# Evaluating Bone Metastases

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**Case Presentation:** Mr. P is a 67-year-old African American man with a known history of stage IIIC prostate carcinoma, originally diagnosed in 2002. He underwent a radical prostatectomy and initially was given leuprolide injections every three months. In 2004, he was diagnosed with bone metastases in the T8 and T12 vertebrae and was started on bicalutamide.

Mr. P’s prostate-specific antigen has been stable since the initiation of bicalutamide. His past medical history includes hypertension and osteoarthritis.

Mr. P presented for a follow-up office visit and routine laboratory work, complaining of a one-month history of progressively worsening right hip pain. He reported significant right hip pain when bearing weight, occurring in the past few days. Mr. P has no thoracic pain from the areas of known metastases.

An initial diagnostic workup, including a radiograph of Mr. P’s right hip, revealed no fracture; however, the radiologist observed what appeared to be an osteoblastic bone metastasis at the right femoral neck. A bone scan was positive for uptake in T8, an area at the right femoral neck, and at T12, an area in the right fifth rib. Mr. P was started on a daily calcium supplementation, IV biphosphonate every four weeks, and analgesics for pain.

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<th>Types of Bone Metastases</th>
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Bone normally undergoes continual remodeling in response to mechanical stress. Osteoclasts and osteoblasts alternately cause bone resorption and repair, respectively. The mineralized bone matrix contains numerous growth factors that are released during the process (Lipton, 2004). The favorable microenvironment of the bone matrix and its ample blood supply are the most likely causes for the high rate of bone metastases in patients with cancer.

Incidence and Prevalence of Bone Metastases

Approximately 60%–84% of patients diagnosed with solid tumors develop bone metastases (Berger & Koprowski, 1999). The third most common site of metastatic disease is the skeleton, and metastasis is the most frequently occurring bone malignancy (Jacofsky, Frassica, & Frassica, 2004). Prostate, breast, lung, kidney, and thyroid cancers account for 80% of skeletal metastases, which occur most often in the spine, pelvis, ribs, skull, and proximal femur (Jacofsky et al.).

The prevalence of metastatic bone disease is highest in breast and prostate cancers, with approximately 65%–75% of patients with advanced disease developing bone metastases. In addition, about 30%–40% of patients with advanced lung cancer and virtually all patients with multiple myeloma develop bone metastases (Lipton, 2004; Smith et al., 2005). Improved survival rates of patients with cancer have led to an increased incidence of metastatic bone disease and subsequent sequelae.

Pathophysiology

Metastasis of tumor cells involves a cascade of events, including detachment from the primary tumor site, invasion of the vasculature, migration and adherence to distant capillaries of the bone, extravasation, and proliferation. Once tumor cells have invaded the bone matrix, they produce growth factors that can directly or indirectly stimulate osteoclasts to degrade the bone. In response, the bone releases growth factors that stimulate tumor cell growth, which establishes a cycle of bone destruction and local tumor growth (Lipton, 2004).
lung, thyroid, kidney, and breast. Tumor cells responsible for the lesions cause increased bone breakdown or resorption, an osteoclastic action. Lesions occur with little reparative bone formation and appear as punched-out holes on radiographs. Osteolytic lesions are associated more often with pathologic fractures than osteoblastic lesions.

Osteoblastic (i.e., sclerotic) lesions cause increased bone formation around tumor cell deposits. Carcinomas, such as prostate and some breast cancers, signal the bone to overproduce osteoblasts, which results in rigid, inflexible bone formation. Stimulation of bone resorption also occurs near the sites of the lesions, but the new bone excess is deposited away from the sites of bone resorption. The result is reduced bone strength and increased risk for fractures and vertebral collapse (Lipton, 2004).

**Identification and Patient Assessment**

In patients with a known primary cancer, the development of bone pain is a hallmark sign of metastatic bone disease. Pain is the most common symptom associated with skeletal disease, and its onset is typically insidious in nature. About 75% of patients diagnosed with bone metastases complain of pain at presentation (Jacofsky et al., 2004). Patients with metastatic disease in weight-bearing bones may present with pain early in the course of disease, whereas those with metastases in bones such as the ribs or sternum may remain asymptomatic until late in the disease, often when a pathologic fracture occurs (Jacofsky et al.). Pain usually is constant, gradually progressive in intensity, and exacerbated by different positions, movements, or changes in body posture (Berger & Koprowski, 1999).

In addition to a comprehensive pain assessment, patients should be assessed for symptoms associated with spinal cord compression, bone fractures, and hypercalcemia, which are potential complications of bone metastases.

**Spinal Cord Compression**

Spinal cord compression (SCC) is defined as the compressive indentation, displacement, or encasement of the spinal cord's thecal sac by metastatic or locally advanced cancer (Fuller, Heiss, & Oldfield, 1997). Evaluation for SCC should include a careful history, physical and neurologic examinations, and radiologic evaluation. Patients should be assessed for back pain and neurologic impairment, including peripheral paresthesias and loss of bladder or bowel control. Magnetic resonance imaging (MRI) is the preferred diagnostic tool used to evaluate SCC. In geographic areas or facilities without MRI, computed tomography (CT) testing may be used. Radiographs also can assist in SCC evaluation associated with bony involvement of the spine or compression fracture. Radiographs identify bony abnormalities in patients with epidural cord compression and determine the presence and location of epidural metastases of patients with back pain (Fuller et al.).

**Hypercalcemia of Malignancy**

Hypercalcemia of malignancy in patients with bone metastases once was attributed to resorption of calcium via the osteolytic process. Healthcare professionals now recognize that hypercalcemia, even in patients with extensive osteolysis, is mediated by factors released by malignant cells that resorb calcium from bone (Warrell, 1997). With the advent of IV bisphosphonates for the treatment of metastatic bone disease, the incidence of hypercalcemia has significantly decreased.

**Diagnostic Workup**

The scan used to identify bone metastases is highly dependent on the known primary carcinoma, which helps determine if the lesion is more likely to be osteolytic or osteoblastic. For example, initial evaluation of bone pain in a patient diagnosed with lung cancer or multiple myeloma should include a radiograph of the affected area. A radiograph can quickly rule out fracture and is superior to a bone scan for the identification of a lytic lesion. Conversely, bone scans are used to identify osteoblastic lesions commonly seen in patients with prostate or breast cancers (Murthy, Rao, & Friedman, 2000).

**Radiographs**

Erosion of the cortical bone surface must be present for bone metastases to be visible by x-ray. Lesions usually appear in the medullary cavity and spread, first destroying the medullary bone and then involving the cortex. Standard x-rays are relatively insensitive for the detection of early or small metastatic lesions, and up to 40% of metastases may be missed (Jacofsky et al., 2004). For consistent detection of osteolytic lesions, 30%-50% of mineral loss or a lesion greater than 1.5 cm typically must be present (Jacofsky et al.). Osteoblastic lesions are more difficult to assess radiographically because they lack bone degradation. Conventional radiography also may be employed to assist in the interpretation of abnormal findings on technetium bone scans (Jacofsky et al.). Radiograph appearance may be purely lytic, plastic, or mixed. Figure 1 illustrates osteolytic metastases.

Bone lesions typically appear as dark spots on an x-ray. Osteolytic lesions appear as punched-out holes as a result of increased breakdown in damaged areas (Peh & Muttarak, 2005). It can be difficult, however, to distinguish between metastases and benign lesions (e.g., osteoarthritis, Schmorl nodes in the spine, bone islands, Paget disease, osteoporosis) on plain film; therefore, biopsy is recommended (Peh & Muttarak).

**Bone and Skeletal Survey**

Bone surveys are radiographs of the entire skeleton, typically performed on individuals with multiple myeloma. The primary goal of a bone survey is to identify osteolytic lesions and fractures. Assessment areas are the long bones of extremities, skull, pelvis, and, sometimes, spine.

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**Figure 1. Radiograph of Osteolytic Metastasis in the Pelvis**

Note. Photo reprinted courtesy of Rocky Mountain Cancer Centers.
Bone Scintigraphy

Radionuclide bone scanning (technetium-99m bone scintiscanning) is very useful in the workup for metastatic bone disease in patients with known or suspected cancer. The identification of bone lesions is dependent on osteoblastic activity and increased blood flow to involved areas, which generally occurs due to reparative processes in response to bone destruction. For this reason, bone scans are particularly sensitive in the diagnosis of osteoblastic bony metastases (Murthy et al., 2000), most notably prostate and breast cancer metastases.

The false-positive rate of bone scans is high because tracer uptake is not specific to metastatic bone disease (Jadvar, 2004; Roudier et al., 2003). Nonmalignant processes, such as osteoarthritis, enchondroma, infection, Paget disease, and stress fractures, also may cause tracer uptake. Biopsy confirmation is recommended, even in patients with known malignancy (Jacofsky et al., 2004).

False-negative bone scan results may occur when lesions are osteolytic, despite the presence of single or multiple bone metastases, because the lesions do not take up the radioisotope as readily as do osteoblastic lesions. In addition, bone scans cannot detect soft tissue or lymph node involvement, which is prevalent with metastatic spread (Jadvar, 2004). When combined with conventional radiographs, bone scans improve the diagnostic accuracy when detecting bone metastases and assessing the response to therapy (Peh & Muttarak, 2005).

Computed Tomography Scan

CT scans provide x-ray images that depict detailed cross sections of organs and bones in the body. The scanning machine takes the images as it rotates around the body and a computer combines the images into one picture, which allows the reader to identify areas of metastasis.

CT scans commonly are used to search for primary disease in the chest, abdomen, and pelvis; look for lymphadenopathy or metastatic disease in the lungs or liver; and evaluate suspected skeletal metastases following bone scintigraphy by characterizing the radiographic appearance of lesions (Jadvar, 2004). They also may be used to evaluate local sites of metastasis and occasionally are performed to provide osseous detail of a bony metastasis (Jacofsky et al., 2004). Osteolytic, osteoblastic, and mixed lesions are depicted well on CT scans (Peh & Muttarak, 2005), which are better at identifying bone metastases than MRIs because they clearly show the shape and exact location of the tumor (see Figure 2). In addition, they commonly are useful in guiding needle biopsies, particularly in vertebral lesions (Peh & Muttarak).

Magnetic Resonance Imaging

MRI uses radio waves in the presence of a strong magnetic field, instead of x-rays, to provide images of soft tissue and bone. Different tissues, including tumors, emit signals based on their chemical makeup. An image of body organs is displayed on a computer screen, illustrating areas with greater or lesser intensity.

MRI is valuable for evaluating back pain, especially for spinal cord or nerve root compression. Sensitivity and specificity for detecting cord compression are 93% and 97%, respectively (Jacofsky et al., 2004). Currently, MRI is used as the gold standard for evaluation of soft tissue masses and also is useful when a bone scan is negative but localized symptoms are present (Jacofsky et al.) (see Figure 3).

Positron Emission Tomography Scanning

Positron emission tomography (PET) with F-18 fluorodeoxyglucose (FDG) scanning detects cancer by observing FDG uptake; malignant tumors have an accelerated glycolytic rate and subsequently greater uptake of FDG as compared to healthy tissue (Malhotra & Berman, 2002). PET scans are a valuable tool for the detection of hypermetabolic tumors but can identify only those larger than 1 cm.

FDG-PET scans often are used to evaluate osteolytic lesions because they tend to have increased uptake of FDG. FDG-PET scans are superior to bone scans in the detection of purely osteolytic bone metastases (Malhotra & Berman, 2002). In contrast, FDG-PET scans tend to have lower sensitivity for osteoblastic bone metastases, which may be because of the acellular nature of blastic lesions. Full evaluation with a bone scan and FDG-PET may be indicated.

Treatment

Complications of bone metastases include neurologic impairment related to SCC, pathologic fracture, pain, and, occasionally, hypercalcemia of malignancy. With newer treatments available for bone metastases, overall survival and quality of life have improved. Specific treatments such as analgesics (e.g., steroids, narcotics), radiation therapy, hormone therapy, and IV bisphosphonate therapies have helped to improve pain related to bone metastases.

Palliative radiation therapy is the standard treatment for pain and prevention of morbidity and disease progression related to bone disease (Haplin, Bendok, & Liu, 2004). Hormone therapy is limited to certain responsive tumors, such as breast cancer or prostate cancer, but does not effectively address the issue of pain (Haplin et al.). Surgical stabilization to prevent pathologic fracture can immediately improve pain, mobility, and independence (Jacofsky et al., 2004). Hypercalcemia is managed with saline hydration, diuresis, and administration of bisphosphonates. Nonpharmacologic modalities such as massage, acupuncture, and relaxation may complement pharmacologic approaches in controlling pain.

Biphosphonates have an analgesic effect (Nelson & Smith, 2004) and have been shown to reduce morbidity associated with osteolytic skeletal metastases (Pickering & Mansi, 2002). Painful exposure of bone in the mandible and maxilla of patients receiving the bisphosphonates...
Case Study Follow-Up

In addition to newly diagnosed bone metastases, Mr. P was at increased risk for skeletal fracture because of his previous cancer therapy. Androgen-deprivation therapy significantly decreases bone mineral density. Patients with metastatic prostate cancer undergoing gonadotropin-releasing hormone and antiandrogen therapy experience bone mineral density decreases of 2%–7% during the first year of therapy (Diamond, Campbell, Bryant, & Lynch, 1998; Diamond et al., 2001). Furthermore, bone mineral density tends to progressively decrease, and the risk of fracture increases with longer duration of androgen-deprivation therapy (Kiratli, Srinivas, Perkash, & Terris, 2001; Oefelein et al., 2001). The femoral neck bone mineral density can decrease by as much as 2%–10% one year after surgical castration in patients with nonmetastatic prostate cancer (Daniell et al., 2000; Eriksson, Eriksson, Stege, & Carlstrom, 1995). Regular monitoring of bone health, especially in men, with a bone density test is warranted.

Mr. P’s bone pain progressively improved after initiation of the IV bisphosphonate. He continues to require oral analgesics on an as-needed basis, and his quality of life currently is well maintained. He understands that he should contact the clinic immediately if he develops new or worsening bone pain, so that further diagnostic workup can be initiated.

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References


