Bone Metastases

Introduction

Background

Metastases from carcinoma are by far the most common malignant tumors involving the skeleton. Imaging has an important role in the detection, diagnosis, prognostication, treatment planning, and follow-up monitoring of bone metastases. In patients with proven nonskeletal tumors, imaging is useful for screening the skeleton to assess metastatic disease and, if it is present, to determine its extent.[1,2,3] In a patient without a known malignancy, a possible diagnosis of bone metastases may be made by recognizing radiographic and other imaging findings. If bone metastases are present or suspected, further imaging or imaging-guided techniques may be required to confirm the diagnosis, to establish the extent of the disease, and to find the primary tumor.

Pathophysiology

Metastases involve bone by means of 3 main mechanisms: (1) direct extension, (2) retrograde venous flow, and (3) seeding with tumor emboli via the blood circulation. Seeding occurs initially in the red marrow; this process accounts for the predominant distribution of metastatic lesions in the red marrow–containing areas in adults. In contrast, bone metastases are usually widespread in children. Retrograde venous embolism is probably the major mechanism when spread from intra-abdominal cancer involves the vertebrae. Increased intra-abdominal pressure causes blood to be diverted from the systemic caval system to the valveless vertebral venous plexus of Batson; this diversion allows the caudal and cranial flow of blood.

As a metastatic lesion grows in the medullary cavity, the surrounding bone is remodeled by means of either osteoclastic or osteoblastic processes. The relative degree of resultant bone resorption or deposition is highly variable and depends on the type and location of the tumor. The relationship between the osteoclastic and osteoblastic remodeling processes determines whether a predominant lytic, sclerotic, or mixed pattern is seen on radiographs.[4,5]

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Frequency

United States

The true incidence of bone metastases is the subject of much debate, and it is not fully known. The probability of bone metastasis originating from a primary site can be assessed only by knowing the prevalence of the cancer and its predilection for bone. Therefore, the frequency of bone metastases depends on the prevalence of the cancer in a particular community. The incidence of bone metastases also depends on the source of the data. For example, results from autopsy studies and from bone scintigraphic studies are different for newly diagnosed, established, and end-stage cancers.

For overall frequencies of carcinoma-caused bone metastases in North America, see Sex.

International

The frequency of carcinoma-caused bone metastases depends on the prevalence of a particular cancer in a given community. The probability of bone metastasis can be assessed only by knowing the regional and local prevalence of the cancer and its predilection for bone.

Mortality/Morbidity

- Bone metastases significantly limit the patient's quality of life and life expectancy.
- Patients with bone metastases frequently have reduced mobility, pain, and bone weakness that predisposes them to pathologic fractures.
fractures, spinal epidural compression, and bone marrow failure.

Race

- The frequency of carcinoma-caused metastases depends on the prevalence of a particular cancer in a given race.
- The probability of bone metastasis can be assessed only by knowing the prevalence of the cancer and its predilection for bone in a particular racial group.

Sex

The frequency of carcinoma-caused bone metastases depends on its prevalence in male or female patients.

- In North America, overall frequencies of carcinoma-caused bone metastases for both sexes involve the following areas, in descending order of frequency: breast, prostate, lung, colon, stomach, bladder, uterus, rectum, thyroid, and kidney.
- In North America, carcinoma-caused bone metastases in men involve the following areas, in descending order of frequency: prostate, lung, bladder, stomach, rectum, and colon.
- In North America, carcinoma-caused bone metastases in women involve the following areas, in descending order of frequency: breast, uterus, colon, stomach, rectum, and bladder.

Related eMedicine topics:
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Age

Bone metastases are usually found in middle-aged and elderly persons. Bone metastases are much less common in children than in adults.

- Seeding occurs initially in the red marrow; this process accounts for the predominant distribution of metastatic lesions in the red marrow–containing areas in adults.
- Bone metastases are usually widespread in children. In children, the most common causes of widespread metastases are neuroblastoma and leukemia; other tumors are relatively rare.

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Anatomy

Bone metastases are often multiple at the time of diagnosis. In adults, the lesions generally occur in the axial skeleton and other sites with residual red marrow, although the lesions may be found anywhere in the skeletal system. Common sites for metastases are the vertebrae, pelvis, proximal parts of the femur, ribs, proximal part of the humerus, and skull. More than 90% of metastases are found in this distribution.

Certain carcinomas may have a predilection for particular skeletal sites. For example, metastases to the bones of the hands and feet are rare, but 50% of hand metastases originate from lung neoplasms (see Image 1). Primary tumors arising from the pelvis have a predilection for spread to the lumbosacral spine.

Presentation

In patients with a known primary carcinoma, the development of bone pain usually is considered to be highly suggestive of bone
metastases. However, Schaberg and Gainor found that 36% of patients with spinal metastases did not complain of bone pain.6 Galasko and Sylvester also found that only 66% of their patients with back pain and a history of previous malignancy had bone metastases.7 Occasionally, patients with bone metastases may present with a pathologic fracture; therefore, checking the state of underlying bone for disease is important if such a fracture is suspected (see Image 2).8 In addition, patients may present with complications of bone metastases, such as neurologic impairment due to spinal epidural compression (see Image 3).

**Preferred Examination**

Technetium-99m (99m Tc) bone scintiscanning (ie, radionuclide bone scanning) is widely regarded as the most cost-effective and available whole-body screening test for the assessment of bone metastases. Conventional radiography is the best modality for characterizing lesions that are depicted on bone scintiscans. Combined analysis and reporting of findings on radiographs and 99m Tc bone scintiscans improve the diagnostic accuracy in detecting bone metastases and assessing the response to therapy.9,10,11 CT and MRI are useful in evaluating suspicious bone scintiscan findings that appear equivocal on radiographs.12,13,14,15 MRI can also help in detecting metastatic lesions before changes in bone metabolism make the lesions detectable on bone scintiscans.16,17,18 CT is useful in guiding needle biopsy, particularly in vertebral lesions. MRI is helpful in determining the extent of local disease in planning surgery or radiation therapy.

The first screening test used for the detection of bone metastases depends on the relative availability of MRI and 99m Tc bone scintiscanning. The selection will become less of an issue when more MRI units are established and when its cost decreases. Factors such as cost and relatively long imaging times, as well as considerations of patient throughput, are important. MRI is estimated to cost 2-3 times as much as 99m Tc bone scintigraphy19,20; fluorodeoxyglucose (FDG) positron emission tomography (PET) costs 8 times as much.21,22,23,24,25

**Limitations of Techniques**

Radiographs are relatively insensitive in the detection of early or small metastatic lesions. Although CT scans are superior to radiographs, CT is also relatively insensitive in showing small intramedullary lesions, and it has the disadvantage of limited skeletal coverage. Bone scintiscan findings are sensitive but nonspecific. Whole-body MRI and FDG-PET are accurate techniques that are currently limited by their high cost.26,27,28,29,30

**Differential Diagnoses**

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**Other Problems to Be Considered**

Secondary osteoarthritis

**Radiography**

**Findings**

Radiography remains the best method for characterizing bone metastases.

Bone metastases may be osteolytic, sclerotic, or mixed on radiographs (see Image 4). Lesions usually appear in the medullary cavity, spread to destroy the medullary bone, and then involve the cortex. Osteolytic metastases are encountered most frequently, especially in breast and lung carcinomas (see Image 5).31,32,33,34 The specific appearance of bone metastases is often useful in suggesting the nature of the underlying primary malignancy.

Metastases from certain primary sites (eg, renal cell or thyroid carcinomas) are almost always osteolytic, whereas those from other sites (eg, prostatic carcinoma) are predominantly sclerotic (see Image 6).35 Other malignancies associated with sclerotic metastases include breast carcinoma, colonic carcinoma, melanoma, bladder carcinoma, and soft-tissue sarcoma. The findings of sclerotic metastases virtually exclude an untreated renal tumor or hepatocellular carcinoma.36
In vertebrae, clues to metastatic involvement include pedicular destruction, an associated soft-tissue mass, and an angular or irregular deformity of the vertebral endplates.

The response to therapy can be evaluated by using radiographs and by correlating the radiographic changes with bone scintiscan findings and clinical and laboratory data. The initial manifestation of healing in an osteolytic metastatic lesion is a sclerotic rim of reactive bone. With progressive healing, sclerosis increases and advances from periphery of the lesion to its center: The lesion shrinks and eventually resolves. For a mixed osteolytic-sclerotic lesion, a healing response to therapy is demonstrated as uniform lesional sclerosis, whereas increasing osteolysis indicates disease progression. Purely sclerotic lesions are more difficult to assess. A sclerotic lesion that shrinks or completely disappears after therapy signifies disease regression, whereas one that grows and causes destruction implies progression. The comparison of current images with previous radiographs is essential, particularly in the detection of subtle lesional changes.

**Degree of Confidence**

Compared with other imaging techniques, radiography is relatively insensitive in detecting bone metastases, especially subtle lesions. As a general rule, only lesions 2 cm or larger are radiographically apparent. Metastases to bone become apparent on radiographs only after the loss of more than 50% of the bone mineral content at the site of disease.

**False Positives/Negatives**

On radiographs, advanced destructive lesions of the cancellous bone may not be visible, particularly in the absence of reactive new bone or cortical involvement. This problem is more apparent in elderly patients with osteopenic bones than in others.

Osteolytic metastases can mimic osteoarthritis both clinically and radiographically; for example, they can mimic subchondral cysts and Schmorl nodes in the spine. Osteolytic foci may resemble amyloidosis, cystic angiomatosis, and infiltrative bone marrow lesions. Sclerotic metastases may be difficult to distinguish from other sclerotic bone lesions such as bone islands, tuberous sclerosis, mastocytosis, and osteopoikilosis.

In assessing the response to therapy, an increasing number of sclerotic bone metastases may be difficult to distinguish from the healing of sclerotic lesions that were not previously identified.

**Computed Tomography**

**Findings**

CT scans are valuable in the evaluation of focal abnormalities seen on bone scintiscans that cannot be confirmed by using radiographs. CT is useful in further assessment of radiographically negative areas in patients who are symptomatic and in whom metastases are suggested clinically.

Osteolytic, sclerotic, and mixed lesions are depicted well on CT scans (see Image 7).

CT is useful in guiding needle biopsy of lesions in bones with complex shapes such as the vertebrae and the ilia (see Image 9).

Skeletal coverage is limited with CT because of its relatively high radiation dose, which makes CT unsuitable as a screening tool.

**Degree of Confidence**

The usefulness of CT in detecting early deposits in bone marrow is limited. Muindi et al and Durning et al found that CT is more sensitive than radiography in the detection of metastatic lesions. CT is vastly superior to radiography in the detection of trabecular and cortical bone destruction, soft tissue extension, and involvement of neurovascular structures (see Image 8).

**False Positives/Negatives**

Although CT is superior to radiography, some advanced destructive lesions of the cancellous bone may not be visible on CT scans, particularly in the absence of reactive new bone or cortical involvement.

**Magnetic Resonance Imaging**

**Findings**

Many authors have shown that MRI is more sensitive than $^{99m}$Tc bone scintiscanning in the detection of bone metastases. However, the use of MRI to screen the skeleton has long been regarded as impractical, although Steinborn et al and Eustace et al have shown that whole-body MRI is a feasible alternative to $^{99m}$Tc planar bone scintiscanning in evaluating the entire skeleton for metastatic disease.
Whole-body MRI requires 40-45 minutes to perform and involves the use of short-tau inversion recovery (STIR) and/or T1-weighted sequences.[41]

Metastatic seeding in the bone marrow is characterized by long T1 relaxation times, whereas T2 relaxation times are variable, depending on tumor morphology. Lesions are seen as focal or diffuse areas of hypointensity on T1-weighted images and as areas of intermediate or high signal intensity on T2-weighted images. Tumor deposits typically appear hyperintense against a dark background of suppressed signal intensity within fat on STIR images (see Images 10-11).

The bull's-eye or halo sign has been reported to be useful in distinguishing metastatic from benign lesions.[42] In vertebrae, additional criteria for malignancy include bulging of the posterior margin of the vertebral body, signal intensity changes that extend into the pedicle, and parossaeus tumor spread (see Images 12-16).

Gadolinium-based contrast agents (gadopentetate dimeglumine [Magnevist], gadobenate dimeglumine [MultiHance], gadodiamide [Omniscan], gadoversetamide [OptiMARK], gadoteridol [ProHance]) have recently been linked to the development of nephrogenic systemic fibrosis (NSF) or nephrogenic fibrosing dermopathy (NFD). For more information, see the eMedicine topic Nephrogenic Fibrosing Dermopathy. The disease has occurred in patients with moderate to end-stage renal disease after being given a gadolinium-based contrast agent to enhance MRI or MRA scans.

As of late December 2006, the FDA had received reports of 90 such cases of NSF/NFD. Worldwide, over 200 cases have been reported, according to the FDA. NSF/NFD is a debilitating and sometimes fatal disease. Characteristics include red or dark patches on the skin; burning, itching, swelling, hardening, and tightening of the skin; yellow spots on the whites of the eyes; joint stiffness with trouble moving or straightening the arms, hands, legs, or feet; pain deep in the hip bones or ribs; and muscle weakness. For more information, see the FDA Public Health Advisory or Medscape.

**Degree of Confidence**

MRI depicts early hematogenous dissemination of the tumor to the bone marrow before reactions in adjacent bone are detectable on $^{99m}$ Tc scintiscans.

Many studies have shown that MRI is more sensitive than $^{99m}$ Tc bone scintiscanning in the detection of bone metastases. Steinborn et al reported sensitivities of 91.4% for MRI and 84.8% for bone scintiscanning.[39] Flickinger and Sanal reported sensitivities of 100% for MRI and 62% for scintiscanning and specificities of 62% for MRI and 100% for scintiscanning.[43] For MRI and scintiscans, respectively, Eustace et al reported sensitivities of 96.5% and 72%, specificities of 100% and 98%, and positive predictive values of 100% and 95%.[40]

**False Positives/Negatives**

Distinguishing between benign and malignant causes of vertebral compression fractures may be difficult.[44] Baur et al reported on the use of MRI diffusion-weighted imaging (DWI) in discriminating between benign and malignant acute vertebral body compression fractures.[45,46,47,48,49] The findings were supported by the work of Spuentrup et al,[50] while Castillo et al found that DWI offered no additional advantage.[51] DWI is highly sensitive to cellularity and the mobility of free water molecules, which are responsible for the differences between benign and malignant fractures. Using a single-shot echo-planar DWI pulse sequence with a high b factor, Chan et al showed that apparent diffusion coefficient values are useful in differentiating benign osteoporotic fractures from malignant vertebral body compression fractures.[52]

**Nuclear Imaging**

**Findings**

$^{99m}$ Tc bone scintigraphy is an effective method for screening the whole body for bone metastases.[53,54] $^{99m}$ Tc diphosphonates, most commonly $^{99m}$ Tc methylene diphosphonate (MDP), is the most frequently used isotope. $^{99m}$ Tc planar bone scintiscans help in detecting metastatic bone deposits by the increased osteoblastic activity they induce; this finding is considered to be an indirect marker of tumor. Indications for bone scintiscanning include staging in asymptomatic patients, evaluating persistent pain in the presence of equivocal or negative radiographic findings, determining the extent of bone metastases in patients with positive radiograph findings, differentiating metastatic from traumatic fractures by assessing the pattern of involvement, and determining the therapeutic response to metastases.

PET can help in identifying bone metastases at an early stage of growth, before host reactions to the osteoblasts occur. FDG-PET depicts early malignant bone-marrow infiltration because of the early increased glucose metabolism in neoplastic cells.[55]

Isotopic imaging methods depict bone metastatic lesions as areas of increased tracer uptake. The classic pattern appears as the presence of multiple randomly distributed focal lesions throughout the skeleton (see Image 17). Findings of a solitary scintigraphic abnormality or just a few lesions may present special problems in the interpretation of findings. Other patterns include diffuse
involvement (superscan), photopenic lesions (cold lesions), normal scintiscans, flare phenomena, and soft tissue lesions.\[^{[53]}\]

**Degree of Confidence**

\(^{99m}\)Tc bone scintiscan findings are nonspecific in determining the cause of increased uptake, particularly in solitary lesions. Bone scintiscans have the disadvantages of poor spatial and contrast resolution. Despite the superior sensitivity of MRI compared with bone scintiscanning, bone scintiscanning continues to be used as the initial screening investigation because of its relatively low cost, wide availability, and usefulness in imaging the entire skeleton.

FDG-PET has limited spatial resolution, and complementary CT or MRI is required to localize an area of increased glucose metabolism.

**False Positives/Negatives**

Sensitivities of \(^{99m}\)Tc bone scintiscans are reportedly 62-89%. Many benign processes and normal variants can produce an area of increased isotope uptake that mimics a metastatic deposit. Solitary areas of abnormal uptake associated with benign processes occur in approximately one third of patients with malignant disease. The differential diagnosis of multiple scintigraphic abnormalities includes metabolic problems (eg, Cushing syndrome), osteomalacia, trauma, arthritis, osteomyelitis, Paget disease, and infarctions. Some metastases may produce normal scintiscan findings. Cold or photopenic metastases may be found in association with lesions of highly aggressive anaplastic carcinomas.

In diffuse metastatic disease, isotopic accumulation may be sufficiently uniform to produce a false-negative impression. Clues to the detection of the so-called superscan include skeletal uptake of greater-than-normal intensity, in relation to the background of the soft tissue and the low or absent uptake in the kidneys (see Image 18). Osteoblastic activity that reflects attempts at bone healing after chemotherapy (ie, flare phenomenon) may misleadingly suggest advancing disease on scintigraphy. The number of false-positive scintiscans can be decreased if the findings are reviewed with the corresponding radiographs.

In a comparative study of 3 modalities, Daldrup-Link et al found sensitivities of 90% for FDG-PET, 82% for whole-body MRI, and 71% for \(^{99m}\)Tc bone scintiscanning.\[^{[56]}\] Similar results have emerged from comparative studies of FDG-PET and \(^{99m}\)Tc bone scintiscans (Ohta, 2001; Kao, 2000).\[^{[57,58]}\] However, Franzius et al found that FDG-PET is less sensitive than bone scintiscanning in the differentiation of bone metastases from osteosarcoma.\[^{[59]}\] FDG-PET shows a high number of false-positive lesions, which require follow-up imaging with other modalities. The use of semiquantitative criteria for tumor FDG uptake in the qualitative evaluation of images may increase the specificity. In skull metastases, the high rate of glucose metabolism in the normal areas of brain may obscure metastases.

**Angiography**

**Findings**

With the advent of CT and MRI, angiography has a limited role in the diagnosis and evaluation of bone metastases. Its current value is in showing devascularization of vascular metastases prior to surgical intervention and in assessing pain palliation in patients with nonresectable metastases.\[^{[60]}\]

**Intervention**

Bone-seeking radiopharmaceutical agents are increasingly used in the treatment of painful bone metastases.\[^{[54,61,62,63]}\] These radiopharmaceuticals have been effective in treating patients with unremitting bone pain that results from terminal bone metastases. The agents include rhenium-186 stannum-ethylhydroxydiphosphonate and strontium-89, with which a reported 80% of treated patients have significant pain relief.\[^{[64]}\]

Vertebroplasty is a technique in which polymethylmethacrylate (PMM), a quick-setting bone cement, is percutaneously injected into a collapsed vertebral body under imaging guidance.\[^{[65,66,67]}\] The primary purpose of vertebroplasty is to relieve pain and to strengthen and stabilize the vertebrae. Vertebroplasty is most often performed to treat osteoporotic fractures; however, its major indications include the treatment of myeloma and bone metastases, particularly in patients who are considered to be poor surgical candidates for vertebrectomy.\[^{[68]}\] Significant pain relief occurs in more than 70% of patients. Complications are rare with a careful technique and include permanent neurologic damage and pulmonary embolization of the PMM.\[^{[69]}\] Cementoplasty is a variation of this technique in which PMM is percutaneously injected into osteolytic metastatic lesions in bones other than the vertebrae (eg, ilia) for pain palliation.\[^{[70,71]}\]

**Multimedia**
Media file 1: Bone metastases to the finger. Radiograph shows a destructive expanded osteolytic lesion in the metacarpal of the thumb in a 55-year-old man with lung carcinoma.
Media file 2: Pathologic fracture. Radiograph shows a displaced fracture through an osteolytic lesion in the distal femur of a 53-year-old woman with lung carcinoma.
Media file 3: Spinal epidural compression in a 70-year-old man with leg weakness. Lateral lumbar myelogram
shows a complete epidural block due to a destructive osteolytic lesion of the L3 vertebral body. Lumbar puncture was performed at the L2-3 level.

Media file 4: Lateral radiograph shows mixed osteolytic-sclerotic bone metastases in the skull vault.
Media file 5: Radiograph shows osteolytic metastasis in the distal femur of a 51-year-old woman with breast carcinoma.
Media file 6: Lateral radiograph shows sclerotic metastasis of the L2 vertebra in a 54-year-old man with prostatic carcinoma.

Media file 7: Axial CT scan shows 2 rounded, mixed osteolytic-sclerotic lesions in the thoracic vertebral body of a 44-year-old woman with lung carcinoma.
Media file 8: Axial CT scan shows a destructive osteolytic lesion in the left acetabulum of a woman with vulval carcinoma. Soft-tissue extension into the pelvic cavity is present.
Media file 9: CT-guided biopsy was performed in the left ilium of a 50-year-old woman with an unknown primary tumor. Axial CT scan obtained with the patient lying prone shows the tip of the 17-gauge bone biopsy needle in the osteolytic lesion. Histologic analysis demonstrated adenocarcinoma of the lung.
Media file 10: Sagittal spin-echo T2-weighted MRI shows hypointense lesions in the T10 and L3 vertebrae in a 66-year-old man with lung carcinoma (same patient as in Image 11). The tumor involves the T10 pedicle.
Media file 11: Sagittal short-tau inversion recovery MRI shows hyperintense lesions in the T10 and L3 vertebrae, with T10 pedicular involvement in the same patient as in Image 10.
Media file 13: Sagittal gadolinium-enhanced spin-echo T1-weighted MRI image shows heterogeneous enhancement of the T11-L2 vertebrae, with prominent epidural component enhancement and spinal canal.
compromise in the same patient as in Images 12, 14, and 15.

Media file 14: Axial spin-echo T1-weighted MRI shows tumor extension from the L1 vertebral body and left pedicle into the left psoas muscle and epidural space, with resultant spinal cord compression in the same patient as in Images 12, 13, and 15.
Media file 15: Axial gadolinium-enhanced spin-echo T1-weighted MRI shows heterogeneous enhancement of the soft tissue component of the L1 vertebral metastatic tumor in the same patient as in Images 12-14.
Media file 16: Axial gadolinium-enhanced spin-echo T1-weighted MRI of the T3 vertebra shows a ring-enhancing lesion and an expansile metastatic left rib deposit in a 43-year-old woman with breast carcinoma.
Media file 17: Typical scintigraphic pattern of bone metastases in a 60-year-old man with nasopharyngeal carcinoma. Posterior technetium-99m bone scintiscan shows multiple randomly distributed focal lesions scattered throughout the skeleton, particularly the spine, ribs, and pelvis.
Media file 18: Posterior technetium-99m bone scintiscan shows diffuse and intense uptake in most of the bones in a 79-year-old man with prostatic carcinoma. Patchy rib lesions are seen. Renal uptake is absent.

References


Keywords

bone secondaries, skeletal metastases, bone metastasis, metastases, metastasis, bone lesions

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Disclosure: Nothing to disclose.

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