Management of metastatic bone disease

Metastatic bone disease is a common cause of pain and disability for patients with advanced cancer. Early detection and appropriate management can limit pain, reduce disability and prevent complications such as hypercalcaemia, pathological fracture and spinal cord compression. In specific cases surgical resection of an isolated bone metastasis may improve survival. This article provides an evidence-based overview of the investigation and management of patients with metastatic bone disease.

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The skeleton is the third most frequent site of metastatic spread after the lung and liver. Epidemiological studies have shown that of 1.2 million new cancers detected per year, approximately 300,000 will develop a bone metastasis.\(^1,2\)
Bone metastases occur in up to 70% of prostate and breast cancer patients during the course of their disease, and in up to 40% of lung, renal cell and thyroid cancer patients.\(^3\)
The spine is the most common site involved, followed by the pelvis, ribs, skull and long bones.\(^2\) Although the treatment of patients with metastatic bone disease is usually palliative, the prognosis can be extremely variable depending on the site of the primary tumour (Box 1).

**Pathophysiology**

Bone is continuously remodelled by osteoclasts (resorption) and osteoblasts (formation). Metastases upset this balance by producing cytokines and growth fractures that promote tumour cell growth and bone resorption.\(^4\) This predisposes to hypercalcaemia and pathological fracture. Pain is thought to arise from stimulation of ionic channels, tumour induced osteolytic mechanisms, production of growth factors or direct nerve infiltration.\(^5\)

How should bone pain be investigated in cancer patients?

All cancer patients developing skeletal pain should be investigated for the presence of bone metastases. Investigation should take the form of blood tests, urinalysis, imaging and consideration of tissue biopsy.

**Blood and urine analysis**

Where the tumour is not known, full blood counts, prostate specific antigen, serum protein electrophoresis and urinalysis for free immunoglobulin light chains (Bence Jones protein) should be requested. Tumour markers
Oncology may have a role in specific cases. Inflammatory markers should be sought to exclude infection.

In the presence of known skeletal metastases, biochemical tests may demonstrate raised serum alkaline phosphatase and calcium concentrations, indicative of high osteoblastic activity from rapid bone remodelling. When detected early, bisphosphonate therapy is an effective treatment for metastatic hypercalcaemia.

**Box 1: Predicted five year survival rates for common tumours metastasising to bone.**¹⁰

<table>
<thead>
<tr>
<th>Tumour</th>
<th>Five year survival</th>
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<tbody>
<tr>
<td>Metastatic prostate cancer</td>
<td>33%</td>
</tr>
<tr>
<td>Metastatic breast cancer</td>
<td>22%</td>
</tr>
<tr>
<td>Metastatic thyroid cancer</td>
<td>44% if well differentiated (survival less than one year if anaplastic type)</td>
</tr>
<tr>
<td>Metastatic lung cancer</td>
<td>2%</td>
</tr>
<tr>
<td>Metastatic renal cancer</td>
<td>25%</td>
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</table>

Imaging

Plain radiographs have an important role in the detection of bone metastases and, particularly, evaluation of fracture risk. However the sensitivity (46%) and specificity (32%)⁷ of plain radiographs are low, as >50% of the bone mass needs to be lost before lesions become visible on x-ray.

Patients with bone pain and equivocal plain radiographs should be investigated further with technetium-99 (Tc99) radionucleotide bone scans. The Tc99 is administered intravenously and absorbed onto hydroxyapatite crystals present in bone matrix. Bone scans have three phases—immediate, early and delayed. Immediate and early phases reflect perfusion and soft tissue hyperaemia. The delayed images reflect skeletal activity with “hot spots” indicative of high osteoblastic activity (Box 2). The sensitivity and specificity of bone scans in combination with plain radiographs for detection of skeletal metastases is 63% and 64% respectively.⁸ Bone scans are most useful in screening for the presence of skeletal metastases, however myeloma and lytic metastases with minimal osteoblastic activity will not be detected.

Magnetic resonance imaging (MRI) has the highest sensitivity (100%) and specificity (88%) for the detection of bone metastases.⁹ MRI is extremely sensitive to bone marrow replacement by abnormal tissue, as the high contrast between fat (marrow) and water (tumour) demonstrates metastatic lesions at an early stage before the cortex is affected. The use of whole body MRI in screening for the early detection of bone metastases is becoming increasingly popular.

**Tissue biopsy**

Biopsy of bone metastases is indicated in certain clinical scenarios:

- To confirm a lesion is metastatic where there is suspicion of an alternative diagnosis (eg. primary bone tumour, infection)
- To diagnose an unknown primary tumour
- To confirm diagnosis of an isolated metastasis where curative resection may improve survival
- Obtaining tissue to assess response to chemotherapeutic, hormonal or immunohistochemical agents.

**Management of bone metastases**

Management is multidisciplinary with involvement of an oncologist, palliative care physician, orthopaedic surgeon and radiotherapist. When the primary tumour is unknown, the patient should be investigated for the cause. When the primary is known, the patient should be considered for appropriate systemic therapy for the underlying cancer, usually hormonal therapy or chemotherapy, and consideration should be given as to whether curative resection would increase survival and limit disability. This may be true for isolated bone metastases in patients with a good prognosis and at least three years interval between detection of primary lesion and development of metastasis.¹⁰ Tumours with a good prognosis include renal cell, well-differentiated thyroid, prostate, colorectal and breast cancer when sensitive to adjuvant therapy. The patient should be
given appropriate analgesics and considered for specific treatments for the bone metastases—bisphosphonate therapy, radiotherapy, radioisotopes or prophylactic surgery.11

**Bone pain**

**Analgesics**
Patients should receive non-opioid, opioid and/or adjuvant analgesics titrated to their requirements as per the WHO analgesic ladder. A Cochrane systematic review showed non-steroidal anti-inflammatory drugs (NSAIDS) were effective in the treatment of cancer pain, particularly when combined with an opioid.12

**Bisphosphonates**
Bisphosphonates inhibit osteoclast-mediated bone resorption and provide a systemic treatment for metastatic bone pain. They are indicated as second-line agents in conjunction with analgesics and radiotherapy, as analgesic effects may take up to six months to become evident.13 In addition to pain relief, good evidence exists to show bisphosphonates reduce the need for orthopaedic surgery, palliative radiotherapy, hypercalcaemia and pathological fractures (collectively known as “skeletal related events”), although they have no effect on the risk of spinal cord compression.14

Intravenous bisphosphonates such as pamidronate (Aredia) are more efficacious than oral agents at reducing skeletal related events.13 Newer third generation agents, such as zolodronate (Zometa) and ibandronate (Boniva), are the subject of clinical trials and gaining increasing use.

**Radiotherapy**
External beam radiotherapy can be extremely effective in relieving pain for patients with bone metastases. Radiation damages the DNA of rapidly dividing cells, specifically targeting tumour cells and inhibiting cell division. Palliative radiotherapy uses higher radiation doses than conventional radiotherapy as rapid symptom relief is prioritised over damage to healthy surrounding tissue. Palliative radiotherapy may be administered as a single fraction (usually 8 Gy) or as part of multiple fractions (20-30 Gy in 5-10 fractions).15 Pain reduction can be expected in 60% of patients with both treatment strategies, with complete pain relief seen in about one third of patients.16 Secondary reduction in opioid requirements can have significant improvements on quality of life for patients on near-toxic opioid doses. The single fraction strategy places less pressure on resources and requires only one hospital attendance, however re-treatment (21.5% single versus 7.4% multiple) and pathological fracture (3% single versus 1.6% multiple) rates are higher than with the multiple fraction protocol.16

When multiple painful metastases are present on one side of the diaphragm half body irradiation (6-8 Gy in a single fraction) should be considered, however risk of side effects particularly myelosuppression are higher. Overall side effects from radiotherapy are mild and short-lived. 30% of patients develop an acute exacerbation of pain in the first 48 hours following treatment for which dexamethasone is effective.17

**Radioisotopes**
When radiotherapy is not appropriate, for example previously irradiated sites or presence of multiple metastases on both sides of the diaphragm, radioisotopes may be used.18 The most frequently used radioisotopes are phosphorus-32, estronium-89 and samarium-153. They are up-taken by bone in

**Box 2: Clinical indications for bone scans**

- Assessment of metastatic bone disease
- Diagnostic assessment for occult bone pain
- Infection: Immediate and early phases are hot in cellulitis; all three phases are hot in osteomyelitis
- Trauma: Occult fractures eg. stress fractures, hip fractures
- Tumour: primary tumours eg. osteoid osteoma, osteoblastoma, especially of spinal origin
- Arthritis: extent and severity especially inflammatory arthopathies eg. ankylosing spondylitis
- Assessment of metabolic bone disease activity eg. Paget’s disease
areas of rapid bone turnover and provide pain relief for between one to six months, however patients need to be monitored for the risks of leukopenia and thrombocytopenia. Additional treatments for bone pain

Chemotherapy, hormonal treatments and prophylactic surgery may all be effective at reducing pain. Radiofrequency ablation, which involves applying high frequency alternating current to a tumour, may provide fast effective pain relief in specific cases. It should not be used near the spine.

Box 3: Mirel’s Score for assessment of pathological fracture risk. Four variables are scored between 1 to 3 giving a total score out of 12. A score of ≥8 predicts high fracture risk and warrants referral.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Risk score</th>
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<tbody>
<tr>
<td>Site</td>
<td>1</td>
</tr>
<tr>
<td>Site</td>
<td>Upper limb</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild</td>
</tr>
<tr>
<td>Lesion type</td>
<td>Blastic</td>
</tr>
<tr>
<td>Size relative to bone diameter</td>
<td>&lt; 1/3</td>
</tr>
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</table>

Figure 1. Anteroposterior pelvic radiograph of a 48 year old lady with breast cancer and painful metastatic deposits in both proximal femur and pelvis. The patient rose from a chair and sustained a pathological fracture of the left proximal femur. The pre-fracture Mirel’s score was 10. Early referral for surgery may have prevented this injury.

Figure 2. Anteroposterior pelvic radiograph of a 65 year old man with lung cancer and painful metastatic deposit (white arrow) in left proximal femur. Endosteal scalloping from cortical destruction can be seen.
Pathological fracture

Pathological fractures cause significant pain and disability for patients and are often a terminal event (figure 1). The Mirel’s classification provides a scoring system to predict risk of pathological fracture, thereby providing a means of prevention. A score of ≤7 predicts low risk. A score of ≥8 predicts high risk and warrants referral to an orthopaedic surgeon for consideration of prophylactic stabilisation.

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References


Spinal cord compression

The spine is the most common site for metastatic bone disease. Vertebral metastasis enlargement causes dural compression with secondary irreversible ischaemic damage to the spinal cord. Patients typically present insidiously with new or worsening back pain and may describe “shooting pins and needles-like pain” down the legs from nerve root compression. These early symptoms should prompt further investigation with MRI, as progression to spinal cord compression results in weak legs, paralysis, urinary and faecal incontinence and permanent disability, by which time the patient may never walk again. Spinal cord compression is an emergency and requires high dose dexamethasone (4mg four times a day) followed by referral to a spinal surgeon or radiotherapist for surgical decompression or radiotherapy.