Metastatic Bone Disease: Evaluation by Functional Imaging in Correlation with Morphologic Modalities

A. H. Elgazzar ¹,² and N. Kazem ²

¹Department of Nuclear Medicine, Faculty of Medicine, Kuwait University and ²Mubarak Al-Kabeer hospital, Ministry of Health, Kuwait.

Abstract

The diagnosis of presence, location and load of metastatic, bone involvement has important implication on patient management and prognosis. This requires collection of data obtained using different imaging modalities. Bone scintigraphy is a highly sensitive and cost-effective screening modality. However, to overcome its lower specificity and its limitation in evaluation of vertebral metastases, CT, PET or MRI can be utilized to verify the nature of suspicious lesions. Expansion of SPECT/CT may fine tune the highly sensitive bone scintigraphy. PET has an emerging and leading role in many tumors, occasionally obviating the need for bone scintigraphy, particularly in evaluation of response to therapy. PET and whole body MRI offers a potentially important tool to provide the earliest clue of bone marrow metastasis. The value of F-18 PET as a sensitive bone imaging tool needs to be further evaluated on a larger scale in different setting including treated and untreated cancer patients and to evaluate also whether potentially better resolution would lead to more benign lesions detection mimicking metastasis such as fractures, inflammatory, infection, and degenerative involvement of bone. The added value of PET-CT is also to be further examined with this regard.

Key words

Bone, metastases, radionuclide, imaging, tumor

Introduction

The most common malignant bone tumors are metastatic bone malignancies. Primary tumors arising from prostate, breast, thyroid, lung and kidney account for 80% of skeletal metastasis (¹). The disease may result in impaired mobility and reduced quality of life and have a significant negative impact on survival. Detecting this disease is crucial since it determines the stage of the primary tumor and consequently affects the modes of management. This review discusses the role of correlative imaging including structural and functional in the diagnosis and management of metastatic bone tumors leading to presenting the current recommendations for effective utilization of the available imaging tools.

Pathophysiology

Apart from cases where direct extension occurs from a primary tumor to adjacent bone, bone metastasis involves spread of the disease from a tissue to distant bone. Following detachment from the primary site, malignant cells should gain access to a suitable transfer media (blood vessel, lymphatic channel) and maintain viability until they lodge in the medullary cavity and successfully establish sufficient blood supply. The most common route of spread is hematogenous. In this regard, the vertebral venous plexus play a fundamental role, where these valve less veins extensively communicate with multiple other venous systems, and accordingly lead to wide spread of malignant cells in the vicinity. The combination of large capillary network and sluggish blood flow provides an optimal environment for growth of the disease. Eighty percent of bone metastasis involves the red marrow rich axial skeleton (²).
Bone response to metastasis

The bone reacts to metastases in two ways, bone resorption and bone formation. Bone resorption involves osteoclast activity, tumor cells and metabolites as well as tumor-associated macrophages and monocytes. Bone formation, occurs mainly as a reactive response to bone destruction and in this case osteoblasts lay immature woven bone that subsequently is converted to lamellar bone. Multiple myeloma and cancers of the lung, thyroid, kidney, and breast characteristically commonly give rise to osteolytic lesions. The tumor cells from these primaries cause increased bone breakdown or resorption, with little reparative bone formation and thus appear commonly as punched-out lesions on radiographs. On the other hand, prostate cancer is a common tumor to form sclerotic skeletal metastases.

Diagnosis of Metastatic bone disease

Clinically, bone metastases lead to different presentations. The most frequent symptom is pain, although it is not uncommon to be asymptomatic. Patients may present with other local effects of bone metastasis (pathological fracture, or nerve/cord compression), metabolic sequels (hypercalcemia, tumor lysis syndrome, or osteomalacia), or even as an incidental abnormal radiological or laboratory findings in an asymptomatic patient.

The evaluation for presence, type, extent, progression and prognosis of bone metastasis requires several imaging modalities. During staging the primary disease, a battery of investigations is carried out to evaluate the primary tumor and nodal and distant metastases. Imaging also helps follow up providing assessment of the response to therapy, detection of recurrence and prognostic information. In general, four main modalities are routinely utilized clinically to assess bone, the third most common site of metastatic diseases, for existence of metastatic lesions. These modalities include standard radiography, CT scan, bone scintigraphy and MRI. PET has been recently added and is increasingly evaluated for detection of bone metastases. The information obtained from these different techniques can be correlatively merged to maximize the diagnostic utility and overcome the limitations of each imaging modality.

Imaging modalities for metastatic bone disease

Standard plain radiographs

Plain radiographs are valuable for evaluation of a specific site of pain. When tumors are seen they could be lytic, sclerotic or both (Figure 1). Delineation of a focal lytic lesion on a standard plain radiograph requires 30 to 50% demineralization, while a minimum of 30% increased mineral content is required for detection of a sclerotic lesion. Therefore, this imaging modality is not sensitive enough. Moreover, lesions in anatomically complex regions as well as negative and uncertain X-ray findings require
further imaging investigations. However standard radiograph is the initial modality of choice as the case with any suspected bone pathology.

**Bone scintigraphy**

Bone scan is the most widely used modality and is the most practical and cost effective screening technique for assessing the entire skeleton. In addition, bone scan is very sensitive in detecting the disease. A very minimal change in bone turn over (5-15%) is sufficient to cause abnormal accumulation in the bone seeking Tc-99m biphosphonate. In an animal model, bone metastasis was evident on bone scintigraphy 1 week after inoculation. A positive bone scintigraphy precedes positive X-ray finding by up to several months [2].

The typical pattern of bone metastases on bone scintigraphy is that of widely disseminated, randomly distributed foci of avid radiotracer retention, usually in the axial skeleton following the distribution of bone marrow including the shoulder girdle with relatively less extensive involvement of the ribs (Figure 2). Metastases to the peripheral bones of the extremities are rare. The interplay between osteoclastic and osteoblastic activity in response to bone injury induced by bone metastasis forms initially a disorganized bone that is particularly a preferential site of bone seeking radiopharmaceutical uptake.

Although very suggestive of bone metastasis, the pattern is not pathognomonic for it, as multifocal skeletal infections (such as TB, brucellosis), multiple insufficiency fractures in metabolic bone disease, or hypertrophic osteoarthropathy may yield a similar pattern [2]. Careful attention to medical history and history of trauma, orthopedic surgery or underlying systemic disease is helpful in exclusion of these mimickers.

To further complicate the issue, there are many atypical forms of bone metastases on bone scintigraphy. Cold lesions on bone scan are seen in aggressive tumors, commonly, multiple myeloma and renal cell carcinoma. Such cold lesions occasionally are difficult to be visualized and are better detected using a high count statistics, high intensity images and a computer screen to review the images. A cold lesion in the sternum constitutes a special problem since normal variant of a photopenic area in the lower sternum is not uncommon. Differentiation from malignancy appears to be related to lesion symmetry, location, midline, and evenly distributed radioactivity surrounding the edge of the photopenic area [6]. Malignant lesions typically occur at the sternal lateral edges and may be surrounded by nonuniform activity. Metastatic lesions may show relatively normal appearance reflecting a point of equilibrium between osteoblastic activity and bone destruction by the tumor. It appears that skeletal lesions may evolve through increased uptake, equilibrium phase and then decreased uptake. In another atypical pattern, the entire axial skeleton may be involved by a load of tumor cells of advanced metastatic disease, causing increased extraction of radiopharmaceutical. This pattern may be interpreted as normal depending on the display intensity. The pattern should also be differentiated from other benign metabolic causes of diffusely increased uptake in the skeleton, or super scan, such as in hyperparathyroidism, and other metabolic bone diseases which also show abnormal uptake extending to the skull, mandible and variable length of long bones in addition to axial skeleton while super scan secondary to metastases shows increased uptake that is usually confined to the axial skeleton. Finally, metastases may unusually

---

**Fig. 2:** Anterior and posterior whole body bone scintigraphy images illustrate the typical pattern of wide spread bone metastases in a 65 years old prostate cancer patient.
present as symmetrical lesions. Certain tumors, particularly neuroblastoma in children, are known to produce this pattern. Symmetrical lesions have also been reported in other tumors such as lung cancer.

Bone scan is highly sensitive to detect metastases. A prerequisite is proper hydration of the patient, proper acquisition with obtaining proper views including obliques of the ribs, caudal view for the pelvis and optional projections to resolve certain difficulties, proper understanding of the scintigraphic patterns and pitfalls. Specificity, however, is low particularly with the atypical patterns. The addition of single photon emission computed tomography (SPECT) technique to bone scintigraphy in difficult cases improves the specificity of the test and provides three dimensional representation of the skeleton, better contrast and better visibility of deeply located lesions. Sedonja et al \(^7\) performed planar scintigraphy and SPECT on 38 patients with lower back pain with confirmed malignant disease and on 37 patients without known malignant lesions. Overall, significantly more metastatic lesions were detected with SPECT (58 of 64 lesions by SPECT; 42 of 64 lesions for planar; \(p < 0.01\)). They also measured lesion-to-background ratios for malignant lesions of the spine and found a significantly higher ratio with SPECT (2.26) than with planar bone scintigraphy (1.86).

Recently, imaging utilizing combined SPECT and CT led to further refinement of imaging and precise anatomical localization of functional lesions evident on bone scintigraphy \(^8\). This technique is particularly attractive as it combines the advantages of the two systems: high resolution images of CT and high sensitivity images of bone turnover in bone scintigraphy. SPECT/CT can be obtained by either of two techniques: software fusion of SPECT and CT data from two different scanners, or more recently an integrated SPECT/CT scanner where usually low dose CT is used for attenuation correction as well for SPECT/CT fusion. In a prospective study \(^9\) on 37 patients with 42 focal lesions of the axial skeleton where planar scintigraphy, SPECT and digitally fused SPECT-CT were obtained, visibility of the lesions was again significantly better with SPECT than with planar scintigraphy (mean value, 3.6 ± 0.6 vs. 2.7 ± 0.6; \(p < 0.0001\)). A specific diagnosis was made with planar scintigraphy in 64% of cases, with SPECT in 86%, and with SPECT fused with CT in all cases. However, differences between the three methods for differentiation of benign and malignant lesions did not reach statistical significance. In a large series, Römer and his colleagues \(^10\) performed 272 consecutive bone scintigraphy examination for confirmed cancer patients, of whom 112 required further workup by SPECT as a definite diagnosis could not be established using whole-body planar scintigraphy alone. In 57 of these patients, SPECT/CT was carried out. Among 52 indeterminate lesions on SPECT of 44 patients, 33 (63%) were found benign on SPECT/CT, 15 (29%) could be classified as osteolytic or sclerotic metastases while 4 (8%) lesions in ribs and the scapula remained indeterminate. In this study SPECT-guided CT was able to clarify more than 90% of SPECT findings classified as indeterminate. However, the readers were blinded to the clinical and the planar scan findings which are known to help the expert reader in clarifying bone scintigraphy findings in some setting. Horger et al.\(^8\) could correctly classify 85% of unclear foci on bone scintigraphy with SPECT/CT, compared with only 36% using SPECT alone. Similarly, another group concluded that SPECT/CT improves the readers confidence to reclassify indeterminate lesions as benign or metastases \(^11\).

**Computed Tomography (CT)**

Multi-slice computed tomography (MS-CT) is the most frequently used modality in oncologic imaging. CT of the thorax and abdomen is frequently used for staging of the primary tumor and in this setting bone metastasis in the imaging field may be detected under bone window. It is also used for guided biopsies. CT images provides fine anatomical details of complex bone structure without overlap and can depict small differences in bone density, and consequently detects small osteolytic lesions and allows evaluation of cortical bone involvement, tumor calcification and contrast enhancement, however it underestimates bone marrow involvement \(^12\).
A limitation of CT is the low soft tissue contrast outside the lung which may cause difficulties in assessing of distant metastases and tumor extension to the surrounding structures.

**Magnetic Resonance Imaging (MRI)**

Metastasis to bone arises from tumor cells seeding in the bone marrow where nutrient blood supply is available. From there, growth of the metastatic tumor to adjacent bone marrow occurs. The importance of MRI is in detecting bone marrow metastasis since it may detect it at much earlier stages than on bone scintigraphy. Normally, age dependent conversion of the hematopoietic marrow to fat occurs at different rates in different parts of the skeleton. In adulthood, a relatively higher proportion of fat is present in the diaphysis of the long bones, while equal proportions of hematopoietic marrow and fatty marrow are present in axial skeleton. Substitution of fatty marrow by hematopoietic marrow (reconversion) occurs progressively in disease process. MRI is the modality that allows direct visualization of bone marrow lesions including malignancies (Figure 3). Bone marrow metastasis leads to decreased signal as opposed to high signal in fatty tissues in T1-weighted images. The changes in T2-weighted signal are more variable. Increase in water content and decrease in fat is common to bone marrow changes due to either infection or metastasis. Direct comparison of MRI and CT showed superior diagnostic accuracy for MRI (98.7%) vs. 88.8% for CT for spinal metastases (13). Additionally, although Tc99m MDP bone scan is still the standard method for initial screening for bone metastases, bone marrow lesions may remain invisible in the absence of osteoblastic response and MRI has been reported to higher accuracy for spinal metastases (14).

Specificity however, is not consistent and is dependent on the choice of acquisition. MRI is also very time consuming and cost ineffective. However for selective evaluation of suspected bone metastases particularly in the vertebral column, it is considered the gold standard since other modalities can be negative including bone scintigraphy.

**Positron Emission Tomography (PET)**

**F-18 fluoride**

F-18 fluoride ion has been available for decades for bone imaging. There is a very high first pass extraction of this ion to bone. The mechanism of uptake in bone is similar to Tc-99m MDP. Fluoride ion diffuses through capillary membrane and exchange of fluoride with hydroxyapatite crystal occurs in extracellular fluid surrounding bone, forming a fluorinated apatite. In areas where bone turnover is high, an increased uptake of both F18 fluoride and MDP is expected. Recently, the improvements in PET scanners lead to re-emergence of F18 fluoride in bone imaging. The tracer provides high sensitivity imaging of bone combined with high quality and excellent resolution properties of PET cameras as compared to gamma cameras. The three dimensional reconstruction of whole body and absolute quantification of bone kinetics provided by the technique makes F18 fluoride favorable. The procedure remains costly and not readily available.

Few studies compared Tc-99m MDP and F18 fluoride. However comparison has not been extensively studied. When bone scintigraphy and F-18 PET were compared regarding detection of osteolytic (from thyroid and lung cancer) and osteoblastic metastases (from prostate cancer), F-18 PET showed higher accuracy in detecting both metastases (5). As compared to F-18 PET, bone scintigraphy had a sensitivity of 82.8% in detecting malignant and benign osseous lesions in the skull, thorax and extremities and a sensitivity of 40% in the spine and pelvis. However, it should

Fig. 3: A representative image of MRI illustrating the excellent resolution in visualizing a metastatic lesion in a vertebra (arrow)
be noted that the study compared planar bone scintigraphy without SPECT which is known to improve lesion detection and characterization in vertebrae.

In a prospective study primarily designed to assess the clinical value of planar bone scintigraphy, SPECT and F-18 fluoride, Schirrmeister and co-workers (15) evaluated 5 newly diagnosed lung cancer patients, of whom 12 had bone metastasis, as verified by MRI and clinical course. All twelve patients were correctly identified by F-18 PET, while bone scintigraphy produced 6 false-negatives and vertebral SPECT reduced that to one false-negative. Clinical management was changed in 6 patients by F-18 fluoride, however, using SPECT in bone scintigraphy have missed only one out of the six patients.

In another prospective study (16), 28 breast cancer patients with suspected and 6 with previously known metastatic bone disease were examined using F-18 PET and bone scintigraphy. All the six patients with previously diagnosed metastatic bone diseases were correctly staged using both modalities, though F-18–PET revealed additional metastases in five of these patients, of whom two patients were identified by bone scintigraphy. Of 28 patients with previously unknown bone metastases, 11 patients were correctly diagnosed as metastatic bone disease and 16 as metastasis free using F-18 PET. There was one equivocal study in a patient with degenerative lesions. With bone scintigraphy, correct diagnosis was provided in 5 metastatic and 11 free from metastasis patients. Seven equivocal studies were described, of whom three had metastatic bone disease. In two patients, degenerative lesions were incorrectly considered bone metastases. F-18–PET allowed change in clinical management in 4 patients: upgrading three patients from stage I or II to stage IV and surgical stabilization of a large vertebral metastasis evident on F-18 PET but not on bone scintigraphy. Hetzel and co-workers (17) studied 103 patients with lung cancer and found that out of 33 patients with bone metastases, 13 were false negative on bone scintigraphy, 4 on SPECT, and 2 on F-18 PET. The clinical management was changed in 8 and 10 patients based on SPECT and F-18 PET imaging, respectively. They concluded that F-18 PET is more effective but remains more costly than SPECT.

F-18 Fluorodeoxyglucose (FDG)

Being a bone seeking agent, F18 fluoride discussed above carries the same problem of high sensitivity but non-specificity of uptake in areas of high turnover. A widely used PET radiotracer offering an alternative method to tackle the situation is F-18 deoxy-glucose. F-18 FDG is a glucose analogue that is taken up by cells through glucose transporters but is not metabolized any further and therefore retained intracellularly. The FDG activity in a cell thus correlates with the number of glucose transporters and glycolytic activity, both of which are increased in tumor cells. F-18 FDG PET is clinically an established diagnostic modality in several primary tumors (including lymphoma, lung cancer and solitary pulmonary nodules). In a single study, F-18 FDG PET can survey the whole body and delineate the primary tumor as well as nodal, distant organ and skeletal metastasis with variable degrees of success in different organs and different primary tumors. Unlike bone seeking radiopharmaceutical uptake on bone surface depending upon adjacent bone reaction, F-18 FDG uptake is in tumor cells. However, other cell with high glucolytic rate also show FDG uptake including inflammatory cells in infected or inflamed bone (18). Still though, identification of seeding of metastases in bone marrow before they induce bone reaction means early detection of metastatic bone disease.

The initial reports comparing F-18 FDG to bone scintigraphy showed mixed results.

Kao et al. (4) found 11 metastatic and 20 benign lesions seen on bone scintigraphy but not on F-18 FDG in 24 patients with a biopsy-proven malignancy and suspected bone metastasis indicating less sensitivity in detecting malignant bone metastases. However, they also concluded that 18FDG-PET showed better specificity than bone scans as 8 metastatic bone lesions with positive FDG-PET findings were not detected on bone scan. Yang and co-workers (19) studied 48 breast cancer patients. Among the 105 metastatic and 20 benign bone lesions, FDG-PET led to
an accurate diagnosis of 100 metastatic and 20 benign lesions while bone scan detected 98 metastatic and 2 benign bone lesions. The diagnostic sensitivity and accuracy of FDG-PET were 95.2% and 94.5%, and of bone scan were 93.3% and 78.7%, respectively.

FDG activity varies among metastasis from different primary tumors. While lymphoma and lung cancer are classical for positive F-18 FDG uptake (Figure 4), prostate cancer is a classical example of false-negative FDG study even in the untreated patients. Yet, one of the observations is that progressive prostate cancer demonstrates FDG activity. In a prospective study (20) on 12 patients with progressive prostate cancer, F-18 FDG detected 157 of 325 bone lesions (48.3%), but it was also noted that when the patient had a prominent tumor burden, osseous metastases were

![Coronal, Sagittal, MIP](image)

**Fig. 4:** FDG-PET study of a patient with non-Hodgkin's lymphoma showing widespread tumor including bone metastases detected readily by F-18 FDG PET. Moreover, cervical spine metastases were more easily detected by PET than by bone scintigraphy. More recently, Larson et al. (21) evaluated a group of 7 patients with laboratory-documented progressive prostate cancer. All the 49 bone lesions seen on bone scintigraphy were also evident on F-18 FDG. However, additional lesions seen on F-18 FDG PET only were progressive in nature. In a retrospective evaluation of 28 patients with bone metastases from breast cancer, Specht et al. (22) interestingly observed that high FDG uptake in a metastatic lesion (as quantified by high standard uptake value) on initial FDG PET was predictive of a shorter time to skeletal-related event defined as need for radiation therapy to stabilize skeletal disease, pathologic fracture, spinal cord compression, surgery to stabilize spine, or hypercalcemia of malignancy.

Similarly, the nature of bone metastasis appears to have an impact on FDG uptake. In a subgroup of breast cancer patients with osteoblastic bone disease, F-18 FDG detected fewer bone metastases than bone scintigraphy (23). Osteolytic lesions show high F-18 FDG avidity as quantified by high standard uptake value (SUV). Gallowitsch (24) reported on a better specificity but lower sensitivity of F-18 FDG for detecting bone metastases in a subanalysis of 38 breast cancer patients demonstrating a lesion-based sensitivity and specificity of 56.5 and 88.9% using FDG, and 89.8 and 74.1% with bone scan. However, this difference was observed in a lesion-based analysis rather than patient-based analysis, where no difference could be observed concerning sensitivity (92.3% for both methods) and even a slightly superior specificity for FDG PET with 92% versus 80% using bone scintigraphy. They noted that the nondetectable lesions using FDG predominantly correlated to radiologically sclerotic or mixed sclerotic/osteolytic lesions.

**Imaging in special situations**

Bone metastases to certain sites and those associated with some common tumors deserve special mention to details. Solitary bone lesions and metastases to the vertebral column exhibit special issues as well as metastases of breast, prostate and thyroid cancers since there are specific considerations and controversies that need to be addressed.

**A. Solitary lesion**

Solitary metastasis occurs in both axial and appendicular skeletons in variable percentages of cancer patients. These lesions are commonly asymptomatic and not suspected clinically. Less than half of these lesions are present on x-rays. These facts further emphasize the importance of obtaining a bone scan of the entire skeleton along with certain spot images routinely in patients with cancer. The incidence of malignancy in solitary lesions varies with the location and may also be linked to the type of the primary tumor (5,25). The incidence is highest in the vertebrae and low in the skull and
extremities (3). Within the vertebral column, the anatomic location is also linked to the probability of malignancy which is highest in lesions of pedicle followed by vertebral body, spinous process and finally the facet joints, which show the least probability (26). Tomoda and co-workers (27) reviewed 1,167 consecutive bone scans of patients with history of lung, breast or prostatic cancer. There were 185 bone scans showing solitary hot spot of which 42 lesions (23%) were malignant, 30 from lung, 8 from breast, and 4 from prostatic cancers. The difference in the frequency of bone metastasis according to the type of primary tumor was not significant.

Not uncommonly, the presence of a solitary lesion represents a diagnostic dilemma. Many imaging modalities are available for etiologic classification of the solitary lesions of bone. The standard radiograph remains the most reliable and most influential in determining whether further imaging is required. Bone scan is nonspecific although certain patterns are known to occur in certain lesions and have more specific diagnostic value. Such patterns include the doughnut pattern of giant cell tumor, the double intensity pattern of osteoid osteoma, and the elongated rib lesion suggesting more the possibility of malignancy (2). The role of Thallium-201 was investigated by Elgazzar et al (25) who studied by visual assessment and determination of lesion-to-background ratios 28 patients with solitary bone lesions. Significant uptake with a mean lesion-to-background ratio of 4.2 was found in malignant lesions in comparison to a mean lesion-to-background ratio of 1.37 in benign lesions. This study used a single acquisition and results can be improved by using dual early and delayed imaging.

CT is commonly used for further assessment of equivocal lesions evident on bone scintigraphy, however, enough cortical destruction should be present for the lesion to be visualized on CT. Furthermore, cortical destruction may be difficult to assess in patients with degenerative changes or severe osteoporosis even when using high resolution multidetector CT. MRI is also not specific enough to resolve the issue of differentiating benign from malignant etiology of the lesions (12). Quantitative FDG PET, however, is the most accurate in differentiation between benign and malignant lesions (5). The new concept of dual point time imaging using F-18 FDG PET has been recently addressed in literature and is based on the finding that malignant cells show prolonged retention of the tracer as opposed to inflammatory and non-malignant cells as in the case of TI-201 and is used to differentiate the two entities (28). Application of this concept to bone lesions is still awaited and may prove to be beneficial.

The definitive diagnosis in some solitary lesions in a patient with known primary tumor can be only arrived at by bone biopsy. Negative biopsies however, must be interpreted carefully and repeated if considered to be non representative.

B. Vertebral Metastases

Planar bone scintigraphy, as previously mentioned, may be false-negative for vertebral metastases because of summation of different structures, including vertebral body, pedicle, and facet joint in one plane on one hand, and because of the high incidence of degenerative changes in the spine on the other hand. More importantly bone marrow lesions may not be seen till enough bone reaction occurs later. SPECT has been found to improve the detection and characterization of focal bone lesions particularly in spine. Overall, because of the lower specificity of bone scintigraphy, patients with equivocal findings and persisting pain in the spine necessitate regional CT or MRI to evaluate the characteristics of the detected scintigraphic changes. MRI is most useful in axial skeleton. MRI has been reported to be more sensitive than scintigraphy in the detection of bone metastases in the axial skeleton.

C. Metastases of specific malignancies

Breast cancer metastases

Bone metastases are frequent in patients with advanced breast cancer (29-32) with 20% to 45% in clinical stage 3 (29-30). This was recently confirmed in a study of 250 patients with breast cancer. The study showed metastases in 3% of
patients with early stage (T1-2 N0-1) compared to 30% of patients with disease of pathologic stage T3-4 or N2 (31). Bone pain is an appropriate indication for bone scanning, either at diagnosis or follow-up, however evidence of metastases is present in only 60% of patients with persistent bone pain (32). The tumor usually produces purely osteolytic or mixed osteolytic/osteoblastic lesions and only rarely osteoblastic lesions radiologically. Standard radiographs are less sensitive and impractical to be used to screen for metastases compared to bone scintigraphy. Bone metastases, which develop most rapidly during the first 2 years, are almost always hot in appearance scintigraphically. Initial and follow up bone scans provide prognostic information by showing the extent of metastatic disease and evaluating the effectiveness of hormonal and other standard breast cancer therapies. Metastatic breast cancer with disease limited to bone has a better prognosis than when other distant sites are involved. Regarding the extent of bone metastases at initial relapse, the subset of patients with initial bone involvement at only one or two sites has been known to have a survival advantage over patients with more extensive metastases. In a recent study (33), patients whose scans showed disease regression had the longest survival, followed by those with a stable scintigraphic and radiographic pattern. The shortest survival was for those patients with disease progression.

Bone scintigraphy was reported to be false-negative for vertebral metastases among patients with estrogen receptor negative or highly proliferative tumors, MRI of the axial skeleton and pelvis is superior. Data also suggest that FDG-PET may have the ability to demonstrate small bone marrow metastases, allowing early detection of bone metastases which has a significant effect on clinical management (34), as in a recent study it changed the treatment recommendation for 4 of 44 patients, compared to what would have been recommended if only information from the bone scanning was available (28). There is a growing interest in bone marrow micro-metastases from breast cancer. The presence of micro-metastatic lesions are predictor of subsequent skeletal metastases and are associated with disease progression and poor survival. Advances in molecular imaging including PET will have a significant role in this issue.

### Prostate cancer metastases

Bone metastases are found in 8-35% of patients with prostatic carcinoma at the time of diagnosis (35). Bone pain has low predictive value for metastatic bone disease. Bone scans have been shown to be vastly superior to radiographs and more accurate than acid phosphatase determinations in the detection of bony metastasis. Jacobson (36) reviewed the bone scan patterns of benign and malignant uptake in 432 patients with newly diagnosed prostate carcinoma in relation to prostate-specific antigen (PSA) levels determined within 4 months of scintigraphy. The majority (69%) of patients with limited skeletal metastases had PSA < 100 ng/ml while almost all patients (89%), with extensive skeletal involvement had PSA >100 ng/ml (36).

In the series of Wymenga, et al (37), bone scan was positive in 19 of 144 (13%) patients with a PSA level of < 20 ng/mL. In another study, 9 patients showed a positive bone scans among 214 patients with PSA <20 ng/ml (38). On the other hand, the bone scan was positive in 51% of patients with a PSA level of > 20 ng/mL. The current recommendations for use of bone scintigraphy preoperatively are for patients with PSA >10-20 ng/ml (39), as less than 1% of patients with PSA <20 ng/ml have skeletal metastases (40). Bone scintigraphy is requested when PSA is rising in treated patients, whether by radical prostatectomy or radiation therapy. However a recent study found alkaline phosphatase (ALP) values correlated better with an abnormal bone scan than did PSA levels. ALP levels of > 0 U/L indicated a 60% chance for the presence of bone metastases. The authors recommended newly diagnosed and untreated prostate cancer patients to undergo bone scintigraphy if there is bone pain or if ALP levels are > 90 U/L. Contrary to other reports that discourage the routine use of a bone scan when the serum PSA level is <20 ng/mL, this study indicated a greater chance of a positive bone scan in patients with low PSA levels (37).
Follow-up bone scintigraphy has been shown to be quite valuable in assessing response to therapy. Fitzpatrick (41) reported that the bone scan demonstrates changes in response to therapy before either acid or alkaline phosphatase, prostate size, or symptomatology demonstrates alterations. Prognostic information can be obtained from bone scan since patients with a positive scan at the time of diagnosis generally do not survive as long as those with negative scans.

FDG-PET is variable in the detection of bone metastases, due to the fact that osteoblastic metastases show lower accumulation than osteolytic metastases, as previously mentioned. Schöder and Larson (42) suggested that FDG, depending on higher glucose metabolism, may selectively detect more aggressive tumors. Shreve and coworkers (43) reported a sensitivity of 65% and PPV of 98% in 202 bone metastases while Yeh and coworkers (44) found that FDG uptake was evident in only 18% of bone lesions shown on the bone scan.

**Thyroid cancer metastases**

Bone scintigraphy is considered to lack sensitivity in detecting bone metastases from thyroid cancer due to the nature of such metastases as causing no or only slight osteosclerotic bone reaction. Sensitivity of bone scan was 64%-85% and specificity, 95%-81%(3). Radioactive iodine (I-131 and I-123) feature specific uptake by both primary and metastatic differentiated thyroid cancer. The combination of bone scintigraphy and whole body iodine 131 scan was 100% sensitive in detecting metastatic bone disease. Following total thyroidectomy and ablation, a rising thyroglobulin level is suggestive of recurrence or metastases and is usually associated with positive I-131 scan findings although 15-20% of cases have negative whole body I-131 scan (45). In addition to I-131 and bone scintigraphy, T1-201, Te99m MIBI and FDG-PET have a complementary role in identifying bone metastases of this tumor particularly in those patients with negative bone and I-131 studies and elevated thyroglobulin levels since they can detect lesions not otherwise detected by a single modality. In particular, there is a growing interest in FDG PET. Phan and coworkers (46) evaluated 24 thyroid cancer patients suspected of having bone metastases using both bone scintigraphy and FDG PET. Among 8 patients with confirmed metastases, 5 were identified on both modalities, 3 patients had bone metastases, only visible on bone scintigraphy. A positive study by Kim et al (47) on 20 patients with differentiated thyroid cancer, elevated serum thyroglobulin but negative I-123 scan that had F-18 FDG PET/CT evaluation showed that the latter identified lesions in 18 out of 20 patients, yielding a sensitivity of 90%. Thirteen of the 18 patients had limited loco-regional disease, while the remaining 5 patients showed distant metastases including 1 patient with bone metastasis. Two patients had negative F-18 FDG PET/CT findings.

FDG PET and Thallium 201 were compared in a study of 32 patients with well differentiated thyroid cancer in combination with I-131 with results in detecting metastases that are 94% concordant (48).

**Follow up of bone metastases**

Scintigraphy has a great value in assessing response of metastatic bone disease to therapy and is superior to morphologic modalities. Bone scintigraphy is still adequate and cost effective modality for routine follow up of metastatic bone disease of many tumors and provides prognostic information. Patients with stable scans have survived as much as twice as long as those with scintigraphic evidence of progressive bone disease.

Moreover, an initial apparent deterioration of some lesions on the bone scan, followed by improvement, may accompany successful treatment of metastatic disease. This flare phenomenon occurs in metastatic disease of many tumors, particularly those of the breast, lung, and prostate. The pattern can be seen after chemotherapy for up to 8 months or even longer (3). Distinction between progression and such pattern of pseudo progression can usually be made in most cases by three months on the follow up bone scan . Citrin et al (49) found that 7 months were required for bone scan to show favorable response but only 4 months to show progression of disease.
is thought if the number of lesions increases or the activity of known lesions dramatically increases. However, waiting for three months after the start of chemo or hormonal therapy to evaluate the efficacy of therapy using bone scans may be impractical. FDG PET provides faster assessment of the response to therapy and differentiating progression from flare effects of therapy and should be used when available in such situation when a quick assessment of therapy response is needed for decision making and in difficult cases of flare pattern on bone scan. F-18 FDG, therefore, was used to evaluate bone metastases before and after endocrine therapy in a patient with metastatic bone disease of prostate carcinoma as seen on bone scans. Bone scan after treatment showed little change compared to that before treatment with more increased uptake in lumbar vertebral lesions. Repeated PET, in contrast, when compared with the pretreatment scan, showed a decrease in FDG uptake indicating favorable response to treatment rather than progression. The information on response to chemo or hormonal therapy is provided more rapidly by PET than by bone scan, giving an opportunity of earlier selection of a more effective therapy in case of unfavorable response.

References

18. Yang SN, Liang JA, Lin FJ, et al. Comparing whole body (18)F-2-deoxyglucose positron emission tomography and technetium-99m methylene...


45 Baudin E, Do Cao D, Cailleux AF, et al. Positive predictive value of serum thyroglobulin levels, measured during the first year of follow-up after


