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Conventional Radiological Profile of Metastatic Bone Disease Based on Its Histopathological Results: A 3-Year Experience

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ABSTRACT

Introduction: Metastasis commonly occurs in the bone, termed metastatic bone disease (MBD). Early diagnosis and intervention are important to prolong and increase the quality of life. Although conventional radiology is less sensitive for diagnosing this disease, it remains the most cost and time-efficient screening method. This study aimed to describe the radiological profile of patients diagnosed with MBD based on its histopathological result.
Methods: This was a descriptive retrospective study using medical records and digital radiological data of patients diagnosed with MBD from 2019-2021 in Dr. Soetomo General Academic Hospital, Surabaya. Variables in this study include gender, age, histopathological result, location of metastases, number of lesions, lesion density, and pathological fracture.
Results: 51 patients were diagnosed with MBD during the period of the study and sorted into 121 cases based on metastases location. MBD is more frequent in older female patients, where lesion mostly originates from the breast, thyroid, and lungs, with adenocarcinoma as the most common histology. Vertebrae were the most common location of metastases. Most lesion tends to be multiple and osteolytic. However, certain lesions from different primary tumor had different predilections. Pathological fracture was present in 55.37% of cases.
Conclusion: MBD needs to be suspected in patients with cancer from the breast, thyroid, and lungs as its incidence is higher. More studies about MBD profiles on a larger scale should be conducted to better represent this disease in the general population.

Highlights:
1. The incidence of MBD tends to be more frequent in older ages and in female patients.
2. The radiological appearance of a lesion tends to differ depending on its primary tumor.
3. Pathological fracture was present in 55.37% of the cases.

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Introduction

Metastatic bone disease (MBD) happens when a cancerous tumor metastasizes to the bone. The bone is the third most common place where metastases occur after the lung and liver.[1] The presence of these diseases signifies poor prognosis and survival rate. Early diagnosis and treatment of MBD aim to promote quality of life, prevent complications and slow cancer progression, and prolong the patient's life expectancy. Several complications and morbidity of this disease include bone pain, pathological fracture, vertebral nerve compression, and hypercalcaemic syndrome.[2]

Epidemiological data in America shows that during 2010-2015, around 5.1% of cancer patients had MBD with lung, prostate, and breast, respectively, as the most common primary cancer.[3] In general, it is estimated that around 400,000 new cases of MBD are diagnosed in America annually.[4] Meanwhile, epidemiological data about the prevalence of MBD in Indonesia are still lacking. Although this disease might originate from almost any cancerous tumor, certain cancer has a predilection to metastasize to the bone. Around 90% of patients with prostate cancer and 60-70% of patients with breast cancer also experience MBD.[5] Other common sources of metastases include the lung, thyroid, and kidney. Based on its histological appearance, the incidence of adenocarcinoma metastasizing to the bone is also a common finding.[6]

The proposed basic mechanism of MBD is based on Paget's seed and soil hypothesis, which states that metastasis is caused by interactions between cancer cells and the target organ's cell. As the theory progresses, it is found that the process of metastasis is staged into intravasation, extravasation, cancer latency, and development of micro and macro-metastasis in which the premetastatic niche of the target organ plays an important role.[7]

In general, MBD is classified according to its lesion density into osteolytic, osteoblastic, and mixed type, each with its own mechanism of metastases. The osteolytic lesion is formed through receptor activator of nuclear factor kappa-B ligand (RANK/RANKL) vicious cycle, along with cytokines such as interleukin-6 (IL-6), IL-8, and parathyroid hormone-related protein (PTHrP) which upregulates osteoclast activity.[8] Osteoclast hyperactivity causes destruction of the bone, hence giving a hypodense appearance on radiology results. This activity also causes hypercalcaemia and pathological fracture. The osteoblastic lesion is formed through the overproduction of endothelin-1 (ET-1), insulin growth factors-1 (IGF-1), WNTs, tumor growth factor-beta (TGF-beta), urokinase-type plasminogen activator (uPA), fibroblast growth factors (FGFs), and bone morphogenic proteins (BMPs) which promotes osteoblast production and activity.[9] Osteoblast hyperactivity causes excessive formation of the bone, showing hyperdense appearance on radiology results. A mixed lesion happens when there is both osteolytic and osteoblastic activity, showing both hypodense and hyperdense lesion on the bone.[8,9]

Conventional radiology is commonly used to assess fracture risk and as a preliminary screening of patients with bone pain. The main advantages of conventional radiology compared to other modalities, such as computed tomography (CT)-scan and magnetic resonance imaging (MRI) in cases of MBD, lies in its cost and time effectiveness, making it the best screening method. However, in patients with asymptomatic bone metastasis, lesion only appears in conventional radiology when around 50-70% of bone structure is destroyed, in which other additional radiological modalities are needed in order to help confirm the diagnosis of MBD.[10] This study aimed to describe the radiological profile of patients with MBD based on its histopathological result.

Methods

This was a retrospective descriptive study using medical records and digital radiological data (conventional radiology/X-ray). Variables included in this study were age, gender, primary cancer, number of lesions, lesion density, lesion morphology, and presence of a pathological fracture. Each variable obtained from radiological results or medical records was sorted based on its histopathological result (primary cancer and histology) and then compared with each other. The radiological and histopathological results of the patients were reviewed once more by specialists in their respective fields in order to be more accurate. This study had received ethical clearance approval from the Ethics Committee of the Faculty of Medicine, Universitas Airlangga, and Dr. Soetomo General Academic Hospital, Surabaya.

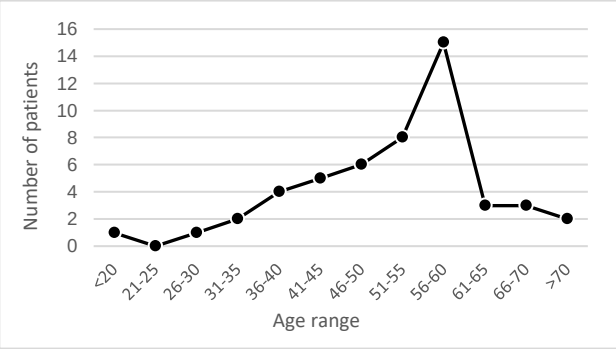
Samples were obtained using a total sampling method according to its inclusion criteria in which the patient had never performed any operation or internal implant fixation procedure or at least the patient had pre-operation radiology results documented during 2019-2021. Biopsy or post-operation histopathological tests were also performed to fulfil these sampling criteria. Medical records and digital radiological results of the sample were obtained from the Department of Radiology, the Department of Orthopaedics and Traumatology, and the Department of Anatomical Pathology. Data analysis using Excel was performed on the sample, as shown in this study.

Results

There were 51 patients fulfilling inclusion criteria during this study period, of which 17 were males (33.33%), and 34 were females (66.67%). The youngest patient found in this study was 5 years old (nephroblastoma/Wilms tumor), and the oldest was 72 years old (unknown origin primary cancer). The incidence of MBD tends to rise with age and peaks at 56-60 years old (29.41%) (Figure 1). The most common origin of metastasis was breast (21.57%), thyroid (21.57%), and lungs (15.69%). There were also cases of MBD from other origins such as prostate (7.84%), nasopharynx (3.92%), gastrointestinal tract (GIT) (3.92%), liver (1.96%), cervix (1.96%), skin (1.96%), kidney (1.96%), pancreas (1.96%), and adrenal (1.96%). Extensive

radiology, biochemical, and histologic examination had been performed on all patients, but in 7 patients (13.73%), the primary cancer was not found, termed as an unknown origin.

Figure 1. Age distribution of patients with MBD in Dr. Soetomo General Academic Hospital, Surabaya



Source: Research data, processed

In Table 1, it can be seen that in female patients, breast (32.35%) was the most common source of metastasis, followed by thyroid (26.47%) and lungs (17.65%). There were also cases of metastases from skin (2.94%), kidney (2.94%), cervix (2.94%), and metastasis of unknown origin (14.71). Meanwhile, in male patients, prostate (23.52%) was the most common source of metastasis. There were also cases of metastasis from thyroid (11.76%), lung (11.76%), nasopharynx (11.76%), GIT (11.76%), liver (5.88%), pancreas (5.88%), adrenal (5.88%), and metastasis of unknown origin (11.76%).

Table 1. Distribution of MBD patients' gender based on the primary cancer in Dr. Soetomo General Academic Hospital, Surabaya

Primary Cancer	Male	Primary Cancer	Female
Prostate	4	Breast	11
Thyroid	2	Thyroid	9
Lungs	2	Lungs	6
Others	7	Others	3
Unknown	2	Unknown	5
Total	17	**Total**	34

Source: Research data, processed

As shown in Table 2, the histopathological test was performed in these patients and adenocarcinoma (52.94%) showed up as the most common histology result, followed by thyroid carcinoma (19.61%) and squamous cell carcinoma (5.88%). MBD from breast cancer showed adenocarcinoma (ductal and non-ductal) in 9 out of 11 histology results (81.81%), thyroid cancer showed thyroid carcinoma (follicular and papillary) in 10 out of 11 histology results (90.91%), lung cancer showed adenocarcinoma in 6 out of 8 histology results (75.00%), and prostate cancer showed adenocarcinoma in 4 out of 4 histology results (100%). Neuroendocrine tumor (NET) was found in 12.50% of lung cancer and 100% of pancreatic cancer, while squamous cell carcinoma (SCC) was found in 100% of nasopharynx cancer and 100% of cervical cancer. Four results were showing non-specific histological appearance from breast (18.18%), thyroid (9.09%), and lung cancer (12.50%), hence termed poorly differentiated carcinoma. Other histology results include hepatocellular carcinoma (HCC) (1.96%), melanoma (1.96%), nephroblastoma (1.96%), and sarcoma (3.92%).

Table 2. Histology results of patients diagnosed with MBD in Dr. Soetomo General Academic Hospital, Surabaya

Histology	N	Percentage
Adenocarcinoma	27	52.94%
Thyroid carcinoma	10	19.61%
NET	2	3.92%
SCC	3	5.88%
Poorly differentiated carcinoma	4	7.84%
Others	5	9.80%
Total	51	100%

Source: Research data, processed

A total of 121 locations of metastasis on the bone were found in 51 patients (Table 3). Note that a single patient might have more than one location of metastasis in the bone. The most metastasis found in a single patient in this study was in 9 different locations. Vertebra (21.49%) was the most common place of metastasis, especially the thoracolumbar segment, followed by femur (19.01%), and iliac (14.88%). Breast cancer tends to metastasize in the femur (22.58%), thyroid cancer to the humerus (29.41%), lung cancer to the femur (31.25%) and prostate cancer to the iliac bone (23.53%). Meanwhile, based on its histology, adenocarcinoma tends to metastasize to the femur (25.00%), thyroid carcinoma to the humerus (25.00%), neuroendocrine tumor to the femur (25.00%), and squamous cell carcinoma to the tibia (37.50%). Other locations of metastasis found in this study include calvaria (2.48%), clavicula (1.65%), scapula (0.83%), sternum (0.83%), costae (1.65%), ischium (4.96%), acetabulum (2.48%), fibula (2.48%), talus (1.65%), tarsal (0.83%), and calcaneus (0.83%).

Table 3. Common metastasis location of patients diagnosed with MBD in Dr. Soetomo General Academic Hospital, Surabaya

Location	N	Percentage
Vertebra	26	21.49%
Femur	23	19.01%
Iliac	18	14.88%
Humerus	12	9.92%
Pubic	11	9.09%
Tibia	8	6.61%
Others	37	30.58%
Total	121	100%

Source: Research data, processed

Lesions from each location on conventional radiology were sorted based on primary cancer (Table 4) and histology results (Table 5). In general, 66.12% of lesion in the bone tends to be multiple, and 33.88% were single.

Table 4. Radiological profile (number of lesions, density of lesion, pathological fracture) of MBD based on its primary cancer in Dr. Soetomo General Academic Hospital, Surabaya

Primary Cancer	Number of Lesions		Density of Lesion		Pathological Fracture
Breast (n = 31)	Single Multiple	8 (25.81%) 23 (74.19%)	Osteolytic Osteoblastic Mixed	14 (45.16%) 1 (3.23%) 16 (51.61%)	19 (61.29%)
Thyroid (n = 17)	Single Multiple	11 (64.71%) 6 (35.29%)	Osteolytic Osteoblastic Mixed	17 (100%) 0 (0%) 0 (0%)	13 (76.47%)
Lung (n = 16)	Single Multiple	7 (43.75%) 9 (56.25%)	Osteolytic Osteoblastic Mixed	11 (68.75%) 0 (0%) 5 (31.25%)	7 (43.75%)
Prostate (n = 17)	Single Multiple	5 (29.41%) 12 (70.59%)	Osteolytic Osteoblastic Mixed	4 (23.53%) 10 (58.82%) 3 (17.65%)	8 (22.22%)
Unknown origin (n = 11)	Single Multiple	8 (72.73%) 3 (27.27%)	Osteolytic Osteoblastic Mixed	5 (45.45%) 5 (45.45%) 1 (9.09%)	5 (45.45%)
Others (n = 29)	Single Multiple	2 (6.90%) 27 (93.10%)	Osteolytic Osteoblastic Mixed	13 (44.83%) 0 (0%) 16 (55.17%)	15 (51.72%)

Source: Research data, processed

Table 5. Radiological profile (number of Lesions, density of lesion, pathological fracture) of MBD based on its histology in Dr. Soetomo General Academic Hospital, Surabaya

Histology	Number of Lesions		Density of Lesion		Pathological Fracture
Adenocarcinoma (n = 64)	Single Multiple	24 (37.50%) 40 (62.50%)	Osteolytic Osteoblastic Mixed	28 (43.75%) 16 (25.00%) 20 (31.25%)	38 (59.38%)
Thyroid carcinoma (n = 16)	Single Multiple	10 (62.50%) 6 (37.50%)	Osteolytic Osteoblastic Mixed	16 (100%) 0 (0%) 0 (0%)	11 (68.75%)
NET (n = 16)	Single Multiple	2 (12.50%) 14 (87.50%)	Osteolytic Osteoblastic Mixed	2 (12.50%) 0 (0%) 14 (87.50%)	2 (12.50%)
SCC (n = 8)	Single Multiple	0 (0%) 8 (100%)	Osteolytic Osteoblastic Mixed	3 (37.50%) 0 (0%) 5 (62.50%)	8 (100%)
Poorly differentiated carcinoma (n = 6)	Single Multiple	3 (50.00%) 3 (50.00%)	Osteolytic Osteoblastic Mixed	6 (100%) 0 (0%) 0 (0%)	3 (50.00%)
Others (n = 11)	Single Multiple	2 (18.18%) 9 (81.82%)	Osteolytic Osteoblastic Mixed	9 (81.82%) 0 (0%) 2 (18.18%)	6 (54.55%)

Source: Research data, processed

Osteolytic (52.89%) was the most common lesion density, followed by mixed (33.88%) and osteoblastic (13.22%). There was a presence of pathological fracture in 55.37% of all cases. Based on its primary cancer, lesion from breast cancer tends to appear on conventional radiology as multiple (74.19%) and mixed (51.61%), thyroid cancer tends to be single (64.71%) and osteolytic (100%), lung cancer tends to be multiple (56.25%) and osteolytic (68.75%), while prostate tends to be multiple (70.59%) and osteoblastic (58.82%). Based on its histology result, adenocarcinoma tends to be multiple (62.50%) and osteolytic (43.75%), thyroid carcinoma tends to be single (62.50%) and osteolytic (100%), NET tends to be multiple (87.50%) and mixed (87.50%), SCC tends to be multiple (100%) and mixed (62.50%). Based on its primary cancer, thyroid cancer had the highest incidence of pathological fracture (76.47%), while prostate had the lowest incidence (22.22%). Based on its histology, thyroid carcinoma had the highest incidence of pathological fracture (68.75%), while NET had the lowest incidence (12.50%).

Discussion

This study showed that MBD was more frequent in females than males (66.67% or 2.00 times). This result was in line with the theory that oestrogen facilitates metastasis to the bone by creating a favorable microenvironment for cancer cells. Studies have shown that estrogen plays an important role in MBD, in which women with estrogen receptor-alpha (ER+) has an incidence of MBD from breast cancer three times more frequent than women with ER-. In prostate cancer, a decrease in the androgen and estrogen ratio is associated with increased chances of MBD.[11]

This study found that MBD tends to rise with age and peaks at 56-60 years old. Another study with 11 years period of study also showed similar results in which cases of MBD rise with age and peak at 61-65 years old.[12] There

might be a slight difference in the age distribution of patients with MBD due to epidemiological differences between study places. Still, the results share the similarity that MBD tends to increase along with age. Increased incidence of MBD is proportionately similar to the incidence of cancer in general due to genome instability, telomere attrition, altered proteostasis, mitochondrial dysfunction, cellular senescence, and stem cell exhaustion, hence increasing genetic errors and mutation and subsequently increasing chances of cancer and metastasis.[13] However, there were some cases where MBD occurs in childhood and in this study, the youngest MBD patient was 5 years old with primary cancer from the kidney (Wilms tumor).

Breast (21.57%), thyroid (21.57%), and lung (15.69%) were the most common source of MBD in this study. Another study showed that breast (18.8%), prostate (17.5%), and lung (13.7%) were the most common source of metastasis.[14] Different studies show a slight difference in the distribution of primary cancer. In general, lung, prostate, thyroid, breast, and kidney represent up to 80% origin of cancer in cases of MBD.[15] Adenocarcinoma was the most common histology result in this study. Other studies also showed that adenocarcinoma is the most common histology in cases of MBD.[15,16] Patients with lung adenocarcinoma tend to show a higher risk of developing MBD than other histology results.[17,18] It is also hypothesized that exosome miR-214 which is highly expressed in lung adenocarcinoma promotes osteoclast differentiation, playing an important role in a vicious cycle of MBD formation.[19] Similarly, another study showed that in prostate adenocarcinoma, bone was the most common location of metastasis (55.33%).[20]

Metastasis in this study tends to occur in the vertebra (especially the thoracolumbar region), femur, and iliac bone. A two-decade period of study on this disease also shows that the vertebra (52.1%), especially the thoracolumbar, femur (17.8%), and pelvis (9.5%) were the most common places of metastasis.[21] Another study showed that spine, pelvis, ribs, skull, and proximal femur were the most common location of metastasis in the bone.[22] This pattern of metastasis to the bone is proportionate to the content of red bone marrow of the bone. Therefore, vertebra, pelvis, and ribs tend to have higher chances of experiencing metastasis.[23] In this study, mixed density tends to occur in lesions originating from breast cancer, osteolytic density in cancer from the thyroid and lung, while osteoblastic density occurs in prostate cancer. This finding was similar to the pathogenesis of MBD which resulted in osteoblastic lesion tendency in prostate cancer, osteolytic tendency in lung and thyroid cancer, while mixed tendency occurs in breast cancer.[24]

In cases of prostate cancer, PTHrP which is highly expressed stimulates primarily osteolytic activity and some osteoblastic activity, induces neovascularization, and promotes tumor growth.[25] RANK/RANKL/OPG system also plays an important role in prostate cancer, in which prostate-specific antigen (PSA) from prostate cancer cells stimulates osteoprotegerin (OPG) overexpression, enhancing osteoblastic activity compared to RANKL expression which enhances osteolytic activity.[26] BMPs which are normally produced by bone cells and promote osteoblastic activity are also released by prostate cancer cells along with WNT, playing a role in the progression of this disease.[27] In fact, WNT and RAS signaling are one of the most crucial factors in the growth of osteoblastic bone metastasis. Other growth factors such as IGF, TGF-beta, epidermal growth factor (EGF), (CXCL12), and annexin A2 (ANXA2) also contribute to a cascade which causes proliferation and activation of osteoblast.[28]

In osteolytic lesions, RANK/RANKL ligands are overexpressed by cancer cells compared to OPG.[29] Breast cancer is also found to release PTHrP which specifically promotes osteolytic lesion formation.[30] Inflammatory mediators and growth factors such as IL-6, IL-6, tumor necrosis factor-alpha (TNF-alpha), and macrophage colony-stimulating factor (M-CSF) further promotes osteolytic activity and enhance RANK/RANKL ligand formation.[31] Meanwhile, in a mixed lesion, both osteoblastic and osteolytic activation cascade is stimulated, causing a mixed lesion appearance.[32] Pathological fracture in this study was found in 55.37% of all cases. Meanwhile, in another study, pathological fracture was found in only 4.4% of cases of MBD.[33] There were significant differences between the incidence of pathological fracture in this study compared to others. Because Dr. Soetomo General Academic Hospital, Surabaya, is a referral hospital, patients who visit this hospital have a bad clinical appearance and prognosis. The presence of pathological fracture signifies later stages of the disease, increasing the mortality rate of this disease.[34]

Strength and Limitations

The strength of this study was that it describes the radiologic appearance of a metastatic lesion in the bone and sorted it based on its primary cancer and histological result which can help doctors make faster diagnoses of primary cancer in patients with suspected MBD. The limitation of this study was that documentation of radiological data in Dr. Soetomo General Academic Hospital, Surabaya, was still conventional. Some patient results could not be retrieved, limiting the study period since older data were gone. Therefore, more extensive studies should be conducted in order to learn more about this disease.

Conclusion

Primary cancer from breast, thyroid, or lungs in female patients and prostate in male patients had the highest incidence of MBD. Osteolytic density appeared in thyroid and lung cancer, osteoblastic density in prostate cancer, and mixed density in breast cancer. Adenocarcinoma was the most common histology in most cases. Through this study, clinicians are expected to understand and help educate patients that certain cancers such as breast and prostate cancer tend to metastasize to the bone. It is also expected that clinicians are able to predict primary tumor based on the radiological appearance in cases of accidental bone metastasis finding.

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Conflict of Interest
The authors declared there is no conflict of interest.

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Ethical Clearance
This study had received ethical clearance from the Ethical Committee for Health Research Dr. Soetomo General Academic Hospital, Surabaya, (No. 0702/LOE/301.4.2/XI/2021) on 29 November 2021.

Authors' Contributions
Designed the study and drafted the manuscript: BA, RS. Collected data and performed background literature review: BA. Performed statistical analysis: BA. Supervised results and discussion: BA, RS, ME, SM. All authors reviewed and approved the final version of the manuscript.

References
1. Zajączkowska R, Kocot-Kępska M, Leppert W, *et al*. Bone Pain in Cancer Patients: Mechanisms and Current Treatment. *International Journal of Molecular Sciences*; 20. Epub ahead of print 2019. [PubMed]
2. Wood SL, Brown JE. Personal Medicine and Bone Metastases: Biomarkers, Micro-RNAs and Bone Metastases. *Cancers (Basel)*; 12. Epub ahead of print July 2020. [PubMed]
3. Ryan C, Stoltzfus KC, Horn S, *et al*. Epidemiology of Bone Metastases. *Bone* 2022; 158: 115783. [ScienceDirect]
4. Jiang W, Rixiati Y, Zhao B, *et al*. Incidence, Prevalence, and Outcomes of Systemic Malignancy with Bone Metastases. *J Orthop Surg (Hong Kong)* 2020; 28: 2309499020915989. [PubMed]
5. Burr DB, Allen MR. *Basic and Applied Bone Biology*. Elsevier Science, https://books.google.co.id/books?id=JfEqugEACAAJ (2019).
6. Riihimäki M, Thomsen H, Sundquist K, *et al*. Clinical Landscape of Cancer Metastases. *Cancer Med* 2018; 7: 5534–5542. [PubMed]
7. Akhtar M, Haider A, Rashid S, *et al*. Paget's 'Seed and Soil' Theory of Cancer Metastasis: An Idea Whose Time has Come. *Adv Anat Pathol* 2019; 26: 69–74. [PubMed]
8. Wu X, Li F, Dang L, *et al*. RANKL/RANK System-Based Mechanism for Breast Cancer Bone Metastasis and Related Therapeutic Strategies. *Front Cell Dev Biol* 2020; 8: 76. [PubMed]
9. Quiroz-Munoz M, Izadmehr S, Arumugam D, *et al*. Mechanisms of Osteoblastic Bone Metastasis in Prostate Cancer: Role of Prostatic Acid Phosphatase. *J Endocr Soc* 2019; 3: 655–664. [PubMed]
10. Downie S, Bryden E, Perks F, *et al*. Diagnosis and Referral of Adults with Suspected Bony Metastases. *BMJ* 2021; 372: n98. [PubMed]
11. Oprea-Lager DE, Cysouw MCF, Boellaard R, *et al*. Bone Metastases are Measurable: The Role of Whole-Body MRI and Positron Emission Tomography. *Front Oncol* 2021; 11: 772530. [PubMed]
12. Janevska V. Demographic and Morphologic Characteristics of Bone Metastases -11 Years Single Center Experience. 2021; 4: 65–76. [Journal]
13. Terracina S, Ferraguti G, Petrella C, *et al*. Characteristic Hallmarks of Aging and the Impact on Carcinogenesis. *Curr Cancer Drug Targets* 2023; 23: 87–102. [PubMed]
14. Hong S, Youk T, Lee SJ, *et al*. Bone Metastasis and Skeletal-Related Events in Patients with Solid Cancer: A Korean Nationwide Health Insurance Database Study. *PLoS One* 2020; 15: e0234927. [PubMed]
15. Schmid-Alliana A, Schmid-Antomarchi H, Al-Sahlanee R, *et al*. Understanding the Progression of Bone Metastases to Identify Novel Therapeutic Targets. *Int J Mol Sci*; 19. Epub ahead of print January 2018. [PubMed]
16. Baliyan A, Punia RS, Kundu R, *et al*. Histopathological Spectrum of Bone Changes in Skeletal Metastasis. *Indian J Med Paediatr Oncol* 2019; 40: 476–480. [Journal]
17. da Silva GT, Bergmann A, Thuler LCS. Incidence and Risk Factors for Bone Metastasis in Non-Small Cell Lung Cancer. *Asian Pac J Cancer Prev* 2019; 20: 45–51. [PubMed]
18. Song Q, Shang J, Zhang C, *et al*. Impact of the Homogeneous and Heterogeneous Risk Factors on the Incidence and Survival Outcome of Bone Metastasis in NSCLC Patients. *J Cancer Res Clin Oncol* 2019; 145: 737–746. [PubMed]
19. Zhang J, Wu J. The Potential Roles of Exosomal miR-214 in Bone Metastasis of Lung Adenocarcinoma. *Front Oncol* 2020; 10: 611054. [PubMed]
20. Deng Y, Bi R, Zhu Z, *et al*. A Surveillance, Epidemiology and End Results Database Analysis of the Prognostic Value of Organ-Specific Metastases in Patients with Advanced Prostatic Adenocarcinoma. *Oncol Lett* 2019; 18: 1057–1070. [PubMed]
21. Hui M, Balu B, Uppin SG, *et al*. Bone Metastases: A Compilation of 365 Histologically Verified Cases Spanning over Two Decades from a Single Center. *Indian J Pathol Microbiol* 2021; 64: 717–724. [PubMed]
22. Høilund-Carlsen PF, Hess S, Werner TJ, *et al*. Cancer Metastasizes to the Bone Marrow and Not to the Bone: Time for a Paradigm Shift! *European Journal of Nuclear Medicine and Molecular Imaging* 2018; 45: 893–897. [PubMed]
23. Onken JS, Fekonja LS, Wehowsky R, *et al*. Metastatic Dissemination Patterns of Different Primary Tumors to the Spine and Other Bones. *Clin Exp Metastasis* 2019; 36: 493–498. [PubMed]
24. Shen F, Huang J, Yang K, *et al*. A Comprehensive Review of Interventional Clinical Trials in Patients with Bone Metastases. *Onco Targets Ther* 2023; 16: 485–495. [PubMed]
25. Edwards CM, Johnson RW. From Good to Bad: The Opposing Effects of PTHrP on Tumor Growth, Dormancy, and Metastasis Throughout Cancer Progression. *Front Oncol* 2021; 11: 644303. [PubMed]
26. Wong SK, Mohamad N-V, Giaze TR, *et al*. Prostate Cancer and Bone Metastases: The Underlying Mechanisms. *Int J Mol Sci*; 20. Epub ahead of print May 2019. [PubMed]

27. Tyson J, Bundy K, Roach C, *et al*. Mechanisms of the Osteogenic Switch of Smooth Muscle Cells in Vascular Calcification: WNT Signaling, BMPs, Mechanotransduction, and EndMT. *Bioeng (Basel, Switzerland)*; 7. Epub ahead of print August 2020. [PubMed]
28. Lin S-R, Mokgautsi N, Liu Y-N. Ras and Wnt Interaction Contribute in Prostate Cancer Bone Metastasis. *Molecules*; 25. Epub ahead of print May 2020. [PubMed]
29. Wang M, Xia F, Wei Y, *et al*. Molecular Mechanisms and Clinical Management of Cancer Bone Metastasis. *Bone Res* 2020; 8: 30. [Journal]
30. Zhang R, Li J, Assaker G, *et al*. Parathyroid Hormone-Related Protein (PTHrP): An Emerging Target in Cancer Progression and Metastasis. *Adv Exp Med Biol* 2019; 1164: 161–178. [PubMed]
31. Rossi M, Battafarano G, D'Agostini M, *et al*. The Role of Extracellular Vesicles in Bone Metastasis. *Int J Mol Sci*; 19. Epub ahead of print April 2018. [PubMed]
32. Hiraga T. Bone Metastasis: Interaction between Cancer Cells and Bone Microenvironment. *J Oral Biosci* 2019; 61: 95–98. [PubMed]
33. Jairam V, Lee V, Yu JB, *et al*. Nationwide Patterns of Pathologic Fractures among Patients Hospitalized with Bone Metastases. *Am J Clin Oncol* 2020; 43: 720–726. [PubMed]
34. Garry P, Edward M, Setiawati R, *et al*. Clinical Features in Metastatic Bone Disease with and without Pathological Fractures: A Comparative Study. *Heal Notions*; 3. Epub ahead of print 25 October 2019. [Journal]