Management of Bone Metastases

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Contents

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Abstract

Orthopaedic surgeons involved in fracture management will occasionally encounter patients with pathological fractures secondary to metastatic bone disease. Advances in cancer treatment have prolonged life expectancy for most patients and increased the probability and prevalence of bone metastases. The diagnosis and treatment of metastatic bone lesions require multidisciplinary input from diagnostic and interventional radiologists, medical and radiation oncologists, pathologists, as well as pain specialists. If the bony lesion is solitary, a biopsy is always indicated to avoid inappropriate treatment of an unsuspected primary bone tumour. Bisphosphonates, arterial embolization, and radiotherapy constitute important adjuncts to surgical treatment. Stabilization and fixation of destructive bone lesions are the primary Orthopaedic goals to afford the patient significant pain relief and ability to bear weight on the affected bone. Because these pathological fractures seldom unite, load-bearing fixation devices are preferred to avoid failure of fixation. Acrylic bone cement may be used to provide immediate stability in lesions with large structural defects. Where there is widespread bony destruction, reconstruction with an endoprosthesis may be more ideal. Prompt and appropriate surgical management of bony metastases can be highly worthwhile and cost-effective by making patients mobile and independent from prolonged hospital care.

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Biphosphanates • Bone metastases • Complications • Cost-benefit • Endoprosthetic surgery • Hip • Mechanisms of fracture • Pathogenesis • Pelvis and acetabulum • Radiotherapy • Rehabilitation • Shoulder and upper limb • Spine • Surgical Treatment-long bones

Introduction

Orthopaedic surgeons involved in fracture management will occasionally encounter patients with an oncological basis for their bone pathology. A pathological fracture occurs through bone weakened by a disease process. Excluding osteoporosis, the most common cause is metastatic disease of bone, and this chapter deals with the principles of management of bone metastases and metastatic fractures.

General Principles and Pathogenesis

Tumours that most commonly metastasize to bone are prostate (32 %), breast (22 %) and kidney (16 %), followed by lung and thyroid. Less common bone metastases are from melanoma, lymphoma and tumours of the gastro-intestinal tract. Spread is haematogenous, and theories for the distribution of metastatic deposits include Paget's 'soil and seed' theory and Ewing's circulation theory. Most metastatic tumour cells enter bones through the sinusoids of red marrow-containing bones such as the vertebrae, ribs, pelvis, and skull. The vascularity of these bones along with increased permeability of the lining endothelium makes them favourable sites for metastasis. The valveless vertebral venous system is thought to account for the large number of spinal metastases.

Bone destruction in metastatic disease occurs when tumour cells secrete growth factors which disrupt the normal balance of bone formation (osteoblastic) and bone resorption (osteoclastic) leading to a predominance of one activity. Multiple myeloma and breast cancer cells release substances such as PTH-RP, IL-6, TNF, PGE2, that in turn activate increased expression of RANK ligand, which induces osteoclast formation and subsequent bone resorption. Studies into the complex biology of bone metastasis have identified several targets for therapies aimed at stopping the imbalance of bone formation and resorption. An antibody to RANK ligand, Denosumab, has shown promise in treating bone metastasis, as well as other osteoclastic-driven diseases [8].

The various tumour-derived growth factors stimulate osteoclastic and sometimes, osteoblastic activity, which is then reflected in the radiological appearance and may be lytic (typically renal), sclerotic (typically prostatic) or mixed (breast). Almost all metastases show increased uptake ('hot spots') on scintigraphy (bone scan), but scintigraphy is of little use in the assessment of response to treatment. Deposits from multiple myeloma and renal metastases are often cold on bone scan.

Diagnosis

Pain is the most common clinical symptom, ranging from a dull ache to a deep intense pain that is exacerbated by weight-bearing, and is sometimes worse at night. The aetiology of this pain is not fully understood, but probably involves the release of chemical mediators of pain such as substance p, prostaglandins, growth factors, bradykinin and histamine. Micro-fractures and infarction of surrounding bone may also contribute to pain. Other complications of bone metastases are:

- Hypercalcaemia
- Impending fracture
- Pathological fracture
- Spinal instability
- Neurological complications
- Marrow suppression.

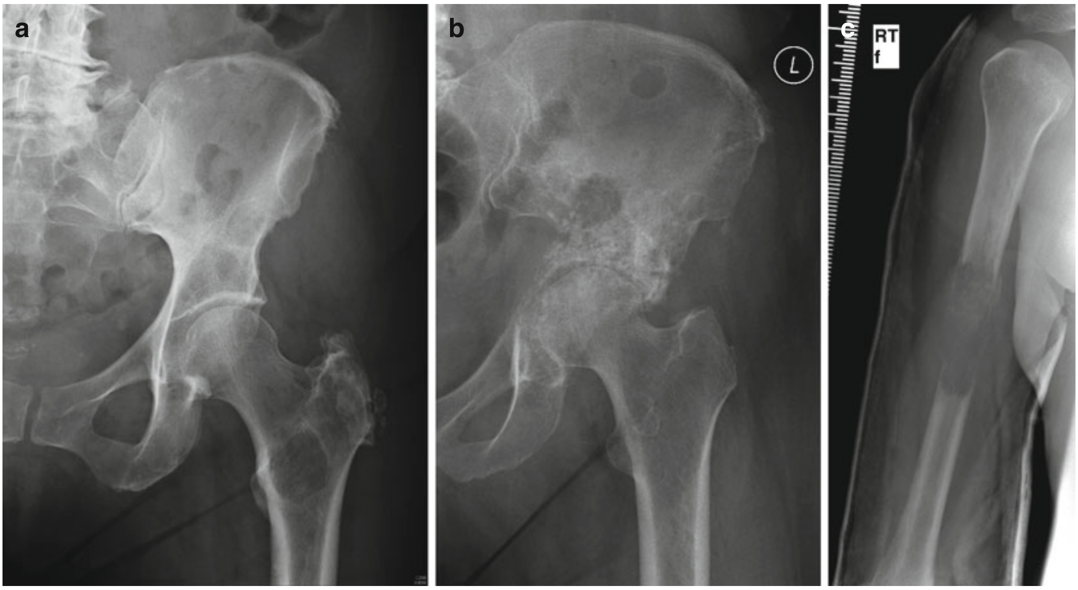

Fig. 1 Radiographic appearances of bone destruction. (**a**) Geographic, (**b**) moth-eaten, (**c**) permeative

Radiographic Appearance

Plain radiographs are commonly used to initially evaluate symptomatic areas, asses the risk of fracture, and aid in the differential diagnosis (Fig. 1).

Radiographically there are three types of bone destruction:

1. Geographical. Large solitary well-defined lytic areas (typically renal mets).
2. "Moth-eaten". Multiple smaller lytic areas which may co-alesce to form larger confluent areas. Margins are usually ill-defined.
3. Permeative. Multiple tiny lytic areas (1 mm. or less) seen principally in cortical bone.

It is important to note that lytic bone lesions may not be evident on plain radiographs until 30–50 % of the bone is involved, at which point the risk of fracture is already high. Consequently, any painful area that does not show any obvious signs on radiographs must be investigated further with a CT scan or MRI.

Not all metastases present as lytic lesions. Sclerotic changes are particularly associated with prostate metastases while breast metastases can produce mixed sclerotic and lytic lesions (Fig. 2).

Fig. 2 (**a**) Osteoblastic lesion from breast cancer. (**b**) Mixed sclerosis and lysis of breast metastases

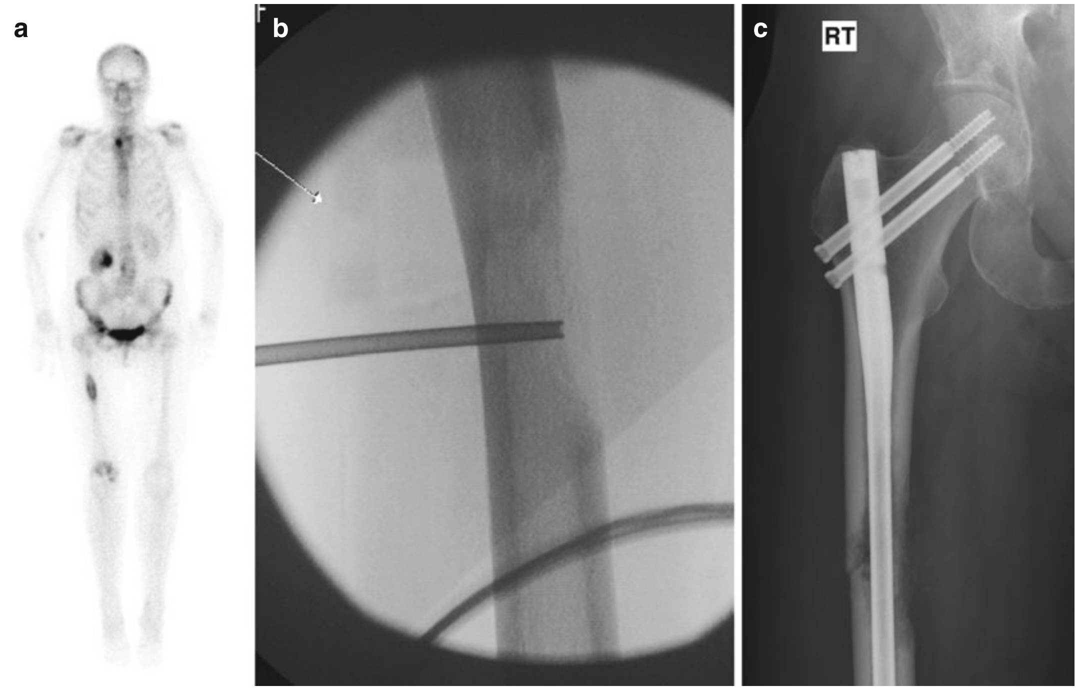

Fig. 3 (**a**) Solitary bone lesion on bone scintigraphy. (**b**) Percutaneous needle biopsy confirms metastatic lung carcinoma. (**c**) Intramedullary nailing to stabilize femur

When Is Biopsy Necessary?

If there is any doubt as to the underlying pathology, and in particular when there is a solitary bone lesion, further investigations including scintigraphy, MRI scan of the lesion and percutaneous bone biopsy should be carried out before definitive surgery (Fig. 3). This will avoid performance of an inappropriate procedure. Nailing of a long bone lesion that proves to be a primary bone tumour is a disaster, spreading tumour cells throughout the marrow cavity, and often precluding limb salvage surgery. Patients with a solitary renal metastasis have a good prognosis if the lesion is treated as a primary neoplasm and radically excised.

Errors in Diagnosis

Despite increased awareness in recent years, centres of Orthopaedic oncology continue to treat examples of the two types of error committed in the management of MBD [12].

Type 1 error: internal fixation of metastatic fractures, particularly those around the hip, with trauma implants such as the DHS, which are load-sharing rather than load-bearing. These implants do not maintain stability when the pathological fracture fails to unite, leading ultimately, and often rapidly, to failure, due either to breakage of the implant or to cutting out of the fixation screws.

Type 2 error: fixation, usually intra-medullary nailing or plating, of a solitary lesion on the assumption that it is a metastatic deposit or fracture but without prior confirmation of pathology. Where the lesion proves to be a primary sarcoma, the consequences for the patient can be disastrous as the entire medullary canal, and indeed the soft tissues throughout the entire operative field, have been extensively contaminated by tumour cells, rendering limb salvage surgery massively more difficult or indeed impossible (Fig. 4).

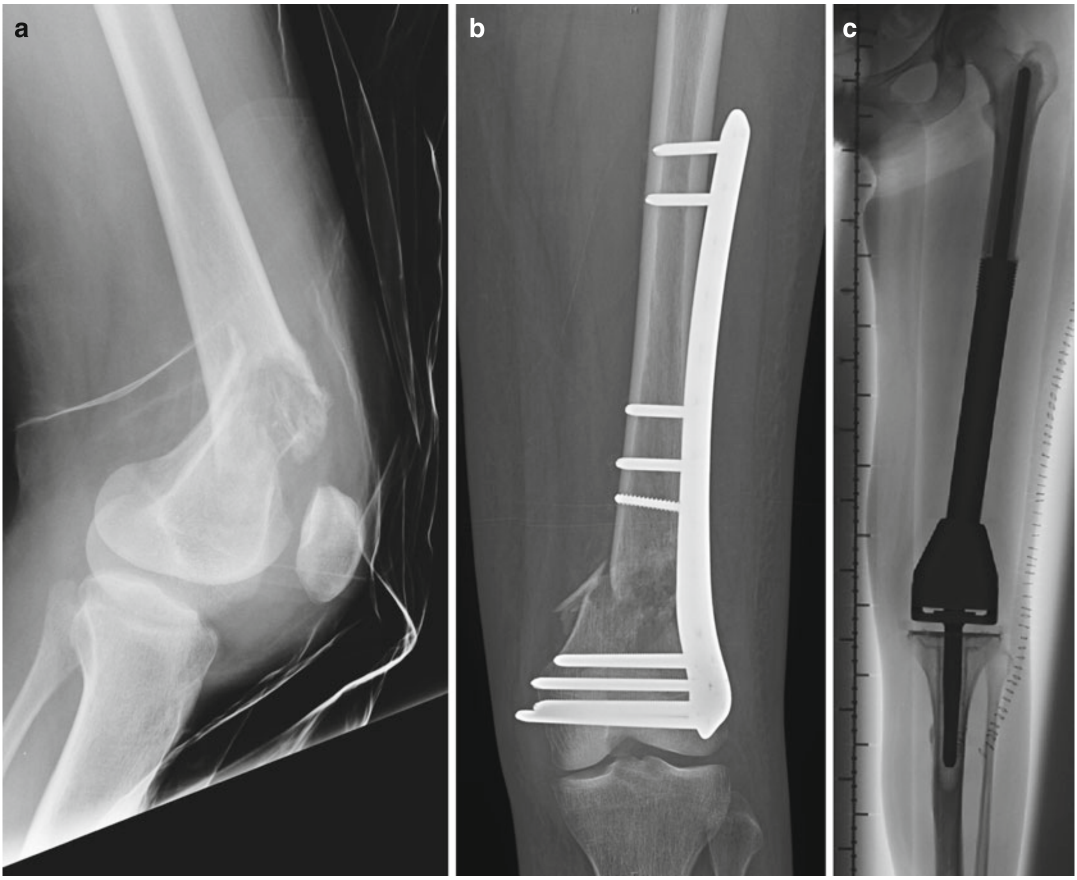

Fig. 4 (**a** and **b**) Internal fixation of presumed metastatic disease. Histological examination of tissue taken during fracture fixation subsequently revealed high grade spindle cell sarcoma. (**c**) Patient treated with extensive endoprosthetic replacement

Mechanism of Fracture and Risk Assessment

With respect to the appendicular skeleton, the mechanism of fracture is significantly different in pathological bone when compared with 'normal' traumatic fractures. Bone destruction may produce a 'stress riser' or an 'open section' defect in a long bone. Fracture will then occur following minor trauma or a twisting movement. Open section defects are particularly weak under rotational stress. Cortical or endosteal defects involving 50 % of the intact diameter of cortical bone cause a decrease of 50 % in bone strength and are associated with a significantly increased risk of fracture.

These are, therefore, low energy fractures and the degree of soft tissue injury is generally small. Significant haematoma formation seldom occurs. Where fracture is likely to occur, prophylactic fixation should be performed before the administration of radiotherapy. It is essential to have a reliable method of predicting the risk of a pathological fracture. A generally accepted 'rule of thumb' is that pathological fracture is almost inevitable when 50 % of a single cortex of a long bone (in any radiological view) has been destroyed. In addition, avulsion of the lesser tuberosity is an indication of imminent hip fracture.

The Mirels scoring system (Table 1), which is widely used in the USA, provides a more reliable

Table 1 Mirels scoring system for metastatic bone disease

Variable	Score		
	1	2	3
Site	Upper limb	Lower limb	Peritrochanter
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Size[a]	<1/3	1/3–2/3	>2/3

The maximum possible score is 12. If a lesion scores 8 or above, prophylactic fixation is recommended before radiotherapy

[a]As seen on plain radiograph, maximum destruction of cortex in any view

and reproducible measure of the risk of pathological fracture, and is regarded as a useful aid to assessment and management, not only for Orthopaedic surgeons, but also for medical oncologists [7]. For scores of eight or above, the risk of fracture is high and prophylactic fixation should be carried out before radiotherapy.

Treatment

Recently, there have been significant improvements in the prognosis for patients with bone metastases, principally because of advances in chemotherapy and hormonal treatments. The improvement has been most marked for patients with breast and prostate carcinoma; of these, patients with breast cancer are more likely to require or benefit from Orthopaedic intervention [2]. In the UK, about 9,000 women with breast cancer develop bone metastases each year, and up to 20 % of patients with metastatic bone disease survive more than 5 years, sometimes requiring repeated palliative interventions and treatment [11]. Although bone is not the most common site for metastatic disease, it is often the most symptomatic. Patients can be relatively untroubled or unaware of lung or liver metastases until the very final stages of their disease but metastatic bone pain is frequently disabling and greatly affects quality of life. The occurrence of pathological fractures also has an effect on survival of patients with malignant bone disease [9]. Metastatic breast and prostate cancer patients with vertebral or non-vertebral fractures are at an increased risk of death.

The role of the orthopaedic surgeon in the management of bone metastases falls into three principal categories [10]:

- Prophylactic fixation of metastatic deposits where there is a risk of fracture
- Stabilization or reconstruction following pathological fracture
- Decompression of spinal cord and nerve roots and/or spinal stabilization.

Radiotherapy

Radiotherapy is generally palliative, and given as a single fraction, but it can stimulate effective bone healing and sclerosis, and, when given prophylactically, can prevent pathological fracture occurring [4]. It will not, however, cure pain of a ‘mechanical’ nature, and only 30–40 % of pathological fractures will unite, even after radiotherapy. Splints and slings can be used in the short term to help stabilize upper limb fractures. For large lytic lesions of the weight-bearing lower extremity, surgical stabilization takes precedence as fractures can occur while radiotherapy is on-going.

Bisphosphanates

The use of these drugs is increasingly important in the management of MBD, not only in reducing bone destruction and avoiding pathological fractures, but also in the management of hypercalcaemia. When ingested by osteoclasts at sites of active bone remodelling, they inhibit further osteoclastic activity and decrease bone resorption. Oral (Clodronate and Ibandronate) and intravenous (Pamidronate 90 mg, Zolendronic acid 4 mg) forms of bisphosphonates are available that have shown some benefit in reducing skeletal-related events (SRE) and pain caused by MBD [1]. Gastrointestinal and renal toxicity are associated and must be monitored as well as the risk for osteonecrosis.

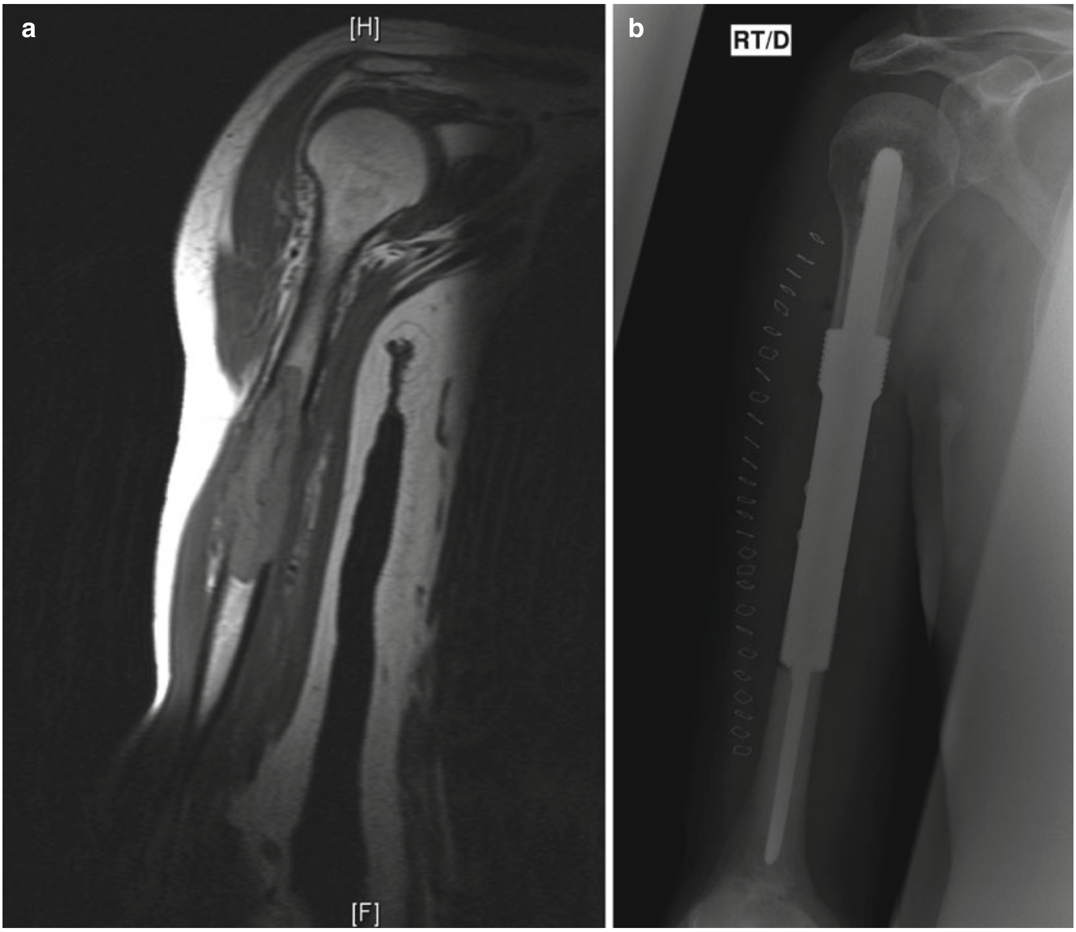

Fig. 5 (**a**) Solitary renal metastates of the humerus. (**b**) Selective arterial embolization was performed prior to excision and replacement with a diaphyseal endoprosthesis

Surgery

Aims of surgery: the aims of surgery are to relieve pain and restore function, and the general Orthopaedic principles underlying the management of impending or actual pathological fractures through metastases are:

- The procedure should provide immediate stability
- The surgeon must assume that the fracture will not unite
- The fixation should aim to last the lifetime of the patient.

The axial skeleton (spine) is the most common site for bony metastases, though surgical intervention is most often carried out in cases involving the femur, humerus or acetabulum. Pathological fracture is invariably a disaster for the patient: fractures involving the lower limb result in loss of mobility, while those affecting the upper limb reduce independence and the ability to care for one's self.

Pre-Operative Preparation and Planning

It is essential that the general condition of the patient is addressed before surgery. Electrolyte imbalance, including hypercalcaemia, must be corrected and fluid balance monitored.

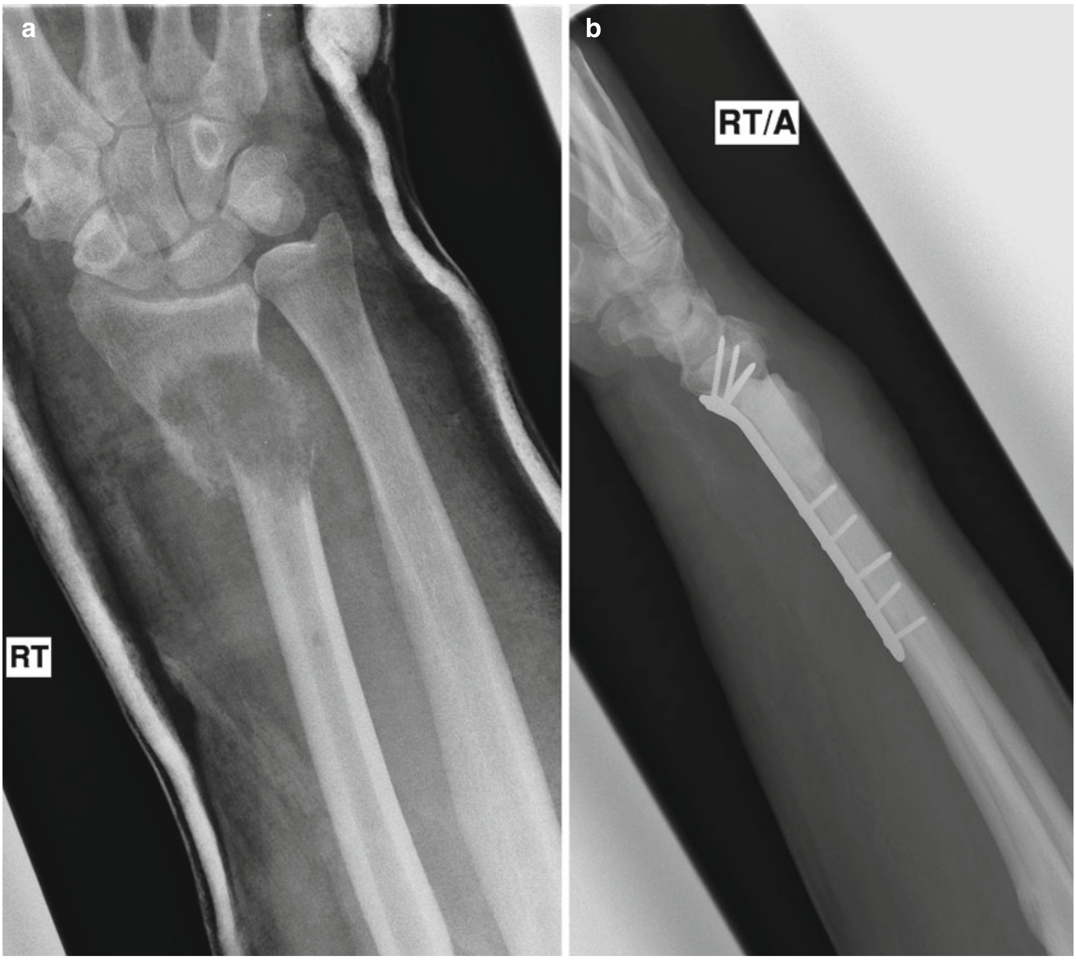

Fig. 6 (**a**) Metastatic deposit in distal radius. (**b**) Treatment with curettage and plate fixation with cement augmentation of the bone defect

Patients with a life expectancy of less than 6 weeks seldom gain useful benefit from major reconstructive surgery.

Apart from the case of solitary renal metastases, the spreading of tumour cells within the medulla by reaming and nailing is acceptable, but the entire bone should be included in the post-operative radiotherapy field.

Certain tumours are known to be very vascular and pre-operative embolization is important, if not essential, prior to surgery for metastatic renal carcinoma. A survival advantage has been shown for solitary renal metastases that are treated with wide resection compared to intralesional surgery and so efforts must be taken to try and get a wide surgical margin in these cases (Fig. 5).

Shafts of Major Long Bones (Humerus, Femur, Tibia)

Because these fractures are unlikely to unite, load-bearing rather than load-sharing devices should be used. Intramedullary nailing is preferred, with locking screws to give rotational stability and to prevent telescoping. Major bone defects can be re-inforced by packing with methylmethacrylate bone cement. Some studies have suggested that there may be some benefit

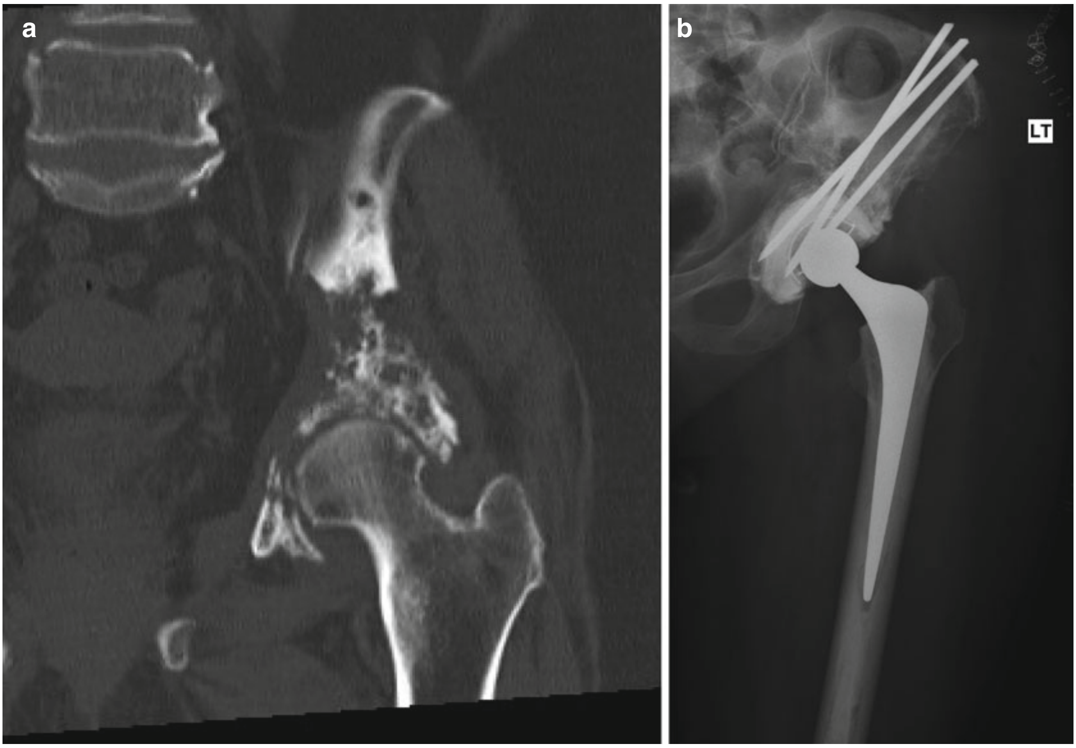

Fig. 7 Acetabular reconstruction with bone cement and threaded rods (Harrington technique) for extensive pelvic metastases

from incorporating chemotherapeutic agents into bone cement, but further research is required before this approach is widely adopted.

Shoulder Girdle and Upper Limb

Metastatic lesions causing fractures of the scapula and clavicle are managed with radiotherapy. In the humeral head, significant destruction is treated by hemi-arthroplasty. In the forearm, however, where stresses are relatively low, plate fixation with cement augmentation can be highly effective (Fig. 6).

Pelvis and Acetabulum

Most pelvic lesions are treated with prophylactic palliative radiotherapy alone. Peri-acetabular lesions, however, may lead to central dislocation of the hip with migration of the femoral head into the pelvis. Patients who have undergone radiotherapy to this area may also suffer pain owing to radiation necrosis of the femoral head or articular cartilage. Total hip replacement with acetabular reconstruction using threaded rods, re-inforcement rings and bone cement can be highly effective in restoring or maintaining mobility. This method of reconstruction is known as the ‘Harrington’ technique (Fig. 7) [3].

Hip: fractures about the hip most often present to the Orthopaedic surgeon and management differs significantly from that of purely traumatic fractures. When a patient with suspected pathological fracture is admitted to a trauma unit, a full medical and radiological assessment should be made initially, speed of surgery being less important than planning and use of the appropriate implant. While there is no virtue in undue delay, these patients are almost always haemodynamically stable. They have not been subject to significant trauma and so can be nursed comfortably on bed rest or traction, for several days if necessary, while appropriate investigations are carried out, such as blood tests, bone scan, abdominal ultrasound or CT and possibly MRI of the hip and biopsy.

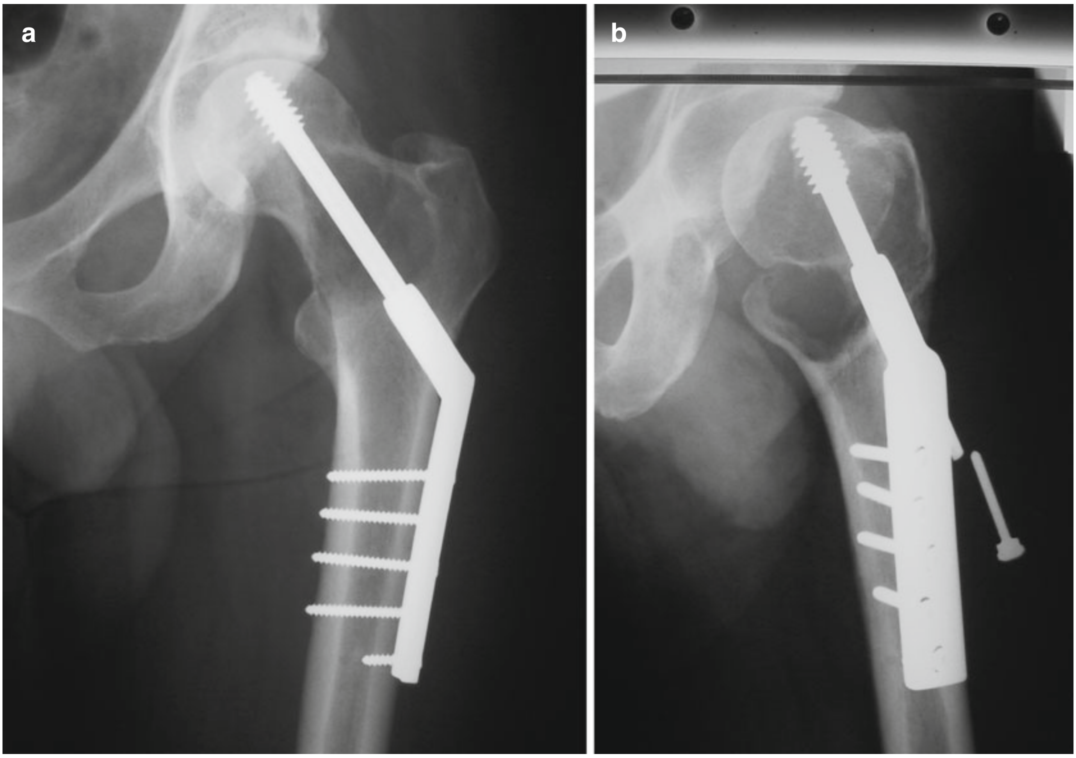

Fig. 8 (**a** and **b**) Failure of fixation of a proximal femoral metastasis treated by a dynamic hip screw. This lesion (once the diagnosis was established) should have been treated with a cemented hemi-arthroplasty

Where destruction is limited to the femoral neck or head, a cemented hemi-arthroplasty or total joint replacement is recommended as a primary procedure, as percutaneous screws and the dynamic hip screw (DHS) have a very high failure rate. Trochanteric fractures may also require cemented arthroplasty if there is significant bone destruction (Fig. 8).

On-lay devices such as the DHS are seldom indicated in pathological-fractures because they have a high rate of mechanical failure (breakage or cutting-out of the screws) if, as is commonly the case, the fracture fails to unite.

Sub-trochanteric fractures or lesions are often stabilized by 'reconstruction' nails with locking screws along the femoral neck. This greatly reduces the risk of subsequent femoral neck fracture, but if the fracture fails to unite then persisting pain may result in revision surgery to a proximal femoral replacement being necessary. Radiographs of the entire femur must be obtained pre-operatively to exclude (as far as possible) more distal disease, and long-stemmed implants may be used to reduce the risk of subprosthetic fracture.

Endoprosthetic Surgery

Extensive bone destruction of major long bones, particularly in the metaphyseal region (hip, knee, proximal humerus), is sometimes so great that reconstruction is impossible without using custom or modular endoprostheses (sometimes called 'megaprostheses') (Fig. 9). These are used principally in the management of primary bone tumours, but where the prognosis justifies major surgery, their use can be highly successful. Such surgery is generally performed in supraregional centres of Orthopaedic oncology.

Spine: the aim of spinal surgery is to relieve pain and maintain or restore neurological function. Spinal cord compression is an oncological

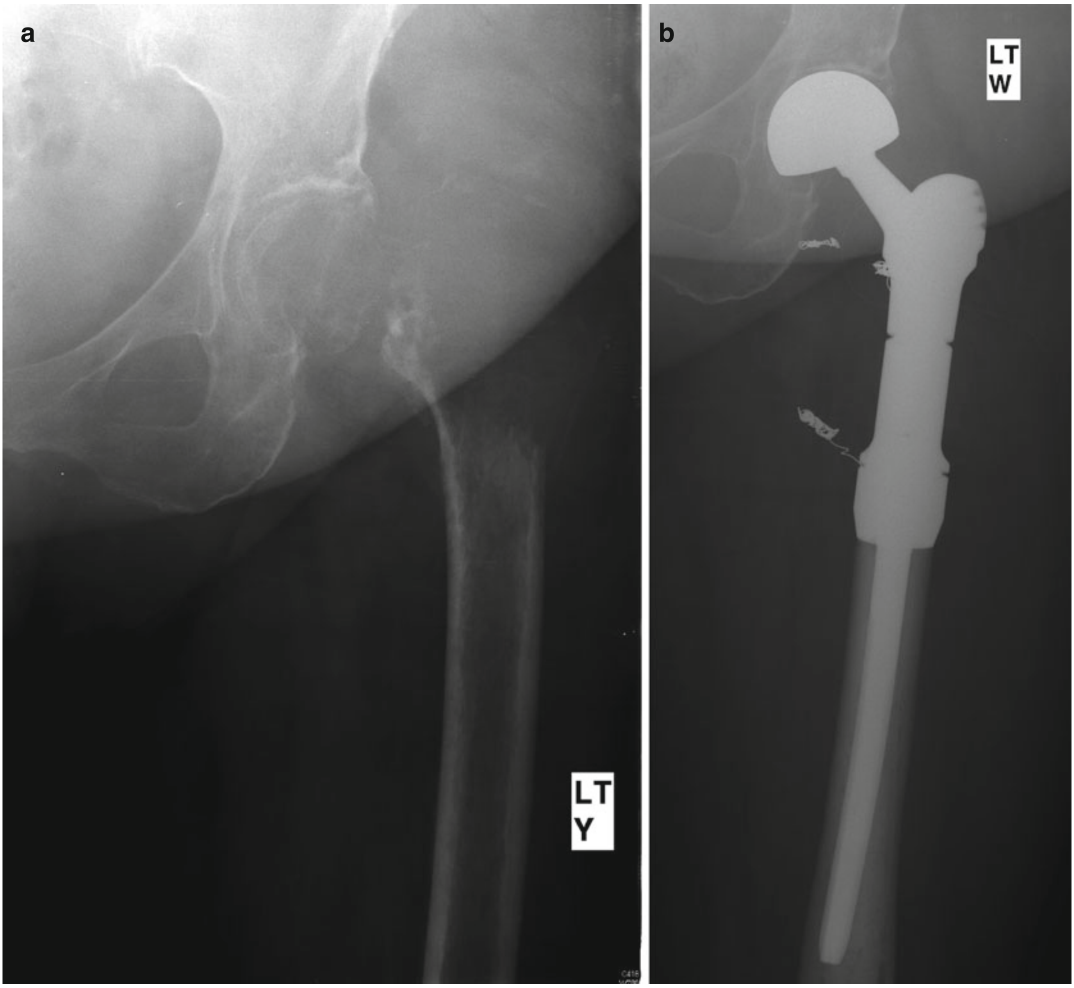

Fig. 9 (**a** and **b**) Proximal femoral endoprosthetic replacement inserted for renal metastases

emergency. MRI (or CT myelogram) is carried out, and high-dose corticosteroids are given, followed urgently by radiotherapy or surgical decompression and stabilization. Surgery can be carried out via anterior or posterior approaches. The choice of treatment depends on many factors, including the site and number of levels affected, whether the compression is partial or complete, the duration of neurological signs and predicted survival (Fig. 10). The ability to ambulate is an important prognostic factor as patients who were ambulant pre-operatively and those who were ambulant after surgery have better survival [5]. This highlights the significance of early diagnosis and treatment to improve outcomes. Pain due to spinal instability will not be cured by radiotherapy.

Post-Operative Care and Rehabilitation

The goal of Orthopaedic management of MBD (bone metastatic disease) is to provide stability to the compromised skeletal anatomy to allow patients the ability to weight-bear and achieve independence and mobility. Fixation techniques should provide enough strength to allow immediate post-operative mobilization and rehabilitation.

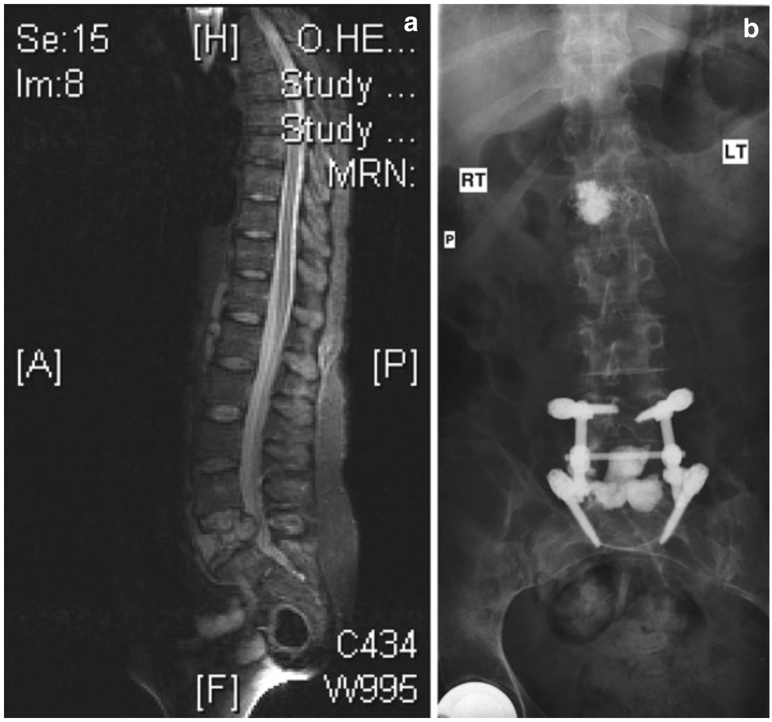

Fig. 10 (**a**) Bone metastases in the lower lumbar vertebrae causing collapse and neurological compression. (**b**) Decompression and stabilization with spinal constructs and bone cement augmentation

Through supervised physiotherapy, patients are encouraged to do early transfers and ambulation. Improved QOL (quality of life) is the end-point that needs to be fulfilled for the terminally ill.

Complications

When dealing with pathological fractures of the femur, reaming and insertion of a long-stemmed cemented implant has been associated with adverse pulmonary and cardiac events [6]. Metastatic bone has abnormal vasculature that accommodates large quantities of debris and marrow from the pressurized insertion of implants. This coupled with compromised pulmonary function in most of these patients leads to an increased risk for fat embolism and sudden intra-operative death. The femoral canal must be completely washed of debris prior to cementation. The amount of pressurization of the cement must be balanced with the risk of emboli.

Pathological fractures generally take longer to heal, if at all, and fixation principles for metastatic bone disease take this into consideration by using non-biological reconstruction techniques such as using large amounts of bone cement to fill cavities or replacing bone with a megaprosthesis. In most cases, these methods provide patients with enough stability to last their expected survival. However, with the advances in diagnosis and treatment of different malignancies, the median survival of patients with MBD is increasing and sometimes, they may outlive their constructs with catastrophic results. In the background of previously irradiated fields and massive bone loss, options are limited and sometimes the only reconstruction is the simplest (excision arthroplasty).

Service Delivery and Cost Benefit

The prompt and appropriate surgical management of bony metastases is highly cost-effective.

The cost of surgery and specialized implants is recovered within days if a previously immobile patient can mobilize, or if a previously dependent patient becomes self-caring. Furthermore, inadequate Orthopaedic treatment often leads to costly revision surgery, causing suffering and potential complications in addition to the financial cost.

The management of these patients requires input from a wide range of specialists, including pathologists, radiologists, oncologists, radiotherapists, palliative care specialists, cancer nurses and pain specialists. In the UK, the Chief Medical Officer has instructed that cancer care be concentrated into cancer centres and cancer units to improve outcomes. The BOA (British Orthopaedic Association) has advised that each trauma team should have a lead clinician for bone metastases. Appropriate Orthopaedic surgery can improve quality and quantity of life for these patients, and Orthopaedic surgeons must participate in multidisciplinary teams to provide optimum care for patients with metastatic bone disease.

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