

# Bone Metastasis: Concise Overview

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A review of diagnostic tools for bone metastasis and therapeutic options for pain and symptom relief.

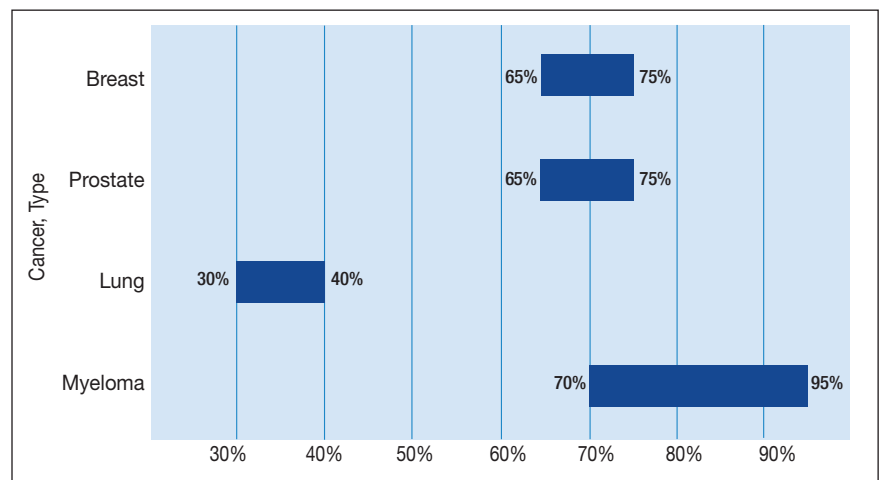
**B**one metastasis is a relatively common complication of cancer, often developing as they advance, especially in prostate cancer and breast cancer. Bone metastasis can profoundly affect patients' daily activities and quality of life (QOL) due to severe pain and associated major complications. Prompt palliative therapy is required for symptomatic pain relief and prevention of the devastating complications of bone metastasis.

## EPIDEMIOLOGY

Bone is the most common and preferred site for metastatic involvement of cancer. Advanced cancers frequently develop metastases to the bone during the later phases of cancer progression. At least 100,000 patients develop bone metastases every year, although the exact number of bone metastases is not known.<sup>1</sup> Multiple myeloma (MM), breast cancer, and prostate cancer are responsible for up to 70% of bone metastases cases.<sup>2</sup> Gastrointestinal cancers contribute least to bone metastases: < 15% of all cases.<sup>2</sup>

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**Figure 1.** The Incidence (Range) of Bone Metastases According to Primary Cancer<sup>2</sup>



The prognosis of bone metastases is generally poor, although it partly depends on the primary site of the original cancer and on the presence of any additional metastases to visceral organs. For example, it is known that survival times are longer for patients with primary prostate or breast cancer than for patients with lung cancer primary tumors.<sup>3,4</sup>

Prostate and breast cancers are the most common primary cancers of bone metastases. At postmortem studies, patients who died of prostate cancer or breast cancer revealed evidence of bone metastases in up to 75% of cases (Figure 1). Regardless of their survival expectancy, however, most

patients with bone metastasis need immediate medical attention and active palliative therapy to prevent devastating complications related to bone metastasis, such as pathologic bone fractures and severe bone pain.

## CLINICAL FEATURES

The most common clinical symptom of bone metastasis is bone pain, which is usually localized and progresses slowly. Patients may experience worsening of pain at night or while ambulating, depending on the site of bone metastasis. Pain may radiate to the lower extremities; however, radiating pain may not always correlate with nerve impingement.

**Table 1. Common Symptoms in Breast Cancer<sup>2</sup>**

| Symptom       | Incidence |
|---------------|-----------|
| Pain          | Up to 75% |
| Hypercalcemia | Up to 15% |
| Bone fracture | Up to 20% |

Other symptoms related to bone metastases include hypercalcemia, spinal cord compression, immobility, vertebral fractures, and fractures of the long bones (Table 1). The most common site of bone metastases is the axial skeleton, with the lumbar spine being the most frequent site of bone metastasis as a single site (Figure 2).<sup>5,6</sup>

### Multiple Myeloma

Multiple myeloma is the second most common hematologic malignancy and is caused by an abnormal accumulation of clonal plasma cells in the bone marrow. Characteristic clinical manifestations include bony destruction and related features of bone pain, anemia (80% of cases), hypocalcemia, and renal dysfunction. Pathologic

fractures, renal failure, or hyper-viscosity syndrome often develops. More than 20,000 new patients are diagnosed with MM and about 11,000 patients in the U.S. die of MM every year. Multiple myeloma is twice as likely to develop in men as it is in women. A large number of MM cases are under the care of VAMCs (about 10%-12% of all MM cases).<sup>7,8</sup>

Abnormal laboratory tests show an elevated total protein level in the blood and/or urine (Bence Jones proteinuria). Serum electrophoresis detects M-protein in about 80% to 90% of patients. Patients may also present with renal failure. The differential diagnosis includes other malignancies, such as metastatic carcinoma, lymphoma, leukemia, and monoclonal gammopathy.

### Pathophysiology

Normal bone tissue is made up of 2 different types of cells: osteoblasts and osteoclasts. New bone is constantly being produced while old bone is broken down. When tumor cells invade bone, the cancer cells produce 1 of 2 distinct substances; as a result, either osteoclasts or osteoblasts are stimulated, depending on

tumor type metastasized to the bone. The activated osteoclasts then dissolve the bone, weakening the bone (osteolytic phenomenon), and the osteoblasts stimulate bone formation, hardening the bone (osteoblastic or sclerotic process).

### DIAGNOSIS AND EVALUATION

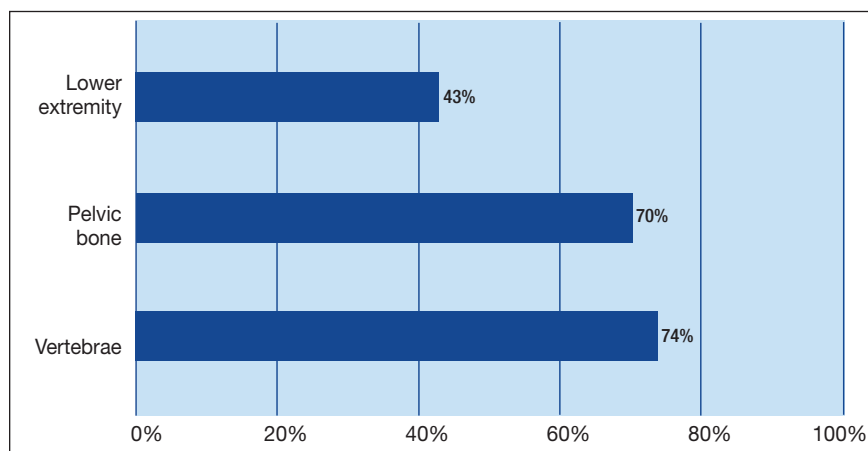
The most important first step in evaluating bone metastasis in a patient is to take a thorough, careful medical history and perform a physical examination. The examination not only helps locate suspected sites of bone metastases, but also helps determine necessary diagnostic studies.

The radiographic appearance of bone metastasis can be classified into 4 groups: osteolytic, osteoblastic, osteoporotic, and mixed. Imaging characteristics of osteolytic lesions include the destruction/thinning of bone, whereas osteoblastic (osteosclerotic) lesions appear with excess deposition of new bones. In contrast to malignant osteolytic lesions, osteoporotic lesions look like faded bone without cortical destruction or increased density.

Although 1 type of lesion generally predominates, osteolytic lesions are most common in renal cell cancers and MM. Bone metastases in prostate cancers are typically characterized by an osteoblastic picture due to excess bone deposition.

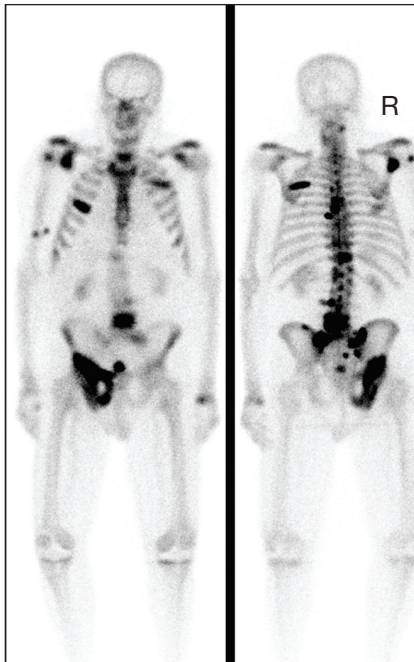
The main choice of imaging study for screening suspected bone metastases is usually the bone scan (Figure 3). Plain radiographs are not useful in the early detection of bone metastases, because bone lesions do not show up on plain films until 30% to 50% of the bone mineral is lost.<sup>5,9</sup> Although most metastatic bone lesions represent a mixture of osteoblastic and -lytic processes, metastatic lesions of lung cancer and breast cancer are predominantly osteolytic

**Figure 2. Sites of Frequent Bone Metastases**



Source: Nakamoto Y, Osman M, Wahl RL. *Clin Nucl Med*. 2003;28(4):302-307.

**Figure 3.** Bone Scan



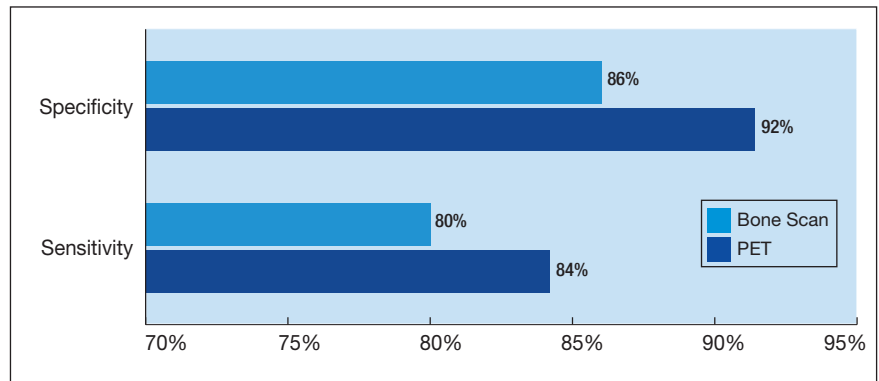
Widespread abnormal uptake is noted throughout the lumbar spine and pelvis. The pattern is compatible with osteoblastic metastatic disease.

in contrast to mainly osteoblastic lesions of prostate cancer metastases.<sup>10</sup>

The osteoblastic process of bone metastases is best demonstrated on a bone scan; however, a positive bone scan does not necessarily indicate bone metastases, because it is not highly specific of metastatic disease. Several benign bone lesions (such as osteoarthritis, traumatic injury, and Paget disease) also show positive readings. Magnetic resonance imaging (MRI) is not useful in screening for bone metastases, but it is better in assessing bone metastases compared with a bone scan, because it is more sensitive, especially for spinal lesions. The reported sensitivity of MRI is 91% to 100%, whereas bone scan sensitivity is only 62% to 85%.<sup>11,12</sup>

Even though the bone scan has been assumed to be the best imaging

**Figure 4.** Median Sensitivity vs Specificity (PET vs Bone Scan)<sup>19</sup>



Abbreviation: PET, positron emission tomography.

study for bone metastases, positron emission tomography (PET) scans can be more useful in detecting osteolytic bone metastases, as they can light up areas of increased metabolic activity. Positron emission tomography scans, however, are less sensitive for osteoblastic metastases. An additional advantage of PET scans is that they can be used for whole-body scanning/surveillance to rule out visceral involvement.

Published studies indicate that bone scans better detect sclerotic bone metastases and PET scans are superior in revealing osteolytic metastases.<sup>13-15</sup> Furthermore, in contrast to bone scans, PET scans can identify additional lesions in addition to bone lesion. According to recent reports, PET provides higher sensitivity and specificity in demonstrating lytic and sclerotic metastases compared with that of the bone scan.<sup>16</sup>

### Breast Cancer

The role of PET for breast cancer is controversial. A study by Lonneux and colleagues found that PET is highly sensitive in confirming distant metastasis from breast cancer, whereas researchers reported a similar sensitivity but higher specificity.<sup>17</sup> Ohta and colleagues reported

that PET and bone scan had identical sensitivity (77.7%), but PET was more specific than the bone scan (97.6% vs 80.9%, respectively).<sup>14</sup> The study conclusion by Cook and colleagues was that PET is superior to bone scan in the detection of metastatic osteolytic bone lesions from breast cancer, whereas osteoblastic metastatic bone lesions from breast cancer are less likely to be demonstrated on a PET scan.<sup>18</sup>

Houssami and Costelloe conducted a systematic review of 16 reported studies that comparatively tested the accuracy of imaging modalities for bone metastases in breast cancer.<sup>19</sup> Sensitivity was generally similar between PET and bone scans in most studies reviewed. Four studies reported similar sensitivity but higher specificity for PET; the median specificity for PET and bone scan was 92% vs 85.5%, respectively (Figure 4).

### Prostate Cancer

Prostate cancer is now established as the “classic” cancer for false-negative results on PET. Positron emission tomography does not perform well in the identification of osteoblastic skeletal metastases from prostate cancer. Yeh and colleagues reported

only 18% positivity with PET.<sup>20</sup> Interestingly, however, progressive metastatic prostate cancer showed a higher yield of 77% sensitivity with PET, perhaps because active osseous disease can be better picked up by PET scans.<sup>21</sup>

### Lung Cancer

For non-small cell lung cancer, both bone scan and PET showed a similar sensitivity for bone metastases detection, but the PET scan was more specific than the bone scan. Lung cancer often metastasizes to bone: up to 36% of patients at postmortem study. Lung cancer with bone metastases has a poor prognosis with median survival time typically measured in months. Most patients with bone metastases develop complications, such as severe pain, bone fracture, hypercalcemia, and spinal cord compression. Bone-targeted therapies play a greater role in the management of lung cancer patients, aiming for delaying disease progression and preserving QOL.<sup>22,23</sup>

## THERAPEUTIC STRATEGY AND MANAGEMENT

Major morbidities associated with bone metastases include severe pain, hypercalcemia, bone fractures, spinal compression fractures, and cord or nerve root compression. This section reviews appropriate management techniques reported in the literature, particularly external beam radiation therapy.

### Radiation Therapy

Pain is the most serious complication of bone metastases. Radiation therapy has been established as standard therapy and an effective pain palliation modality. Up to 80% of patients achieve partial pain relief, and > 33% of patients experience complete pain relief after radiation (Figure 5).<sup>24,25</sup>

Although a 3,000 cGy given over a 2-week period has been commonly used, a standard dose-fraction radiation treatment regimen has not been established.

Several randomized studies have been performed in the U.S. and Europe to evaluate various dose-fraction schedules of external beam radiation therapy. According to the Radiation Therapy Oncology Group (RTOG) study reported by Tong and colleagues, the low-dose, short-course radiotherapy was as effective as various prolonged high-dose multifraction radiation regimens.<sup>24</sup>

The RTOG study was a randomized clinical study comparing various radiation schedules; 1,500 cGy in 1 week; vs 2,000 cGy in 1 week; vs 2,500 cGy in 1 week; vs 3,000 cGy in 2 weeks; or 4,050 cGy in 3 weeks. The conclusion was that local radiotherapy was an effective therapy for symptomatic and palliative therapy of bone metastases. Furthermore, low-dose radiotherapy was as good as various higher dose protracted courses of radiation treatments in terms of overall response rates (ORRs).<sup>24</sup>

Nearly 96% of patients eventually reported minimal pain relief to their palliative course of radiotherapy and experienced at least some pain relief within 4 weeks of radiation therapy. Complete pain relief was attained in 54% of patients regardless of the radiation dose-fraction schedules used. The median duration of complete pain response was about 12 weeks; > 70% of patients did not experience relapse of pain.<sup>26</sup>

Hartsell and colleagues investigated the efficacy of 800 cGy in a single fraction compared with 3,000 cGy in 10 fractions as part of a phase 3 randomized study of symptomatic therapy for pain palliation.<sup>27</sup> The results showed 66% ORRs with similar complete and partial response rates (RRs)

for both radiation groups. The complete RRs were 15% in the 800 cGy single-fraction arm vs 18% in the 3,000 cGy therapy arm, whereas partial RRs were 50% and 48% in the single vs the 3,000 cGy arms, respectively. However, there was a higher rate of retreatment for patients treated with the 800 cGy single-fraction radiotherapy. The 800 cGy single-fraction radiotherapy program seems rather popular in Canada and in European countries but is currently not widely used in the U.S.

### Surgical Therapy

The surgical indications for managing bone metastases can vary, depending on disease location, surgeon's preference, and patient's overall disease status and related morbidities. Pain relief of fractured long bones (humerus, femur, or tibia) is crucial. The main goals of surgical intervention in these cases include the restoration of stability and functional mobility, pain control, and improving QOL. Weight-bearing bones (humerus/tibia) are especially at risk of bone fracture, and compromise of these is an indication of surgery. Postoperative external-beam radiation is recommended in most cases to eradicate residual microscopic disease or tumor progression.<sup>28</sup>

### Radiopharmaceutical Therapy

Bone-seeking radiopharmaceuticals are effective and have been widely used for pain palliation. The usual indications for radiopharmaceutical therapy include diffuse osteoblastic skeletal metastases demonstrated on bone scan, painful bone metastases not responding well to analgesics, and hormone-refractory metastatic prostate cancer. At present, strontium-89 (Sr-89), samarium-153 (Sm-153), phosphorus-32 (P-32), and radium 223 dichloride are radionuclides

**Table 2. Radiopharmaceutical Agents**

| Agent         | Half-life (d) | Pain Relief (%)    |
|---------------|---------------|--------------------|
| Strontium-89  | 50            | 60-92              |
| Samarium-153  | 2             | 60-80              |
| Phosphorus-32 | 14            | 85 (breast cancer) |
| Radium-223    | 11            | 60-70              |

currently accepted as attractive therapeutic modalities for pain management (Table 2).

The clinical response is not immediate, and the average time to response is 1 to 2 weeks, but sometimes much longer. The main adverse reaction of systemic radiopharmaceutical therapy is myelotoxicity, such as thrombocytopenia and/or leukopenia. Occasionally, a so-called flare phenomenon of a transient pain increase may develop as well.<sup>29,30</sup>

### Systemic Pharmacotherapy

Bisphosphonates are drugs commonly used to treat bone metastases. The benefits of bisphosphonate therapy are bone pain relief, the reduction of bone destruction, and the prevention of hypercalcemia and bone fractures. Bisphosphonates are typically more effective in osteolytic metastases and easily bind to bone,

inhibiting bone resorption and increasing mineralization.<sup>31,32</sup> Also, recent clinical studies suggest that bisphosphonates may inhibit tumor progression of bone metastases.

Zoledronic acid is currently one of the most potent bisphosphonates and is effective in most types of metastatic bone lesions.<sup>33</sup> Denosumab, another drug, diminishes osteoclast activity, leading to decreased bone resorption and increased bone mass.<sup>34,35</sup> Denosumab is useful in preventing complications as a result of bone metastases from solid tumors and has been recently approved by the FDA for treatment of postmenopausal osteoporosis and the prevention of skeletal-related events (SREs) in cancer patients with bone metastases.

### Adverse Effects

Zoledronate and bisphosphonates in general are not recommended for patients with kidney disease, including hypocalcaemia and severe renal impairment. A rare but well-known complication of bisphosphonate administration is osteonecrosis of the jaw, which is somewhat more common in MM, especially after dental extractions. General nonspecific adverse effects include fatigue, anemia, muscle aches, fever, and/or edema in the feet or legs. Flulike symptoms and generalized bone discomfort can also be seen shortly after the first infusion (Table 3).

### Breast Cancer

Bisphosphonates have been shown to effectively prevent SREs in breast cancer patients with bone metastases.<sup>36</sup> For example, zoledronic acid is the most effective bisphosphonate and has been demonstrated to significantly delay the time to development of a first SRE, reducing the overall SRE rate by 43%.<sup>37</sup>

### Lung Cancer

According to Rosen and colleagues, lung cancer patients with bone metastases who received zoledronic acid (4 mg every 3 weeks) experienced a 9% reduction in SREs, a relative delay in median time to a first SRE, and a significantly reduced incidence of SREs.<sup>37</sup>

### Prostate Cancer

Zoledronic acid is the only bisphosphonate that proved effective in the treatment of prostate cancer patients with bone metastases. Zoledronic acid significantly reduced the risk of SREs (36%) and bone pain as well as delayed the median time to first SRE (nearly 6 months).<sup>38,39</sup>

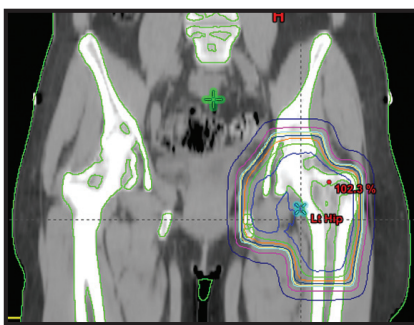
### Multiple Myeloma

Bisphosphonates are recommended for bone metastases to prevent new bone lesions. Studies have shown pamidronate (90 mg every 4 weeks) resulted in a 41% reduction in SREs at 9 months and a 25% reduction at 21 months.<sup>40,41</sup> Oral clodronate, another agent, also significantly reduced SREs and pain in patients with MM.<sup>42</sup>

### CONCLUSION

Metastatic cancer with bone metastases occurs as cancer advances and spreads to the bone from the primary site of the original solid cancer. Nearly 70% of patients with prostate and breast cancers and about 30% to 40% of patients with

**Figure 5. Radiation Therapy Port Arrangement**





**Table 3. Commonly Used Systemic Therapeutic Agents for Bone Metastasis**

| Dosage <sup>a</sup>                           | Therapeutic Use                          | Adverse Effects  |
|---|--|--|
| Zoledronic acid<br>4 mg IV every 3 to 4 weeks | MM<br>Bone metastasis                    | Renal toxicity, ONJ, anemia, hypocalcemia, fever, nausea, fatigue  |
| Pamidronate<br>90 mg IV every 4 weeks         | Bone metastasis<br>MM                    | Fatigue, weakness<br>fever, dyspnea  |
| Denosumab<br>120 mg SC every<br>4 weeks       | Prevention of<br>SREs<br>Bone metastasis | Infection (GUT, URT),<br>nausea, diarrhea,<br>weakness, ONJ (rare),<br>hypophosphatemia,<br>hypocalcemia |

<sup>a</sup>Warning: The exact dosage varies on disease entities and clinical situation, and health care professionals should consult with authorized sources before prescribing to patients.

Abbreviations: GUT, genitourinary tract; MM, multiple myeloma; ONJ, osteonecrosis of jaw; SC, subcutaneous; SREs, skeletal-related events; URT, upper respiratory tract.

lung cancer develop bone metastases. In addition, up to 95% of MMs involve bone. The most frequent and important symptom of bone metastasis is pain. In addition, bone metastasis causes bone fractures, hypercalcemia, and spinal cord and nerve compression. Imaging studies, such as bone scans and PET studies, are useful tools in diagnosing bone metastases.

Therapeutic management of bone metastases is expanding and rapidly evolving. For better therapy outcomes, treatment should be both individualized and coordinated among the care team, including a medical oncologist, radiation oncologist, surgeon, and radiologist. Available therapeutic modalities include radiation therapy, radiopharmaceutical therapy, surgery, and systemic pharmacotherapy (zoledronate, pamidronate, and denosumab). ●

#### Author disclosures

The authors report no actual or potential conflicts of interest with regard to this article.

#### Disclaimer

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