). These two conditions dominated radiotherapy use in the study population, which was mainly under 65 years old and slightly more female (53%). Among bone metastasis patients, breast cancer (33%) was the most frequent primary cancer type, followed by prostate, unknown primary, and lung cancer. Pain was the most common presenting symptom, followed by pain with neurological symptoms. Another single center prospective study on pattern of bone metastasis in breast cancer patients done in Ethiopia showed vertebrae is the most involved site of skeletal metastasis in 87 % of cases followed by pelvis, ribs and sternum. More than half of those cases were lytic, followed by mixed lesion. Sclerotic breast metastasis accounts only 21% of cases. The same study found out 9% of breast cancer with skeletal metastasis occured in males.[4, 14]

3. Objectives

3.1. General objective

- To assess the profiles of metastatic bone disease among patients with systemic malignancies

3.2. Specific objective

- To assess the common primary malignant tumors which metastasize to the bone
- To assess the pattern(common site) of skeletal metastasis in patients with metastatic bone disease
- To assess the common initial presenting symptoms of patients with MBD
- To assess the determinant factors affecting the quality of life of patients with MBD
- To assess the therapeutic interventions given for patients with skeletal metastasis

4. Methodology

Study Design: Retrospective cohort study.

Source population: Oncologic patients on follow up at TASH; oncology and orthopedics departments.

Study population

Patients with skeletal metastasis referred to TASH, oncology and orthopedics departments in the study period.

Sample Size Determination

The sample siz calculation was done using single population proportion formula.

$$n = \frac{\left(Z_{\alpha/2}\right)^2 p(1-p)}{d^2}$$

n- Sample size, α- Critical value corresponding to 95% confidence interval (CI),

P-estimated prevalence rate for the population, P- value of 13% was taken from previous local research

d- Margin of error to be tolerated for which 5% is taken.

Zα/2-standard normal variable at 1-α % confidence level

$$n = \frac{(1.96)^2 (0.13)(0.87)}{(0.05)^2} = 174$$

Sampling technique

All cancer patients with the diagnosis of skeletal metastasis in the study period were included.

- ✓ Inclusion criteria- those with

a) Biopsy proven (from bone tissue sample) primary tumor that present with skeletal metastasis

b) Known cancer cases with radiologic multiple bone lesions

- ✓ Exclusion criteria
  a) Those with solid primary bone or soft tissue sarcoma
  b) Patients with hematologic malignancy (lymphoma, multiple myeloma, leukemia)
  c) Patients where the primary cancer was not found (cancer of unknown primary) and those with incomplete data

Study area

This study was conducted in Tikur Anbessa Specialized Hospital (TASH) in Addis Ababa, Ethiopia. Tikur Anbessa Specialized Hospital (TASH) is currently the main hospital giving comprehensive cancer diagnosis and treatment services in Ethiopia It serves hundreds of thousands of clients per year. Orthopedics and Trauma Surgery department in TASH is the mother department in orthopedics with 20 consultants of different sub-specialties including one musculoskeletal tumor and reconstructive surgeon and 54 orthopedics and trauma surgery residents. The clinical oncology department of the hospital has 8 consultants and 38 clinical oncology residents.

Study period

The study was conducted between July 2022 and June 2024 in Oncology and Orthopedics departments of TASH.

Data collection

Data were collected from patient's charts using structured questionnaire which was adopted from other similar studies and validated by my advisor after pilot study was done. Data was gathered on patient characteristics such as gender and age at presentation, as well as clinical information including symptoms, type of primary cancer, the location and radiographic nature of bone metastases, treatment received, performance status, and whether visceral metastases were present. Since skeletal survey using bone scan is not routinely done in the hospital, only symptomatic bone metastasis or that skeletal metastasis which were detected incidentally during routine imaging work up were selected in our cohort. The site of bone metastasis and the radiographic nature of bone lesion were collected from the x ray and CT scan reports. If patient was getting treatment for the primary malignancy and no additional treatment given for the skeletal metastasis, it was considered as a non-treatment group. The performance status of

patients at the initial presentation with metastatic bone disease was done using ECOG grading system.

Data Quality Control

Continuous evaluation and tallying of the collected data were carried out by principal investigators

Data analysis

Collected data were computed to SPSS statistics version 27. Descriptive analysis was done and categorical variables were expressed in numbers and percentages, continuous variables were expressed in mean and standard deviations. To assess the determinants factors affecting the functional status of patients, bi-variate logistic regression analysis was done for independent variables such as age, sex, pathologic fracture, neurologic deficit and visceral metastasis. Those variables with P-value of less than 0.25 in the bi-variate analysis were selected as a candidate variable for multi-variate analysis. A P value of less than 0.05 was considered statistically significant in the multivariate analysis.

Ethical considerations

Ethical approval was obtained from Addis Ababa University, College of Health Science, Orthopedics and Clinical oncology departments.

5. Results

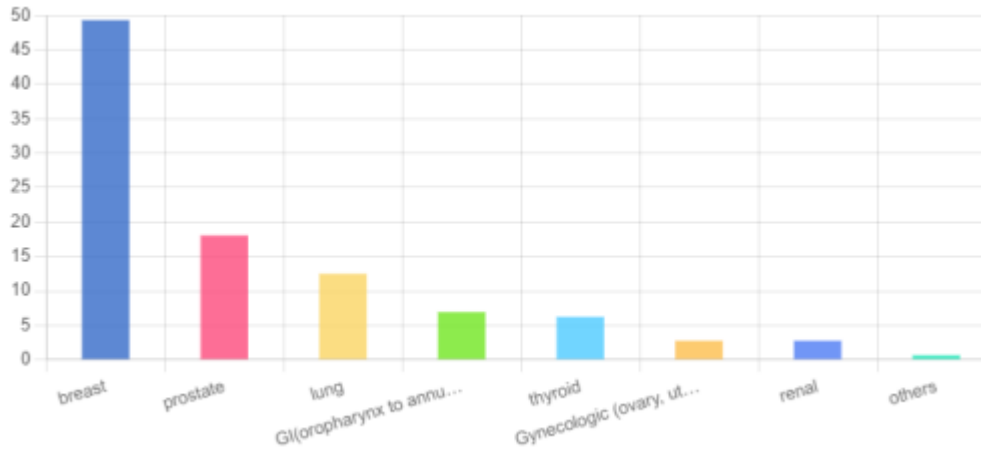
This study analyzed data from 144 patients diagnosed with metastatic bone disease at TASH between July 2022 and June 2024. These patients were selected from an initial group of 222 based on the completeness of their clinical and radiological records. The study population consisted of predominantly women (64.6%) compared to men (35.4%), with a mean age of 50.8 ± 1.1 years. While the majority of patients were between 35 and 64 years old (63.9%), the highest incidence was observed in the 35-49 age bracket (54 cases, 37.5%). The youngest patient in the study was a 26-year-old female diagnosed with metastatic breast cancer.

Table 1; Socio-demographic data of study participants

Variable		Frequency	Percentage
Gender	Male	51	35.4
	Female	93	64.6
Age(years)	20-34	21	14.6
	35-49	54	37.5
	50-64	38	26.4
	65-79	25	17.4
	80 and above	6	4.2

Breast cancer accounts nearly half of the primary cancer (49.3 %), followed by prostate cancer (18.1%), lung cancer (12.5%), gastro-intestinal cancer (6.94%), thyroid cancer (6.25%), renal and gynecologic malignancies (2.78% each). Breast cancer accounts for 74.2 % of metastatic bone disease in females whereas prostate and lung cancer accounts for 50.9% and 17.6 % of metastatic bone disease in males respectively. There was slight female predominance in thyroid cancer (56% female versus 46% male) and male predominance in gastrointestinal cancer (60% male versus 40% female) whereas the sex distribution was equal for lung and renal cancer. There were 3 male patients with metastatic breast cancer.

Figure 1; Percentages of primary origin of metastatic bone disease

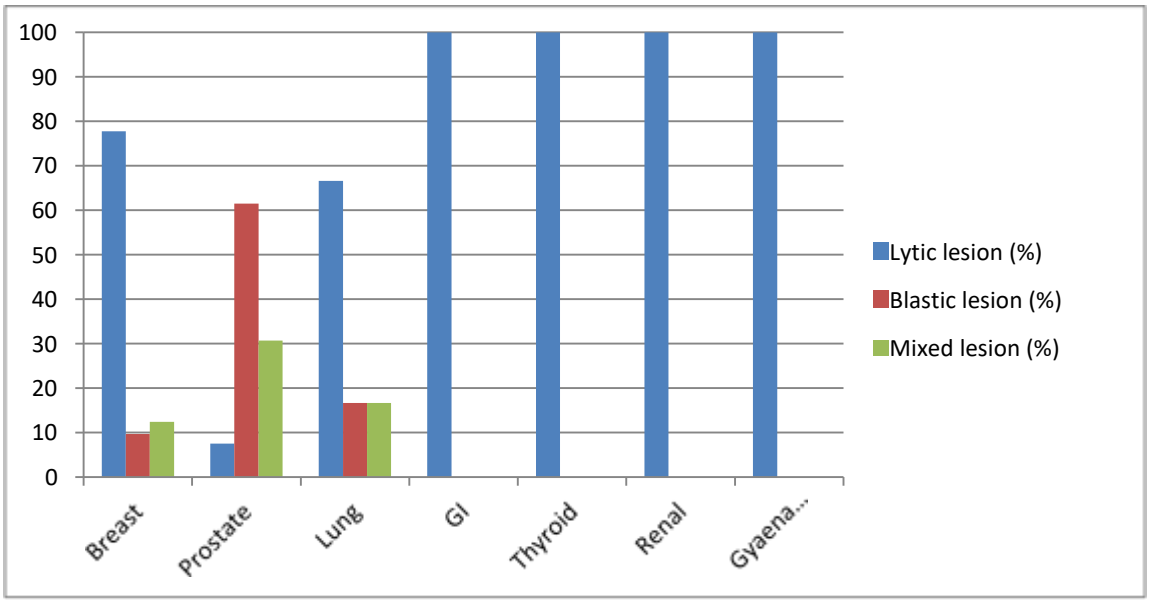


Axial skeleton was the predominant site of bone metastasis (78 cases, 54.7%). Isolated appendicular metastasis occurred in 16 cases (11.1%) and 50 cases (34.7%) had both axial and skeletal metastasis. Among the axial skeleton, thoracic spine was the most frequently involved site followed by lumbar spine, 58.3% and 40.9% respectively. The remaining axial skeleton (cervical spine, sacrum, ribs, and sternum) has almost equal incidence of metastatic involvement (18.1%, 8.1% and 14.6%). Skull was involved in only 1.4% of cases. Lower extremities were more involved than upper extremities in those patients with appendicular skeleton, 37.5% and 11.1% respectively. Shoulder girdle and proximal humerus were involved in 31.9% and 18.1% of cases. There was one case involving the distal fibula and another case involving the femur shaft.

The most common presenting symptom of patients with bone metastasis was pain without pathology fracture (41.7%). Routine imaging conducted for general oncologic workup revealed bone metastasis as an incidental finding in 25% of patients. Pathologic fracture of axial or appendicular skeleton occurred in 14.6% of cases and symptomatic spinal cord/nerve root compression occurred in 11.8% of our cohort. Small proportion of patients presented with musculoskeletal swelling or lump and spinal cord compression on imaging without neurological symptoms (4% and 2.7% respectively). Skeletal related event was the initial presenting compliant in 10.4% (n=16) of patients before the primary cancer was diagnosed. Among those 16 patient, 31.3% patients presented with pain, another 31.3 % presented with pathological fracture, 25% had neurologic symptoms and 12.5% of patients presented with lump or swelling.

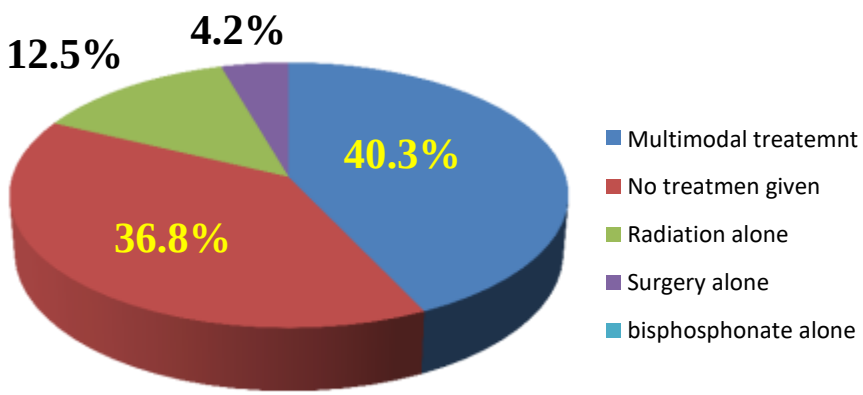
The metastatic bone lesion was lytic in 68.1%, blastic in 18.8% and mixed in 13.2% of the cases. Among patients with lytic lesion, 17.3% had pathologic fracture whereas 10 % of mixed lesions and 3.8% blastic lesions had pathological fracture respectively. Approximately 45.8% of skeletal metastasis occurred within 2 years of primary cancer diagnosis where as in 20.8% of patients, skeletal metastasis and primary cancer were diagnosed simultaneously. Skeletal metastasis occurred after 6 years of primary cancer diagnosis in 5.6% of cases. Small proportion of patients had skeletal metastasis after 3-4 years of primary cancer diagnosis (10.4%) and after 5-6 years of primary cancer diagnosis (6.3%). Skeletal metastasis was diagnosed before primary cancer diagnosis in 11.1 % of patients.

Figure 2; Primary cancer with their corresponding type of bone lesion



Of 144 patients, 40.3% of patients got multimodal treatment targeting the metastatic bone disease where as 38.6% of patients did not get any form of treatment to the skeletal metastasis other than the treatment given to the primary cancer. Surgical treatment was given to 4.9% of patients'. Among those who got surgical treatment, hip hemiarthoplasty was done for 3 patients, pathologic fracture fixation done for 3 patients and excision was done for 1 patient. Nearly one third of patients (31.3%) got at least one form of the treatment with in a month of the metastatic bone disease diagnosis. Approximately 25.7% of patients were treated with in 1-3 months of the diagnosis and 6.3% of patients were treated with in 4-6 months after skeletal metastasis was diagnosed. The remaining 6.2% of patients had to wait more than 6 months.

Figure 3; Treatments given to the skeletal metastasis



Of the 144 patients, 47 (32.6%) had other organ involvement and 97 (67.4%) patients had only skeletal involvement. Regarding the functional status of patients, 69.5% had good performance status (68.1% ECOG-1 and 1.4% ECOG-0) while 29.9 % had poor performance status (23.6% ECOG-2, 4.9% EGOG-3).

We observed that the presence of visceral metastasis significantly affects the performance status of patients at the initial diagnosis of bone metastasis (adjusted odds ratio: 2.66; 95% CI, 1.10-6.43; P=0.03). Besides, as compared to breast cancer patients, metastatic bone disease from prostate and GI origin significantly affects the patient's performance status (adjusted odds ratio: 9.87; 95% CI, 1.93-50.78; P=0.006 and adjusted odds ratio: 6.73; 95% CI, 1.30-34.83; P=0.023 respectively). Sex of the patient and the presences of pathologic fracture do not significantly affect the performance status of patients at the diagnosis of metastatic bone disease (P-value 0.275 and 0.137 respectively).

6. Discussion

From July 2022 to June 2024, 144 patients with metastatic bone disease were included in this retrospective study. The study population consisted of approximately two women for every man (64.6% female, 35.4% male), with a mean age of 50.8 years. A majority of patients (63.9%) were aged 35 to 64, with the highest incidence of metastatic bone disease in the 35-49 year age range, followed by the 50–64-year range.Wisanuyotin et al showed that of the 102 patients with upper extremity skeletal metastasis, females were more affected than males (47.1% males versus 52.9% females. The mean age at diagnosis of upper extremity skeletal metastasis was 61 years (range, 28–82 years). Among 1,849 patients with skeletal metastases from solid primary tumors in a study by Hong et al., breast cancer (18.8%), prostate cancer (17.5%), and lung cancer (13.7%) were the most frequently observed primary cancers. The median time to bone metastasis after the initial cancer diagnosis was 18.9 months, with a slightly higher incidence in men (53%) than women (47%). Oniankitan et al, a study done in Togo, found that males were more affected than females by metastatic bone disease (68.8% men, 31.2% women).[13, 15, 16] In our study population, females were predominant because of high proportion of breast cancer cases and we observed that our patients were younger.Thus, skeletal metastasis should not be overlooked even in young patients.

The propensity for cancer cells to metastasize to bone is influenced by several anatomic,genetic and biological factors of osseous tissue and the malignant cells. Coleman's study showed that close to 73% of breast cancer, 68% of prostate cancer, 42% of thyroid cancer and 35% of lung cancer metastasize to the bone in their clinical course. Wisanuyotin et al showed the most common primary cancer which underwent upper extremity skeletal metastasis was lung (31.4%) followed by liver (14.7%), breast (12.7%), thyroid (7.8%), kidney (3.9%), cholangiocarcinoma (2.9%). A study done in Togo by Oniankitan showed prostate cancer (57.1%) was the first responsible for bone metastases followed by breast cancer (15.6%). A large series involving 382,733 study participants in US by Hernandez observed the most common primary cancers were breast (36%), lung (16%), and colorectal (12%). The mean age at bone metastasis was 64 years in the same study.[13, 15, 17, 18] In our study, breast and prostate cancer were the most frequent primary cancers that metastasized to the skeleton, followed by lung, thyroid, and gastrointestinal malignancies, consistent with other similar studies. Among female patients, breast cancer was the most common primary, while prostate and lung cancers were most prevalent in male patients as the primary sources of skeletal metastases.

Axial skeleton is more frequently involved than the appendicular skeleton by metastatic disease.This is partly due to the higher amount of red bone marrow in the axial skeleton and due to the Batson venous plexus. In Singh et al's study, bone metastases were found in long bones in 43% of cases, in axial bones in 40.4% and in both locations in 16.6% of cases. A retrospective study done by Tsuya among patients with skeletal metastasis from non-small cell lung cancer showed the spine was the most common site (50%), followed by the ribs (27.1%). In the same study ileum and femur were involved 10% and 5.7% of cases while scapula and humerus were involved in 2.9% of cases. Among 102 patients with upper extremity skeletal metastases in Wisanuyotin et al.'s study, the prevalence of metastases was highest in the humerus (64.7%), followed by the clavicle (13.7%) and scapula (12.7%). Acral metastases occurred with a frequency of 7.8% of cases.[2, 15, 19, 20] In our cohort, axial skeleton was the commonest site of bone metastasis(54.7%). Isolated appendicular metastasis occurred only in small proportion of our patients (11.1%) and in 34.7% of patients both axial and appendicular metastasis was observed.
Among the axial skeleton, thoracic spine was the most frequently involved sit followed by lumbar spine, while cervical spine, sacrum, ribs and sternum had almost equal incidence of involvement by metastasis. Lower extremities were more involved than upper extremities in those patients with appendicular skeletal metastasis. Pelvic girdle and proximal femur were

the predominant sites of lower extremity metastasis while shoulder girdle and proximal humerus were the only involved upper extremities in our study population. There was one case of distal fibula metastasis from advanced lung cancer. Our research findings were in agreement with majority of other similar studies.

Patients with bone metastasis are at risk of developing skeletal complications, such as pathological fractures, hypercalcemia, spinal cord injury, and intractable pain, which may require bone surgery and/or radiotherapy. These skeletal-related events (SREs) severely compromise the quality of life for those with advanced cancer and a poor prognosis. Pain of variable severity was the commonest symptom of metastatic bone disease as shown in Singh et al. A study done by Tsuya among 70 patients with skeletal metastasis from non-small cell lung cancer showed 78.6% of patients had localized pain, 20.0% had hypercalcemia, 15.7% had spinal cord compression and 7.1% had pathologic fractures. Similar study done by Chow observed 50-75 % of patients presented with bone pain.[2, 8, 19] In our study, the most common presenting symptom (41.7%) was pain in the absence of pathologic fracture or neurologic deficient. Pathologic fracture of either the axial skeleton or appendicular skeleton was observed in 14.6% of the patients. Vertebrae and femur neck were the two most common sites of pathologic fracture whereas femur shaft pathologic fracture occurred in one patient. Neurologic deficit was seen in 11.8% of our cohort. Approximately 25% of patients were asymptomatic and skeletal metastasis was incidentally diagnosed while imaging was done for general oncologic work up. Skeletal related events (SREs) were the initial presenting compliant in 15 (10.4%) patients before the primary cancer was revealed. Among those 15 patients, one- third of patients presented with pain, another one-third presented with pathological fracture, 25% presented with neurologic symptoms and the remaining presented with lump or swelling. In conclusion, the skeletal related events among our study population were similar to most of the recent literatures, pain of varying severity being the most presenting symptom.

Metastatic bone disease can appear as osteolytic, osteoblastic, or mixed lesions on radiography or CT scans. Pathological fractures are a more common finding in patients with osteolytic lesions compared to those with mixed or sclerotic lesions. However, these fractures are less often seen in patients with lung cancer, due to their typically shorter survival, and in patients with prostate cancer, where lesions are predominantly osteoblastic. According to a study by Singh et al., osteolytic lesions were most prevalent (67.1%), with sclerotic lesions less common (24.3%), and

mixed osteolytic and osteoblastic lesions observed in 7.9% of cases. The most common lesion type in our study was osteolytic (68.1%), followed by sclerotic (18.8%) and mixed (13.2%) lesions. We observed that breast and lung cancers commonly presented with osteolytic lesions, prostate cancer with sclerotic lesions, and thyroid, renal, gastrointestinal, and gynecologic malignancies with osteolytic bone metastases, aligning with findings in other similar studies. Our results corroborate the results of prior similar research.

Studies on the timing of bone metastasis revealed varying results. A U.S. study by Hernandez et al., with 382,733 participants, found a mean time of 1.1 years from primary cancer diagnosis to bone metastasis. Conversely, a Korean study by Hong et al., involving 1,823 patients, reported a mean time of 18.9 months, and also showed that the shortest intervals from primary diagnosis to bone metastasis were observed in lung (9 months), breast (14.9 months), and prostate cancer (17.4 months) patients. Oniankitan et al. found that in 29.9% of patients, a primary cancer diagnosis was already known at the time of bone metastasis diagnosis. However, in the majority of cases (77.1%), bone metastasis was diagnosed before the primary cancer was identified. In those patients with known primary cancer at the time of bone metastasis diagnosis, the mean time between these diagnoses was 4.4 ± 3.5 years.[13, 16, 17] We found that, for 68% of patients in our study, the mean time between primary cancer diagnosis and the development of metastasis was 2.3 years. In 20.8% of our patients, skeletal metastasis and primary cancer were diagnosed concurrently. In contrast, the diagnosis of skeletal metastasis preceded the primary cancer diagnosis in 11.1% of cases.

The management of metastatic bone disease demands a multidisciplinary approach. Treatment is directed towards symptom palliation and the prevention of skeletal-related events (SREs), while concurrent anti-cancer therapies are used to reduce tumor load at both skeletal and extra-skeletal locations. Preservation of bone integrity, along with improved mobility and ambulation, are also important therapeutic aims. Treatment options encompass both local approaches, such as surgery and/or radiotherapy, and systemic treatments, including chemotherapy, endocrine therapy, radioisotopes, and agents like bisphosphonates, which inhibit bone resorption. Wisanuyotin et al.'s research on upper extremity metastatic bone disease showed that surgery was employed in 50% of cases, palliative care in 44.2%, and radiation therapy alone in 5.8%. Another study done in Germany among 1,094 patients with skeletal metastasis from breast cancer, 52% of patients were treated with palliative radiotherapy alone whereas 6% of patients were treated surgically.[6, 15, 21] In our study, multimodal treatment was given for 40.3% of patients but 38.6% of patients did

not get any forms of treatment to the skeletal metastasis other than the treatment given to the primary cancer. Surgical treatment was given to 4.9% of our patients'. The surgical procedures included hip hemiarthoplasty (3 patients), pathologic fracture fixation (3 patients) and excision (1 patient). Nearly one third of patients (31.3%) got at least one form of the treatment with in a month of the metastatic bone disease diagnosis. Approximately 25.7% of patients were treated with in 1-3 months of the diagnosis, while 6.3% of patients got treatments within 4-6 months of skeletal metastasis diagnosis. The reaming 6.2% of patients had waited more than 6 months to get any form of treatment for the bone metastasis. In conclusion, we found the surgical procedures done for metastatic bone disease was low in our study compared to other studies.

The presence of metastatic bone disease significantly impacts patients' quality of life, leading to increased pain, reduced mobility, a higher incidence of fractures, and spinal cord compression. In our study, 69.5% of patients had good performance status (ECOG-0 or 1), whereas 29.9% had poor performance status (ECOG-2,3 or 4). The presence or absence of visceral metastases to vital organs and the type of primary cancer are crucial for predicting the prognosis of patients with bone metastases. Studies consistently show that patients with extra-skeletal metastases to vital organs have worse survival outcomes compared to those without. As an example, Coleman et al., in a study of 367 breast cancer patients with bone metastasis, reported a median survival of 1.6 years for those with extra-skeletal spread compared to 2.1 years for those with bone metastasis alone. Kuru et al.'s retrospective study involving 470 patients with metastatic breast cancer demonstrated five-year survival rates of 73%, 46%, and 22% for solitary skeletal metastasis, multiple skeletal metastasis and visceral metastasis respectively. Hong et al. also found that the overall survival of patients with bone metastasis is largely determined by the prognosis of the primary cancer, with longer survival in breast and prostate cancer and shorter survival in lung cancer.[9, 16, 18] Approximately one-third of our patients (32.6%) had extra-skeletal metastasis whereas the remaining two-third of our patients (67.36%) had metastasis confined to the skeletal system. In our study, patients with visceral metastasis were 2.68 times more likely to have poor performance status at the initial diagnosis of bone metastasis (P-value=0.023). Besides, patients with skeletal metastasis from prostate and gastrointestinal origin were 9.87 times more likely to have poor performance status compared to patients with breast cancer (P-value of 0.006 and 0.023 respectively). Sex and the presences of pathologic fracture do not significantly affect the performance status of patients at the diagnosis of skeletal metastasis (P-value 0.275 and 0.137 respectively).

Several limitations must be acknowledged for this study. The retrospective design and the small sample size are primary limitations. Additionally, the use of only CT and x-ray to identify visceral and bone metastases may have resulted in an underestimation of cases, particularly in the visceral and multiple bone metastases groups. The utilization of bone scans and PET scans might have yielded a greater number of such cases.

7. Conclusion

In summary, metastatic bone disease could occur even in young patients and clinical suspicion is paramount important. In our study we found the most common primary cancers which metastasize to the bone were breast, prostate, lung, thyroid and gastrointestinal in origin. Majority of patients presented with pain of varying severity despite incidental findings were seen in a quarter of our patients. Most of the skeletal metastasis were osteolytic and predominantly involves the vertebrae, pelvic girdle, proximal femur, shoulder girdle and proximal humerus. Multimodal treatment was found to be the commonest treatment approach to patients with metastatic bone disease despite few surgical treatments given for skeletal metastasis. The presence of visceral metastasis and the type of primary tumor significantly affects the prognosis of patients.

8. Recommendations

The burden of metastatic bone disease is substantial, affecting patients' quality of life and also placing a considerable strain on their families. Thus, creating awareness, early diagnosis and appropriate treatment of cancer is pivotal. Providing early appropriate care for cancer patients with skeletal metastasis can be improved by;

- Giving health education about early diagnosis and treatment of cancer among the community
- Opening additional comprehensive cancer centers in the regional states so that waiting lists for palliative care in the referral centers can be minimized
- Providing additional radiotherapy machine so that patients can get on time palliative

radiotherapy

- Providing accessible and affordable surgical implants such as mega-prosthesis, knee and hip replacement implants, intercalated segment spacers
- Improving the number of musculoskeletal oncology and reconstruction surgeons in the country
- Establishing metastatic bone disease multidisciplinary team in the hospital to give holistic palliative care

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Annex 1: questionnaire

Research questionnaire on profiles of metastatic bone disease

Demographic data

- Sex a) male b) female
- Age a) less than 20 yrs b)20-34 yrs c)35-49 yrs
  d) 50-64 yrs e) 65-79 yrs f) above 80 yrs
- Address a)Urban b)Rural
- Religion a) Orthodox Christian b) Protestant Christian c) Catholic Christian
  d) Muslim e) others--------

Clinical data

I. What was the initial presenting skeletal related event of the patient at the first visit?
   a) Asymptomatic(incidental finding while examination or imaging done for general work up)
   b) Pain without fracture
   c) Pathologic fracture
   d) Swelling/lump
   e) Spinal cord compression on imaging without neurologic deficit
   f) Spinal cord or nerve root compression with neurologic deficit

II. Is the skeletal related event the initial presentation of the primary malignancy before the primary origin is identified?
   a) yes b) no

III. Is the primary origin of the malignancy known? A)yes b) no

IV. If yes, what is the primary origin?
   a) breast b) lung c) prostate d) thyroid e) renal f) GI(oropharynx to annus, hepatobilliary, pancreas, spleen) g)Gynecologic (ovary, uterus, cervix)
   h) others

V. Site of bone metastasis?

a) Axial skeletal metastasis b) Appendicular skeletal metastasis c) both

VI. Which part of axial skeleton is affected by the metastatic disease?

a) Skull b) Rib c) Sternum d) cervical spine
e) thoracic spine f) lumbar spine g) Sacrum

VII. Which appendicular skeleton is affected by the metastatic bone disease?

a) Upper extremities b) Lower extremities

VIII. Which upper extremity is specifically affected by the metastatic disease?

a) Shoulder girdle b) proximal humerus c) humerus shaft d) distal humerus e)proximal radius/ulna f) radius/ulna shaft g) distal radius/ulna h) acral metastasis

IX. Which lower extremity is specifically affected by the metastatic disease?

a)Pelvic girdle b) proximal femur c) femur shaft d) distal femur e) proximal tibia/fibula f) tibia/fibula shaft g) distal tibia/fibula h) acral metastasis

X. What is the radiographic nature of the lesion?

a) Lytic b) Blastic (Sclerotic) c) Mixed

XI. Time from diagnosis of primary cancer to the diagnosis of the first bone metastasis?

a) less than 12 months b) 1-2 years c) 3-4 years d) 5-6 years e) more than 6 years

f) Skeletal related event comes before primary lesion diagnosis

XII. Time from the diagnosis of bone metastasis to therapeutic intervention targeting the bone metastasis?

a) Less than a month b) 1-3 months c) 4-6 months d) 7-9 months
e) more than 9 months

XIII. What therapeutic intervention is given to the patient targeting the bone metastasis?

a) Radiotherapy b) bisphosphonate c) surgical intervention d) Chemotherapy
e) hormonal therapy f) no therapeutic intervention given

XIV. What surgical intervention is done for those who are operated for the skeletal related event?

a) Prophylactic fixation b) pathological fracture fixation c) hemiartheroplasty (hip)
d) amputation e) metastatectomy f) endoprosthesis reconstruction

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XV. Does the patient have visceral metastasis at the diagnosis of the first bone metastasis?

a) Yes b) No

XVI. What is the performance status of the patient with bone metastasis at the initial visit according to ECOG?

a) 0 b) 1 c) 2 d) 3 e) 4 f) 5