Management of skeletal metastases

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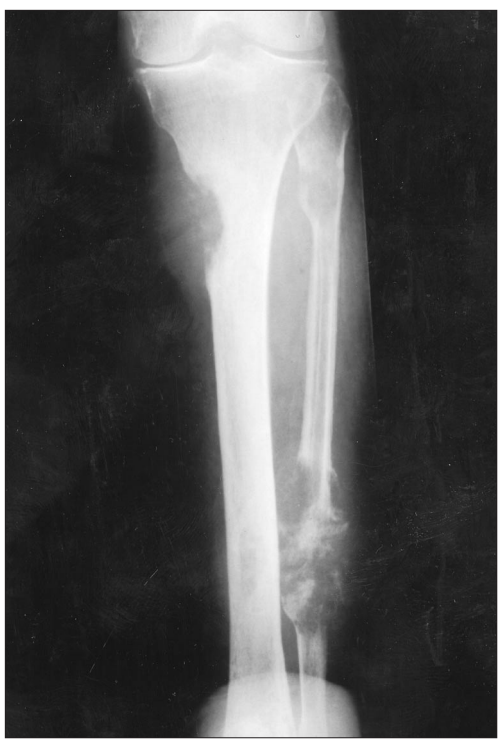
Bone is a frequent site of tumour metastasis and is the third most common site of metastatic carcinoma. With advances in the use of immunotherapy, hormonal manipulation, chemotherapy and radiation for the palliation of patients with metastatic bone disease, significant improvements in survival, wellbeing and overall quality of life have been achieved.

Bone is the third most common site for metastatic carcinoma after the lung and liver (Athanasou, 2001). Improvements in diagnosis and the use of adjuvant/hormonal therapy have increased 5-year survival over the past three decades by 20% for breast cancer and 30% for prostate cancer (Papagelopoulos et al, 2002). Bone metastases are the initial presenting feature of cancer in only 3% of patients; however, bone involvement was evident in autopsy in up to 85% of patients who had died of cancer of the lung, breast or prostate (Papagelopoulos et al, 2002).

Figure 1. Uterine metastatic bone disease of the tibia and fibula.



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Bone is a well-vascularized tissue, and tumour cells reach the bone via the bloodstream where bone resorption appears to be required for the establishment of a tumour metastasis. Tumour cells may secrete humoral factors that stimulate osteoclast activity, promote angiogenesis and increase osteoblastic activity.

Most metastases involve the spine, pelvis and long bones (*Figure 1*); however, one in 10 people with bone metastases may develop a pathological fracture requiring fixation. Metastatic disease of the spine, ribs and pelvis can often be managed effectively with radiotherapy.

With advances in the use of immunotherapy, hormonal manipulation, chemotherapy and radiation for the palliation of patients with metastatic bone disease, significant improvements in survival, wellbeing and overall quality of life have been achieved. Currently, 50% of patients with carcinoma and 85% of women with breast cancer will be alive 5 years following diagnosis (Harrington, 1995).

CLINICAL FEATURES

Pain is the most frequent clinical symptom of metastatic bone disease. The exact cause of the pain remains unclear. Several theories have been postulated:

- Stimulation of nerve endings in the endosteum as a result of the release of chemical agents from necrotic bone tissue
- Stretching of the periosteum
- Growth of the tumour, causing surrounding soft tissue inflammation
- Fracture.

The nature of the pain is variable, from a dull ache present at night to severe localized pain on weight-bearing. It must be remembered that bone and joint pain in a patient with a known cancer may be related to more common causes, such as spinal stenosis or osteoarthritis.

Pathological fractures are said to occur in up to 29% of patients with bone metastases (Tillman, 1999). Risk of fracture is dependent on the site of the lesion, the nature of the pain, the nature of the lesion (blastic or lytic) and the size of the tumour (*Figure 2*).

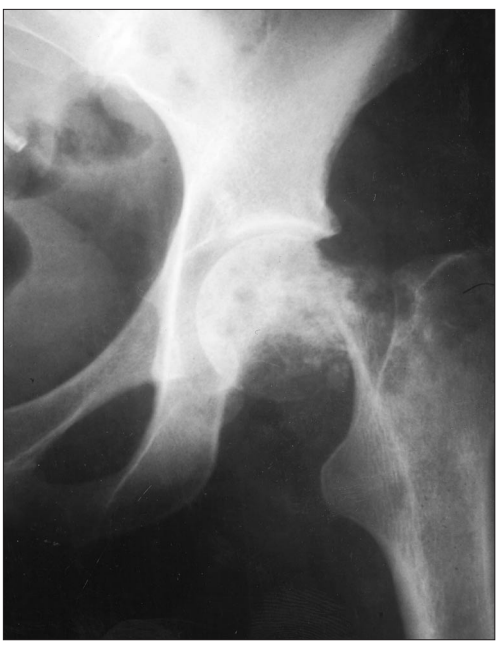
DIAGNOSIS

Although skeletal metastasis may complicate any type of carcinoma, it occurs most frequently with cancer of the lung, breast, kidney, thyroid, prostate and colon. The patient may present with a known primary cancer; however, symptomatic or quiescent bone disease may be the initial presentation.

A thorough history and examination is mandatory, with a comprehensive evaluation of the social and functional background of the patient (*Table 1*). A metastatic blood screen that includes full blood count, erythrocyte sedimentation rate, calcium, alkaline phosphatase and prostate-specific antigen levels, urine and plasma electrophoresis should be performed.

The use of serum assays to diagnose and monitor patients who have metastatic bone disease is currently under investigation. These include markers of osteoblastic activity (bone Gla protein and procollagen-I carboxyterminal peptide) and osteoclastic activity (deoxypyridinoline and pyridinoline-crosslinked carboxyterminal telopeptide). Prostate-specific antigen is strongly predictive of metastastic disease.

Figure 2. Pathological fracture of neck of femur resulting from metastatic breast disease.



Radiographic investigations include anterior/posterior and lateral views of the bone affected, chest radiograph and bone scintigraphy. Bone scintigraphy shows increased uptake in diseased bones, and is the most useful and sensitive technique in identifying metastases. Metastases in bone are commonly multiple, and clinically-silent lesions may be identified by this technique. Some tumours, such as metastatic renal carcinoma, may be cold on bone scan.

On plain radiographs, most metastatic carcinomas are osteolytic. Lesions may be solitary or multiple and either well or poorly defined. There may be permeative or moth-eaten bone destruction and spread of the tumour through the cortex into the surrounding soft tissues. Renal, thyroid and colonic carcinomas are almost always osteolytic; breast and lung carcinomas are also usually osteolytic. Some tumours are associated with a prominent osteoblastic response and produce sclerotic metastases, such as prostate disease.

Although sensitive, bone scintigraphy is not specific for metastases. The benign causes for increased uptake include trauma (stress fracture), infection and benign bone tumours. Chest and abdominal computed tomography (CT) may be indicated on clinical grounds, and used to source an unknown primary cancer.

If there is doubt about diagnosis, even with a known primary cause of cancer, a tissue biopsy before commencing definitive management is recommended. A planned needle or Trucut biopsy of the most accessible lesion under imaging is satisfactory. A magnetic resonance image (MRI) or CT of the lesion is performed before biopsy, as a primary bone tumour may present in a similar fashion. When a biopsy is undertaken, certain basic principles are followed:

TABLE 1.
Investigations required for patients with metastatic bone disease

Serological	Full blood count
	Bone profile (calcium/alkaline phosphatase)
	Inflammatory markers (erythrocyte sedimentation rate/ C-reactive protein)
	Prostate-specific antigen levels
	Myeloma screen (urine and plasma electrophoresis)
Radiological	Anterior/posterior and lateral view of bone involved
	Chest X-ray
	Bone scintigraphy (chest/abdomen)

- The biopsy tract should be sited and planned to avoid contamination and accommodate definitive surgery
- The biopsy should only violate a single compartment
- Samples should be sent for histological and microbiological examination.

A more difficult scenario arises when the bone metastases are the initial presenting feature. Rougraff et al (1993) found that history, examination and chest X-ray will identify the primary diagnosis in 51% of patients. With CT of the chest, abdomen and pelvis, whole body bone scintigraphy and tissue biopsy, the primary site was identified in 85% of patients.

NON-OPERATIVE MANAGEMENT

Treatment of bone metastasis can be either systemic or local. Systemic treatment includes chemotherapy, hormonal therapy, administration of radionucleotides or bisphosphonates. Local therapy includes radiation therapy, operative intervention or a combination of both, and is tailored to the primary disease.

Radionucleotides

Radionucleotides should ideally selectively localize to areas affected by metastases, with higher concentrations deposited in areas of increased bone destruction, while sparing the surrounding soft tissue. Several examples include iodine-131 for thyroid cancer, and yttrium-90, phosphorous-32 and strontium-89 for the treatment of breast and prostate cancer.

Bisphosphonates

Bisphosphonates bind to hydroxyapatite crystals and inhibit their growth, aggregation and dissolution. Their affinity for bone mineral is the basis for their diagnostic use as bone-scanning ligands, and for their therapeutic use as inhibitors of bone resorption.

Pamidronate and clodronate are particularly promising adjuvants for the systemic treatment of bone metastases. Although they act quickly to reduce hypercalcaemia, long-term administration is necessary to treat widespread osteolytic disease. Tumour growth at the site of metastasis is not altered by the use of these drugs; they should therefore be used in conjunction with other types of therapy to control progression of disease.

TABLE 2.
Scoring system for risk of long bone pathological fracture

		Score	
Variable	1	2	3
Site	Upper limb	Lower limb	Peritrochanter
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Size (proportion of bone shaft diameter)	<1/3	1/3–2/3	>2/3

Chemotherapy

Many chemotherapeutic options are available dependent on the type of carcinoma. Chemotherapy, especially in myeloma or metastases not at risk for fracture, may induce regression sufficiently so that no further local therapy is required.

Radiation therapy

Radiation can be extremely effective at decreasing bone pain resulting from progression of a tumour. Radiation may be given as a single dose (4–8 Gy) or as fractionated doses over several days. The single-dose option is easier for the patient and has been shown to be as effective as fractionated therapy. Multiple lesions require multiple-site or hemibody irradiation.

SURGICAL MANAGEMENT OF SKELETAL METASTASES

'The principal role of the orthopaedic surgeon in the management of skeletal metastases is:
a. To undertake prophylactic fixation of metastatic deposits when there is a risk of fracture
b. To stabilize or reconstruct bone after pathological fracture
c. To decompress the spinal cord and nerve roots and/or stabilize the spine' (Tillman, 1999).

Mirels (1989) has reviewed prognostic indicators of pathological fracture and assimilated a score based on the four risk factors that he found were clinically and statistically significant (*Table 2*). A score of 7 was associated with a 5% risk of fracture, a score of 8 had a probability of fracture of 15% and a score of 9 was almost diagnostic, with a 33% risk of fracture. Prophylactic fixation is recommended with a score of 9 or above.

More accurate measurement of bone involvement is indicated with CT or MRI. The advantages and disadvantages of intervention must then be weighed up by the surgeon and patient. The sites most commonly affected, which require prophylactic fixation or definitive fixation post-fracture, are the proximal femur, humerus or pelvis.

Metastasis rarely occurs distal to the elbows and knees. Metastatic spread into a joint occurs most commonly in the hip and knee, and is asso-

ciated with a primary tumour of the lung, breast or prostate. Renal carcinoma may present as a solitary metastasis, mimicking the presentation of a primary bone tumour, and is thus more suitable for a custom-made or modular endoprosthesis.

Long bone metastasis

Metastases involving the long bones of the femur and humerus are common (*Figure 3*). Fixation with an intramedullary device because of its more favourable biomechanical properties is recommended as fracture union may not occur, especially if adjuvant radiotherapy is used (*Figure 3*). Prophylactic fixation is more easily accomplished than post-fracture stabilization.

Peri-articular metastasis

If sufficient disease-free bone stock remains, debulking and stabilization is the least invasive method of treatment. When this option is not available, reconstruction with total joint replacement or custom-made/modular endoprostheses must be undertaken (*Figure 4*). These are major surgical procedures, and the benefits must be carefully weighed up against the potential complications. Infection is a risk in this commonly malnourished, immunosuppressed patient group.

Spinal metastasis

Spinal surgery is performed to decrease pain, decompress the neural elements and restore mechanical stability to the spine. In rare instances of radiation-resistant tumours (e.g. sarcoma, renal cell carcinoma), therapeutic surgical resection may serve as the primary treatment modality.

Surgical intervention can be either primary followed by adjuvant therapy (e.g. radiation-resistant tumours, mechanical instability from bone destruction) or post-treatment (e.g. with progression following radiotherapy or chemotherapy).

The approach (anterior/posterior) and method of fixation is dependent on the level and extent of the tumour. Spinal surgery for metastatic bone disease is complex, and is only performed in specialist centres.

Recently, the procedure of injecting polymethylmethacrylate percutaneously into the vertebral body has been introduced (Barr et al, 2000). This may avoid surgery in some cases, but has a risk of neurological complication.

Pelvic/acetabular metastasis

Periacetabular and pelvic metastases are common. Most pubis, ischium or sacroiliac/iliac-wing metastases can be managed with radiotherapy; however, impending fractures of the acetabular floor may require complex reconstructive surgery.

CONCLUSION

Several classification systems exist to quantify the extent of bone destruction. The choice to perform surgical reconstruction should be considered only after a thorough and careful assessment of associated mechanical requirements, a practical classification of the structural defect and identification of associated clinical morbidities have been reviewed.

Surgery should only be undertaken with a life expectancy of 6 weeks or more for fracture fixation, and 6 months or more for complex reconstructive procedures. **HM**

Figure 1 *is reproduced from Athanasou (2001) by kind permission.*
Conflict of interest: none.

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Further reading

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Menendez L (2002) *Musculoskeletal Tumours.* Orthopaedic knowledge update. American Academy of Orthopaedic Surgeons, Rosemont, Il

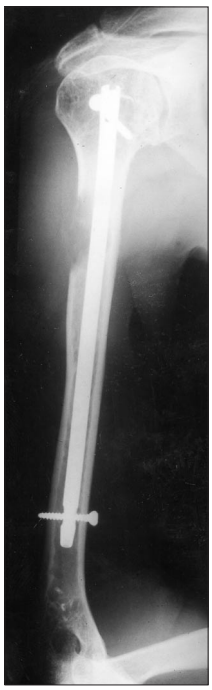

Figure 3. Intramedullary locked nailing of an incipient pathological fracture of the humerus secondary to lung carcinoma.

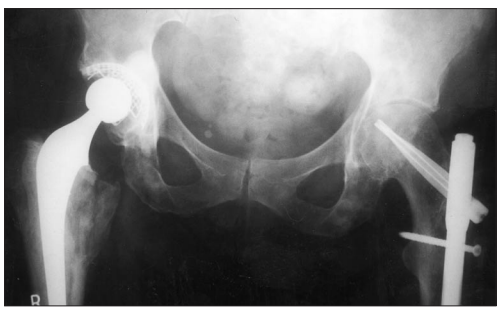

Figure 4. Total hip replacement and intramedullary nail fixation of metastastic breast disease.

KEY POINTS

- Survival and quality of life can be improved with a multidisciplinary approach to the management of skeletal metastases.
- A tissue diagnosis is essential before considering reconstructive surgery.
- Pathological fractures require early fixation.
- Surgery should only be undertaken with a life expectancy of 6 weeks or more for fracture fixation, and 6 months or more for complex reconstructive procedures.