Management of metastatic disease of the appendicular skeleton

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Summary

Treatment advances have resulted in improved prognosis for patients with cancer metastatic to bone. The management of appendicular skeletal metastases requires a multi-disciplinary approach. The overall disease prognosis is important in determining the appropriate surgical treatment of metastases, with simple measures for those with the poorest prognosis and resection with reconstruction for those expected to survive more than 1 year. This article reviews management options available for patients with skeletal metastases affecting the appendicular skeleton and broaches the controversies of prophylactic fixation of impending fractures.

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Introduction

Advances in multi-modality management mean that the prognosis for patients with cancer continues to improve.\textsuperscript{1,2} Furthermore, advances in chemotherapy have conferred improvement on both local and systemic control of malignancies. Figures from the American Cancer Society (1995–2000) quote an age-adjusted 5-year survival of 88% for breast cancer and 99% for prostatic cancer.

Bone is the third most common site of metastatic disease after lung and liver. Harrington\textsuperscript{3} demonstrated that, at post-mortem, 84% of patients with breast or prostate carcinomas had skeletal metastases. Figures for thyroid, lung and renal carcinomas were 50%, 44% and 37%, respectively.\textsuperscript{4} Those cancers most likely to metastasise to bone are:

Prostate

Skeletal metastases are very common in prostate cancer. At autopsy, 84% of those with prostatic adenocarcinoma have skeletal metastases, while in 1982, of 20,000 new cases of prostate cancer, 21.5% of patients presented with clinical stage D (metastatic) disease. Skeletal metastases are generally associated with a poor prognosis. Only 23% of patients survived 5 years from initial diagnosis, and the 10-year survival rate is 10%. The bones most commonly involved are the vertebrae, sternum, pelvic bones, ribs, and femora. The most common sites for pathological fracture are the medial cortex of the proximal femur and the vertebral...
bodies, these two carrying heavy loads. In a prospective study of 112 patients with bone metastases from prostate carcinoma, 10% developed pathological fractures.\textsuperscript{5} Eighty-four percent of prostatic skeletal metastases are osteoblastic, 12% are mixed osteolytic and osteoblastic. Pure osteolytic metastases are rare.\textsuperscript{6} The bony metastases are characterised by an excess of abnormally dense bone. This indicates that there is increased bone turnover. Both osteoblastic and osteoclastic activities increase, but the relative amount of osteoblastic activity exceeds that of the osteoclasts, and bone formation is the net result. Treatment of osteoblastic metastases is principally hormonal and radiotherapy. Predictors of skeletal morbidity include the extent of bone involvement, severity of pain, serum alkaline phosphatase level, and urinary deoxypyridinoline levels.\textsuperscript{7} Even in those cases in which fractures do occur, the rate of healing approaches that of normal bone. Normal healing, in conjunction with effective radiotherapy and hormonal manipulation, limits the need for surgical stabilisation to only about one-fourth of the patients who develop a pathologic fracture.

**Breast**

Bone is the first site of metastasis in 26% of breast cancer patients. It is the most common site of metastatic disease, both at presentation and as the site of first recurrence.\textsuperscript{8} Up to 85% of breast cancer patients develop skeletal metastases at some stage in the disease process. Higher incidences are seen in those with steroid receptor positive lesions and well-differentiated lesions.\textsuperscript{8} Up to one-third of these patients develop a major complication\textsuperscript{2} and approximately 17% require orthopaedic surgery.\textsuperscript{10} Two-thirds of these because of femoral metastases. Dür\textsuperscript{4} reported a 20% surgical complication rate in these patients. Radical resection of solitary lesions in breast cancer does not appear to improve survival, and therefore intraslesional surgery, methyl methacrylate augmentation and stabilisation is often most appropriate.\textsuperscript{8} Survival in breast cancer patients with skeletal metastases is increasing with newer adjuvant therapies. Patients with osteoblastic breast metastases or osteolytic metastases with no risk of fracture are usually treated with radiotherapy. The mean survival of patients after the first metastasis is detected was 34 months in 1992\textsuperscript{11} and is likely to be longer now. The role of bisphosphonates in the prevention of skeletal events in metastatic disease and in the prevention of metastases is currently being explored.

**Kidney**

Between 30% and 60% of patients with renal cell carcinoma have skeletal metastases at the time of primary tumour diagnosis.\textsuperscript{12} In between 1% and 3% of cases the metastatic lesion is a solitary skeletal metastasis. Lesions are often aggressively osteolytic, progress rapidly and are highly vascular. The skeletal pathology can be the presenting complaint in metastatic renal cell carcinoma. Fifty percent of renal metastases are synchronous\textsuperscript{13,14} and there appears to be a survival advantage for synchronous over metachronous skeletal metastases.\textsuperscript{15} Pre-operative embolisation of the vascular supply to the tumour is useful in reducing intra-operative bleeding.\textsuperscript{15–17} Typically, renal metastases respond poorly to radiotherapy in terms of healing but bone pain responds reasonably well.\textsuperscript{18,19} Chemotherapy and hormone therapy are also relatively ineffective.\textsuperscript{17} Isolated metastases with a prolonged latent period should be treated by en-bloc resection rather than stabilization.\textsuperscript{12,20,21} The 5-year survival of patients with a solitary bone metastasis from renal cell carcinoma has been quoted as high as 55%.\textsuperscript{21} The evidence is variable and Fuchs\textsuperscript{14} reported no survival advantage of wide excision over intralesional surgery. Thirty-five percent of patients with locally advanced renal tumours have skeletal metastases. Nephrectomy for patients with a solitary skeletal metastasis and a synchronous primary renal tumour appears to confer a survival advantage\textsuperscript{14} (88% versus 66% 1-year survival, 31% versus 0% 5-year survival).

**Lung**

Skeletal metastases usually occur in small cell carcinoma. Up to 60% of patients with lung cancer develop skeletal metastases. Lung cancer metastasis most commonly affects the spine, ribs, pelvis, and proximal long bones. A unique feature of this lesion is its ability to spread to the bones of the hands and feet. Half of all metastases to the hand bones are from lung, as well as 15% of lesions in the feet. Lung cancer metastases normally (approximately 75%) appear purely lytic, with poor margination, no matrix and cortical destruction, but may also be blastic. The prognosis is usually poor\textsuperscript{22} and the bone disease aggressive. There are also a number of reports in the literature of metastases from lung carcinoma to skeletal muscle. Systemic symptoms may also occur, such as those due to hypercalcemia and hypertrophic pulmonary osteoarthropathy. Lung cancer with metastasis to bone is one of the most aggressive tumours and has a very unfavourable prognosis. The average survival after the diagnosis of a metastasis is about 6 months. There is virtually no role of curative surgery.

**Thyroid**

Approximately 4% of thyroid malignancies metastasise to bone and are usually osteolytic. Of these around half are present at the time of initial diagnosis. It is typically adenocarcinomas that metastasise. Seventy percent of metastases occur in the axial skeleton.\textsuperscript{23} The 10-year survival of patients with thyroid carcinoma metastatic to bone is 13% from the time of diagnosis of the first skeletal metastasis.\textsuperscript{23} Treatment is usually surgical with adjuvant radiotherapy. Bone pain from thyroid metastases responds well to bisphosphonate therapy.\textsuperscript{24} If the lesion is solitary, aggressive wide local excision plus appropriate reconstruction as for a primary bone tumour may be the desirable treatment. Thyroid tumours can be highly vascular and pre-operative angiography and selective embolisation may be needed. Radioactive iodine\textsuperscript{131} has been found to be beneficial in some cases and has been demonstrated to be a prognostic indicator.\textsuperscript{23}

**Gastro-intestinal**

Bone metastases are relatively rare and usually osteolytic. Colorectal tumours carry a better prognosis than gastric and
pancreatic. Hatfield reported routine bone scanning of pancreatic primary carcinomas based on a detection rate of 6%. Kathan reported a 6.6% incidence of skeletal metastases from colorectal primary tumours. Eighty-three percent of these were in combination with lung, liver and brain metastases. Bone lesions are principally of the axial skeleton. Solitary skeletal metastasis from colonic carcinoma was rare, with an incidence of only 1.1%. Besbeas reported from Memorial Sloan-Kettering Cancer Center the incidences of osseous metastases were 8.9% from rectal carcinoma and 5.1% from colonic carcinoma. Of these, 14 (1.8%) had osseous metastases only. The mean period from manifestation of skeletal metastasis to death was 13.2 months. In gastric primaries, skeletal metastases are more common to the axial skeleton, principally affecting the thoraco-lumbar vertebrae. Osteoblastic metastases are not uncommon from gastric carcinomas.

Gynaecological

The reported incidence is approximately 10% of ovarian, 2–5% of cervical and less than 2.5% of uterine carcinomas metastasising to bone, most frequently to the axial skeleton. Skeletal metastases are usually associated with more advanced local disease. Cervical cancer metastasises to the lungs more frequently than it does to bone. Blastic metastases are rare and axial metastases are much more common than appendicular. However, when investigated at post-mortem, in a study between 1948 and 1984, autopsies were performed on 305 patients with primary carcinomas of the cervix, endometrium, ovaries, fallopian tubes, vulva, and vagina. Skeletal metastases were detected pre-mortem and at autopsy in 49 cases (16.1%) of gynaecological primaries. These were 20 (40.8%) of cervical carcinoma, 17 (34.7%) endometrial, 7 (14.3%) ovarian, 4 (8.2%) vulval, and 1 (2%) fallopian tube. This suggests the true incidence may be higher. The skeletal metastases tend to behave aggressively and should usually be treated by simple osteosynthesis techniques.

One-third of new cancers diagnosed are breast tumours in females and prostatic in males. These provide the largest burden of metastatic patients to the orthopaedic oncologist.

Principles of management

Carcinomas are much more likely to metastasise to bone than sarcomas. The axial skeleton is seeded more than the appendicular skeleton, presumably due to the persistence of red bone marrow in the former. The ribs, pelvis and spine are usually first affected. Batson’s vertebral venous plexus allows cells to enter the vertebral circulation without first passing through the lungs. The sluggish blood flow in this plexus is more conducive to tumour survival, perhaps accounting for the high rate of prostate cancer metastasis to the spine. It is a valveless system that also allows retrograde tumour embolisation.

Pain, pathological fractures and hypercalcaemia are the major sources of morbidity in patients with bone metastasis. The other common complaint is difficulty mobilising. Pain is the most common symptom found in 70% of patients with bone metastases. Pain has been attributed to stretching of the periosteum by the tumour, nerve stimulation in the endosteum, tumour growth leading to local soft tissue inflammation or by pathological fracture. The pain is usually dull in character and constant. It becomes gradually progressive and night pain not relieved by rest should alert the surgeon to a potentially sinister cause. Pathological fractures are most common in breast cancer due to the lytic nature of the lesions. They are less common in lung cancer due to short survival and in prostate cancer, when the lesions tend to be osteoblastic. Lytic bone metastases must be greater than 1 cm across and have destroyed 30–50% of the bone density in order to be seen by X-ray. Up to 1 of patients with skeletal metastases may suffer pathological fractures. Even when pathologic fractures occur the degree of soft tissue damage is small and extensive haematoma is rare. They do not require internal fixation in the middle of the night and appropriate planning is desirable. These fractures can be stress fractures initially that progress to full-blown pathological fractures without expedient management. Hypercalcaemia is usually due to calcium release from malignant bone destruction. The serum calcium should be measured in all patients with bone pain and malignant disease and before undertaking surgery for skeletal metastases. Hypercalcaemia should be addressed by rehydration and bisphosphonates.

Metastatic bone lesions can be described as osteolytic, osteoblastic and mixed. The osteolytic lesions are most common where the destructive processes outstrip the laying down of new bone. Osteoblastic lesions result from new bone growth that is stimulated by the tumour. For most primary tumours the long-term survival following pathological fracture has more than tripled in the past 25 years. Options for management of skeletal metastases include radiotherapy, surgery, chemotherapy, hormonal therapy and immunotherapy. Improved medical treatment of cancers has resulted in increased survival and this requires thought to be given as to the most appropriate surgical procedure. It is desirable that skeletal metastasis management be through a multi-disciplinary team. Patients with a predicted survival of less than 6 weeks require analgesia and radiotherapy. More than 6 weeks warrants consideration of fracture stabilisation and more than 6 months, endoprosthetic reconstruction. Put in simple terms, the recovery from the operation must be shorter than the anticipated survival.

Damon identified four key principles in the surgical management of metastatic bone lesions. Firstly, patient selection is critical, in that the operation is appropriate for the predicted survival of the patient. Secondly, the construct must be stable enough to allow full weight-bearing immediately. The third principle is that all areas of the bone that are affected by tumour are addressed in any planned reconstruction and finally post-operative radiotherapy is utilised to minimise disease progression. Where the bone has been reamed, the entire bone should be irradiated.
The aims of surgery for patients with skeletal metastases are no different to the aims in other aspects of orthopaedics—pain relief, preserving or restoring function and maximising the quality of life. Occasionally, for the solitary renal or thyroid metastasis, cure may also be a goal. It is important not to look for a short-term fix to what may well be a long-term problem.

**Investigation and diagnosis**

A thorough history and examination is mandatory in all patients, including examination of the breasts in all female patients and the prostate in all males. Metastatic disease is most common in patients over 40 years of age, and lymphoma and myeloma are also common. Table 1 outlines the investigations that are often employed in the investigation of patients with suspected skeletal metastases.

Radiographs should be taken in two planes including the joint above and below, so as to enable all lesions within the bone to be identified and stabilised. Plain radiographs offer good integration of the overall bone structure and alignment, though initially metastases may be subtle or invisible. Radiographic features of skeletal metastases are variable. Tumours can be:

- osteolytic (Fig. 1), osteoblastic (Fig. 2) or mixed (Fig. 3). Lytic metastases are often much more extensive than on initial radiologic impression;
- solitary or multiple;
- well or poorly defined;
- permeative and/or destructive;
- varied in their soft tissue involvement.

A Computerised Tomography (CT) scan or a Magnetic Resonance Imaging (MRI) scan may be appropriate, depending on the site of the lesion. CT scans are best for assessing bone quality, bone destruction, calcified tumour matrix and cortical erosions. MRI scans are highly sensitive and specific and are superior at demonstrating marrow replacement, skip lesions, quantifying oedema and assessing neurovascular involvement.

Bone scintigraphy will show the intrasosseous extent of lesions. It may also show multiple hot lesions (Fig. 4A), but beware of cold lesions (myeloma, renal cell carcinoma). It is also useful for demonstrating singularity versus multiplicity.

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Investigations in patients with metastatic bone disease.</th>
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<tbody>
<tr>
<td></td>
<td>Known primary</td>
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<tr>
<td>Serological</td>
<td>Full blood count</td>
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<td></td>
<td>Bone biochemistry</td>
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<td></td>
<td>Liver function tests</td>
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<td></td>
<td>Coagulation screen</td>
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<td></td>
<td>Group and save</td>
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<tr>
<td>Radiological</td>
<td>AP/lateral of whole bone</td>
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<tr>
<td></td>
<td>CT/MRI bone</td>
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<tr>
<td></td>
<td>Chest radiograph</td>
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<tr>
<td></td>
<td>PET scan or isotope bone scan</td>
</tr>
<tr>
<td>Biopsy</td>
<td>Not necessary</td>
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</tbody>
</table>

Figure 1 Osteolytic metastasis of the proximal femur in a 47 year old female with metastatic breast cancer.
of lesions and for identifying asymptomatic lesions. Isotope scans often reveal lesions to be much more extensive than initial radiographs suggested. Positron Emission Tomography (PET) scanning is emerging as a useful technology and we utilise it in the majority of our patients to determine the extent of tumour disease (Figs. 4B and C). F18-FDG (fluorine-18 fluorodeoxyglucose) is a glucose analogue taken up into tumour cells. This enables the most active and viable part of the tumour to be identified and this is the appropriate portion of the tumour to target on biopsy. A combination of these modalities will help to identify other sites (metastases), both skeletal and visceral, that may potentially require treatment.

Angiography is not commonly indicated. Specific indications are large pelvic tumours and those tumours where pre-operative embolisation is considered. Those patients with
metastatic renal cell carcinoma should be considered for pre-operative embolisation, as torrential bleeding may be encountered at surgery.

If ever there is a doubt, and especially if the lesion is solitary, a biopsy should be performed. The “whoops” operation (intramedullary nailing of a primary bone tumour) can have catastrophic consequences, disseminating tumour cells throughout the bone marrow, rendering the limb unsalvageable and having a negative impact on survival. An MRI scan (or PET scan) should be performed prior to the biopsy to allow for appropriate planning of the biopsy. The biopsy should be a core needle biopsy through a surgical stab incision with violation of only a single compartment. The biopsy can be performed on an outpatient basis, although we prefer a general anaesthetic with frozen section. The biopsy should be well planned in case surgical resection is subsequently needed. This can be performed at the time of the planned nailing procedure; a frozen section is performed and, assuming confirmation of metastasis, the nailing can proceed. It is worth remembering the general principles of biopsy: usually a longitudinal incision (the person doing the biopsy should be aware of the approach for definitive resection), single compartment violation, no neurovascular violation, meticulous haemostasis and a drain, if warranted, exiting in the line of the incision. The isolated hip lesion is worthy of special consideration, as chondrosarcoma needs to be excluded. In 15% of cases the primary tumour is never (or only posthumously) identified. With the advent of PET scanning this figure will fall. Our staging investigations for the unknown primary at present consist of only a PET scan and CT chest. With the advent of PET–CT this may become the only investigation necessary for the unknown primary (Fig. 5).

Medical management

Radiotherapy

Radiotherapy is a well-established and effective local treatment for patients with painful bone metastases. Ninety percent of patients with painful osseous metastases experience some relief of pain and 54% eventually obtain complete relief, often in combination with other analgesia. The effect of the radiotherapy is thought to be modulated by humeral mediators.

Three systematic reviews and a meta-analysis have demonstrated an equivalence of pain relief achieved by radiotherapy delivered as a single fraction and that delivered in multiple fractions. Single fraction doses of 4–18 Gy have all produced some response. Four gray produces overall response rates of approximately 45–59%. Two randomised trials have demonstrated 8 Gy as a single fraction to be superior to 4 Gy. Eight gray produces response rates of 70–85%. Results from 6 Gy treatments are only slightly lower. Doses above 8 Gy do not produce measurably superior response rates but produce toxicity in some situations.

Detailed analysis of the largest study, the Dutch Bone Metastasis Study confirmed 8 Gy is equivalent to 24 Gy in six fractions, with response rates of 71%. In this study 14% of patients responded completely requiring no analgesia and experiencing no pain. A similar figure of 15% has been reported after 10 Gy. The mean time to response was 3 weeks and the mean duration of response was 18 weeks. This is typical of many studies. Mean response duration to 52 weeks has been described in some series. Seventy percent of patients achieve durable relief, maintained for the rest of their life.

Most studies show better response rates in breast cancer, prostate cancer and myeloma metastases than in lung, kidney or colorectal cancer. The Dutch Bone Metastasis Trial showed response rates of 78% in breast cancer and 79% in prostate cancer. Other histologies do respond to radiation treatment; the lung cancer response rate was 58% and other histologies 60–65%. Some studies have not shown a difference between histologies.

Re-treatment of patients with painful bone metastases is also effective. Regardless of their response to initial treatment, up to 90% respond to a re-treatment. Mithal reported an 84% response rate to a second treatment with no relationship to primary tumour type or site of metastasis. Jeremic reported a 46% response rate to re-treatment in initial non-responders and a 73% response rate in those who had responded previously. The Dutch Bone Metastasis Trial

Figure 5 PET scanning in the unknown primary. The scan demonstrates a glucose avid bone lesions in the ischium and a lesion in the oesophagus consistent with an oesophageal primary.
reported a 66% response to re-treatment. The best response to re-treatment is in breast cancer with an 89% response rate in those who initially responded and an 82% response rate in a group of non-responders to initial radiation therapy.

Some evidence exists that multiple fraction courses may be more effective in patients with solitary bone metastases. Additionally, where normal tissue tolerances are approached, especially around the spinal cord, it may be necessary to deliver the radiotherapy in a series of fractionated doses.

Other radiation techniques

Hemibody irradiation is an alternative to localised radiation where metastases are widespread. This is commonly seen in prostate cancer. Treatment is delivered using 6–8 Gy in a single dose to the upper, middle or lower part of the body. Response rates up to 77% are recorded. Nausea and vomiting and haematological suppression occur in up to 30% of patients.

Radioisotopes. The advantages of this modality are that all osseous sites are addressed simultaneously. Because uptake is selectively into bones, irradiation of normal tissues is limited. Treatment is administered as a single outpatient injection. Their use is limited by the requirement for good renal function and bone marrow reserve, often not present in patients with advanced malignancy. The common isotopes are Strontium-89 (\(^{89}\)Sr), and Phosphorus-32 (\(^{32}\)P). Samarium-153 and Rhenium-186 are also reported.

Strontium-89 decays by beta emission with a half-life of 60 days. It is absorbed into bone matrix. Elimination is through the kidneys, requiring careful disposal of urine for 7–10 days. There is little gamma emission, so patients are not a radiation hazard to their families. Most work on this modality has been in prostate cancer and response rates of 75% are reported. One study showed equivalence with external beam radiotherapy. There can be a transient flare of pain in 10% of patients at 1–2 weeks. The principal toxicity is haematological, with a drop of up to 50% in blood counts (white cells and platelets) that nadirs at 4–8 weeks and can last up to 12 weeks.

The use of iodine-131 (\(^{131}\)I) specifically targets thyroid cancer metastases.

Systemic therapies

Definitive palliative treatment of the primary malignancy produces improvement in bone pain in most patients.

Hormonal manipulation has a response rate of about 50% in breast cancer-related bone metastases, and 70–80% with prostate cancer.

Chemotherapy can be effective in breast cancer and other malignancies. The goals of hormonal manipulation and chemotherapy in skeletal metastatic disease are pain control, disease stabilisation and a reduction in the risk of skeletal morbidity.

Bisphosphonates are a bone-targeted therapy. They act by inhibiting osteoclast-mediated bone resorption. Compared with placebo, they reduce the frequency of all skeletal-related events—pain, pathological fracture, hypercalcemia and the requirement for radiotherapy. These effects have been most clearly seen with pamidronate and zoledronate in osteolytic bone disease due to breast cancer and multiple myeloma, although zoledronate in particular can be effective in other solid malignancies (including lung, kidney and colorectal). They are administered as oral or intravenous agents. The pharmacokinetics differ for the two routes of administration, with oral bisphosphonates having low and variable absorption rates. Intravenous bisphosphonates show a biphasic pharmacokinetic pattern, with rapid renal clearance of approximately 50% in the first 24 h and urinary elimination persisting for many months. Pamidronate has been a standard of care for treating complications of bone metastases and there is increasing evidence for the efficacy of zoledronate.

Prediction of fracture risk

The prediction of fracture risk and prophylactic fixation of impending fractures is controversial. In general, osteolytic lesions are more likely to fracture than osteoblastic metastases. Permeative and focal areas of osteolysis are equally likely to fracture. If more than 50% of the bone diameter is involved, then there is increased risk of fracture. Similarly, an area subject to higher stress is more prone to fracture, examples being the femoral neck, intertrochanteric and subtrochanteric regions of the femur and supracondylar and diaphyseal regions of the humerus. Persisting pain from a metastatic lesion despite medical treatment has also been found to be statistically significant in predicting increased risk of pathological fracture. Cortical lesions extending for more than 2.5 cm are also at increased risk of fracture.

Harrington proposed four risk factors that he felt warranted prophylactic stabilisation based on several studies.

1. Cortical bone destruction greater than 50%.
2. A lesion of more than 2.5 cm in the proximal femur.
3. A pathological avulsion fracture of the lesser trochanter.
4. Persisting stress pain despite irradiation.

Mirels’ score is a weighted scoring system to analyse the risk of pathological fracture in long, weight-bearing bones. It combines four radiological and clinical risk factors. A score of 4–6 indicates a lesion has a low risk of fracture and can be irradiated safely, but a score of 8 or higher demands prophylactic internal fixation prior to irradiation (Table 2).

<table>
<thead>
<tr>
<th>Variable</th>
<th>Score</th>
</tr>
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<tbody>
<tr>
<td>Site</td>
<td>Upper limb</td>
</tr>
<tr>
<td>Pain</td>
<td>Mild</td>
</tr>
<tr>
<td>XR appearance</td>
<td>Blastic</td>
</tr>
<tr>
<td>Size</td>
<td>$&lt;1/3$</td>
</tr>
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Table 2 Mirels’ scoring system for risk of pathological fracture (1989).

- Harrington proposed four risk factors that he felt warranted prophylactic stabilisation based on several studies.
- Mirels’ score is a weighted scoring system to analyse the risk of pathological fracture in long, weight-bearing bones. It combines four radiological and clinical risk factors. A score of 4–6 indicates a lesion has a low risk of fracture and can be irradiated safely, but a score of 8 or higher demands prophylactic internal fixation prior to irradiation (Table 2).
CT and MRI are more accurate at assessing bone destruction by tumour. The risk of a fracture developing depends on the load applied to the bone and the strength of that bone. Bone strength is itself proportional to activity level and lifestyle as well as extent of tumour disease.

Hipp and colleagues\textsuperscript{51} proposed a system whereby an estimate of the load-bearing capacity of a bone can be calculated taking into account defect size, overall bone density and the range of load-bearing requirements. This has been validated for the spine, but not peripheral bones.

Van der Linden\textsuperscript{52} followed 102 patients with 110 femoral metastases and the only risk factors they found to predict fracture were axial cortical involvement greater than 30 mm and circumferential cortical involvement of greater than 50%. They concluded that Mirel’s scoring system would result in unnecessary prophylactic fixation.\textsuperscript{52} They had, however, excluded patients with suspected impending or actual pathological fracture.

All these different methods only serve as a guide. The simplest approach, and the one we use, is that if the lesion is in the weight-bearing skeleton and causes mechanical pain, especially on weight bearing, then it should be stabilised, whereas if it is not then it can be treated by radiotherapy.

Wedin,\textsuperscript{53} in his review of 192 patients treated surgically for skeletal metastases, showed a crude failure rate of 9% for prophylactic fixation compared with 15% for fixation following pathological fracture. They did, however, have two peri-operative deaths directly related to intramedullary nailing of the femur.\textsuperscript{54}

Surgical management

Surgical management of appendicular metastases should never be considered in isolation. It should always be part of a multi-disciplinary team approach, including orthopaedic surgeon, medical and clinical oncologist, radiologist and pathologist plus appropriate paramedical and support staff. Immediacy of surgery is less important than pre-operative planning.\textsuperscript{30} Primary bone tumour should always be excluded, as nailing of a long bone lesion that turns out to be a primary tumour (the “whoops” procedure) is a disaster that often precludes limb-salvage surgery and compromises long-term survival. Surgery may be considered in those lesions that progress following radiotherapy or fail to respond to it.

The aim of surgery for metastatic disease is usually the palliation of symptoms. This includes the relief of pain and the restoration of the ability to walk. It is essential to preserve stability and function. Palliative surgery is unlikely to result in an increased duration of survival. Pathological fractures are prone to slow union and any surgery should aim to improve fracture healing or render it unnecessary by endoprosthetic replacement. The introduction of cement into a fracture site, or the use of local radiotherapy, both slow fracture union. Conservative management should be reserved for the bedridden with a poor life expectancy. The surgical construct should be strong enough to allow immediate mobilisation. Capanna et al.\textsuperscript{6,55} grouped patients into four classes and subdivided the treatment accordingly (Table 3).

Surgical management of spinal metastases is indicated for decompression of the spinal cord and/or nerve roots and to stabilise the spine. This is outside the scope of this review and has been covered in a recent edition of this journal.\textsuperscript{56}

As we have outlined earlier, the goal of metastatic surgery is usually to improve mobility and quality of life for the patients remaining time. The surgeon must take into account the degree of functional impairment, the general condition of the patient and their life expectancy. Bauer and Wedin\textsuperscript{53} reported five positive criteria for survival: absence of visceral metastases, absence of pathological fracture, solitary skeleton metastasis, a primary tumour that is breast, prostate, lymphoma or myeloma, but not lung cancer. Katagiri\textsuperscript{57} has recently proposed and validated a prognostic scoring system for patients with skeletal metastases (Tables 4 and 5). This enables an estimate to be made as to the patient’s chance of survival and the appropriate type of surgical or non-surgical management to be chosen. With a score of 0–2, a nearly 90% chance of 1-year survival should lead the surgeon towards resection and reconstruction rather than simple osteosynthesis techniques.

Pre-operative planning is essential. Hypervascular lesions (renal, thyroid and myeloma) may be subjected to

\textbf{Table 3} Surgical options for differing types of metastases (from Capanna 1999 and 2001).\textsuperscript{6,55}

<table>
<thead>
<tr>
<th>Metastasis</th>
<th>Surgery</th>
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<tbody>
<tr>
<td>I     Solitary metastatic lesion</td>
<td>Aim for long-term cure</td>
</tr>
<tr>
<td>I     Primary with good prognosis (thyroid, prostate, sensitive breast, renal and colorectal)</td>
<td>Wide resection + endoprosthesis replacement (EPR)</td>
</tr>
<tr>
<td>I     More than 3 years since primary detected</td>
<td></td>
</tr>
<tr>
<td>II    Pathological fracture at any site</td>
<td>Proximal femur/humerus—resect and EPR</td>
</tr>
<tr>
<td>II    Diaphyseal—a scoring system is used to predict survival and depending on score: simple osteosynthesis, reinforced osteosynthesis or EPR</td>
<td></td>
</tr>
<tr>
<td>III   Impending fracture in weight-bearing bone</td>
<td>As II</td>
</tr>
<tr>
<td>IV    Osteoblastic metastasis all sites</td>
<td>Conservative management</td>
</tr>
<tr>
<td>IV    Osteolytic metastasis non-structural</td>
<td></td>
</tr>
<tr>
<td>IV    Osteolytic metastasis no impending fracture</td>
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embolisation. Median blood loss has been demonstrated to be lower in spinal, pelvic and appendicular metastases from renal cell primaries when embolisation is utilised on the preceding day or day of surgery. The whole bone must be assessed (MRI or PET or isotope bone scan) as an implant that ends at a more distal lesion will be a stress riser. It is also possible to perforate the cortex at a lesion. Polymethyl methacrylate (PMMA) bone cement augmentation of internal fixation is a useful adjunct that has little effect on bone healing and provides good symptomatic relief. Thought must also be given to the reconstruction utilised. In their series from our unit, Marsden et al. reviewed 69 patients with proximal femoral metastases. Of the 41 that underwent internal fixation, 8 (19.5%) required revision fixation at a mean time of 11 months. This compared with 1 of 28 (3.6%) of those undergoing total hip arthroplasty. Similar results were demonstrated by Wedin, where a 14% revision rate (at a median time to failure of 8 months) was necessary for osteosynthesis techniques compared with a 2% rate for endoprosthetic replacement. The rate of failure was highest in renal metastases and distal femoral metastases. The early failures were due to poor implant choice (hip screws, sliding hip screw, femoral plate and an unlocked nail). Later failures were due to non-union, stress fractures or tumour progression. In Wedin’s series of breast cancer metastases managed throughout Stockholm, there was an 11% (14 of 129) re-operation rate. The most common site for failure was the proximal femur (9 of 60)—of these, seven were treated by osteosynthesis and two by endoprosthesis. Les again showed a higher failure rate for intralcal surgery than wide excision, and also a survival advantage for wide excision.

It is also desirable to avoid placing incisions at sites of previous radiotherapy to reduce the incidence of wound healing complications and infection. Care should also be paid to tension free soft tissue coverage and closure.

### Amputation

Amputation is always an option in metastatic disease. However, for patient psychology and acceptance it is infrequently performed. Indications include, local control of unremitting disease, painful non-union of pathological fractures (either non-treated or those where osteosynthesis techniques have failed), and involvement of skin, soft tissues and neurovascular structures. Severe lymphoedema may also warrant amputation, as may post-irradiation neuropathy and fibrosis. It may also be appropriate where reconstruction is impossible, the limb is functionless, catastrophic bleeding occurs at the tumour site, in the presence of overwhelming sepsis or for pain management. Forequarter amputation for involvement of the brachial plexus and axillary vessels in metastatic tumours is an effective pain relieving procedure.

### Femur

Reconstruction of the pelvis and acetabulum is a complex issue outside the scope of this review. There are numerous techniques including cages, saddle prostheses and extra-corporal irradiation and reimplantation. The topic has been well covered in a review by Choong. Appendicular metastases are commonest around the proximal femur and the knee. The proximal femur is the most common site for pathological fracture and demands surgery in all except those with a life expectancy of less than 6 weeks and the bedridden. Algan and Horowitz have demonstrated good outcomes in terms of pain relief and function with low morbidity in 29 patients with hip lesions that were metastatic. A pre-operative PET scan, bone scan or MRI scan of the entire femur should be performed to assess dissemination locally. If the acetabulum is not involved, we still advocate a cemented total hip replacement rather than a bipolar prosthesis, although others preferred the inherent stability of the bipolar prosthesis. Calcar replacement prostheses may be necessary, as may tumour endoprostheses (Fig. 6). For a lesion confined to the femoral head, a conventional hip replacement may suffice. When using a tumour endoprosthetic replacement, we choose to

### Table 4

<table>
<thead>
<tr>
<th>Prognostic factor</th>
<th>Score</th>
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<tbody>
<tr>
<td>Rapid growth</td>
<td>Hepatocellular, gastric, lung carcinoma</td>
</tr>
<tr>
<td>Slow growth</td>
<td>Breast, prostate, thyroid carcinoma, multiple myeloma, lymphoma</td>
</tr>
<tr>
<td>Moderate growth</td>
<td>Other carcinoma and sarcoma</td>
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### Table 5

<table>
<thead>
<tr>
<th>Prognostic score</th>
<th>Survival rate (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>6 months</td>
</tr>
<tr>
<td>0–2</td>
<td>98</td>
</tr>
<tr>
<td>3–5</td>
<td>71</td>
</tr>
<tr>
<td>6–8</td>
<td>31</td>
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</table>
use a double purse-string technique in the retained hip capsule to enhance stability. We also retain a sliver of greater trochanter in metastatic lesions, freezing it with liquid nitrogen prior to reattaching the trochanteric fragment to the prosthesis. This is of course not an option in primary bone tumours where margins are critical. Retaining the greater trochanter and the abductors also enhances stability. The length of the femoral stem should bypass the most distal lesion by two bone diameters. Tumour endoprostheses should be considered when the proximal bone is too weak to provide stable fixation.\(^1\) Pelvic (acetabular) metastases may require complex periacetabular reconstruction at the time of surgery, however, if the lesion is confined to the acetabulum then the management may be restricted to radiotherapy.

Internal fixation of metastatic femoral neck fracture is unwise given the association with an unacceptably high risk of further subsequent pathologic fracture and the fact that they rarely unite.\(^10\) We avoid the sliding hip screw construct, as it results in stress on the device during ambulation. Tumour progression is highly likely to result in failure of such a fixation device. There is also a stress riser, following radiotherapy, at the distal end of the implant. We therefore prefer to use a cephalo-medullary nail, locked proximally and distally for maximum stability, which is biomechanically superior. In more proximal lesions a conventional arthroplasty or a tumour endoprosthesis is used.

For the proximal femur, PMMA augmented internal fixation is no better in terms of failure than simple internal fixation. Endoprosthetic reconstruction remains a better option. Cemented implants are preferred if radiotherapy is to be given (and we advocate radiotherapy in everyone) as the radiotherapy may affect bone ingrowth or ongrowth in uncemented prostheses.

A significant proportion of femoral metastases are subtrochanteric or diaphyseal (Fig. 7). Once a primary bone tumour has been excluded, these can be treated by antegrade intramedullary nailing using a cephalo-medullary nail such as the Reconstruction Nail (Smith and Nephew, Cambridge, UK) or the Long Proximal Femoral Nail (Synthes, Welwyn, UK). These nails are biomechanically stronger than conventional nails. Cardiopulmonary complications are relatively common. Barwood\(^{57}\) reported an incidence of 24% acute oxygen desaturation and hypotension, and of these 27% died. Peak intramedullary pressures during reaming have been shown to reach 450 mmHg, whereas only 100 mmHg can cause embolisation of marrow contents.\(^{68,69}\) In the absence of a fracture, higher pressures occur due to the absence of an "exhaust vent".\(^{70}\) Consideration should therefore be given to venting the femur (somewhere between the site of the proximal and distal interlocking screws) during the nailing procedure, as this reduces intramedullary pressure by more than 50%,\(^{71}\) or alternatively opening the metastasis prior to nailing.\(^{54}\) Venting can also be carried out both proximally and distally\(^{72}\) but does risk extra-skeletal spread of disease. Increases in intramedullary pressures can also be reduced by using only small, progressive increases in reamer diameter and slow advancement of the reamer.\(^{68}\) Cardiopulmonary complications can further be reduced by pulsatile lavage of the medullary canal.\(^{72}\) There are reported incidences of on-table and immediate post-operative deaths where bilateral intramedullary nailings have been performed either in one sitting or staged\(^{54,73}\) as well as single femoral nailings.\(^{69,73,74}\) In Kerr’s series from Bristol, the incidence of death was 100% for bilateral femoral nailings and 13% for unilateral.\(^{73}\) There is little difference in mortality irrespective of whether the nail is inserted reamed or unreamed. Other authors have reported no increase in mortality with bilateral sequential nailings.\(^{75}\) Where there is significant proximal bone stock loss, and stable fixation is unlikely to be achieved, consideration must be given to a proximal femoral replacement. Solitary diaphyseal lesions, particularly from a renal

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**Figure 6** Proximal femoral replacement following resection of the metastasis in Fig. 1.

**Figure 7** Lytic metastasis of the femoral diaphysis from a non-small cell lung primary. Based on Mirel’s scoring this lesion would score 10 as the patient had functional pain and therefore the lesion was treated by cephalo-medullary nailing.
or thyroid primary, may be resected and treated by intercalary reconstruction.

Prophylactic stabilisation of a diaphyseal lesion is technically easier than fixation after a fracture has occurred and patients frequently make a rapid recovery from surgery.

Capanna has introduced a scoring system for diaphyseal lesions based on survival, biomechanics, the defect size and response to adjuvant therapy. Dependent on the score, the treatment recommended was either osteosynthesis or implant (endoprosthetic reconstruction). Osteosynthesis was subdivided into minimal (Rush nails), simple (locked intramedullary nails) or reinforced (locked intramedullary nails with PMMA cement augmentation). This system is yet to be validated.

Distal diaphyseal femoral lesions have been treated successfully by retrograde nailing with good pain relief and function achieved in most patients, although its use should not be over extended. Short nails are inappropriate as they will lead to stress risers and therefore a long nail should be inserted.

Curettage and supplementary internal fixation is also an option in the distal femur (Fig. 8). Additional local measures can be utilised after curettage to sterilise the margins, including phenol, alcohol, and cryotherapy. Cryotherapy with liquid nitrogen has been shown to be the most effective. PMMA bone cement can also be added prior to internal fixation to stabilise the construct with successful results. 60 It is also possible to add chemotherapeutic agents, appropriately targeted, to the PMMA cement without disturbing the mechanical properties of the cement 76,77 or the effects of the chemotherapeutic agent. 76

In the distal femur if more than 50% of the epiphysis or metaphysis is replaced by tumour then endoprosthetic replacement is our preferred treatment (Fig. 9). We have used a rotating hinge prosthesis with good effect.

Tibia

Endoprosthesis replacement of the proximal tibia, whilst an option, is not as successful as in the distal femur, principally because of problems with the soft tissue cover. Where possible we try to retain the tibial tubercle and the attached patellar tendon. We also swing a medial head of gastrocnemius as a flap around the front of the prosthesis to cover the implant. This often necessitates a split skin graft to obtain skin cover.

Internal fixation with a tibial nail must be sufficiently sound as to allow early weight bearing. Therefore, nails should be locked both proximally and distally. It may be necessary to augment fixation with PMMA, and the whole bone must be addressed.

If less than half the epiphysis or distal tibial metaphysis is involved by tumour then satisfactory outcomes (pain relief, avoidance of fracture) can be obtained with curettage, cementation and plate fixation.

Figure 8 (A) Lytic lesion in the distal femur (renal cell metastasis). Initial treatment (B) was a locked cephalomedullary nail. Ongoing pain and tumour progression necessitated a further procedure and the lesion was curetted and fixation augmented with PMMA cementation (C).

Figure 9 (A) Distal femoral metastasis from metastatic malignant melanoma treated by (B) distal femoral replacement.
Foot and ankle

Metastases distal to the knee are far less common than those occurring more proximally. Usually radiotherapy suffices for most metastases but pain can be unremitting and resistant to radiotherapy. Options for treatment include local curettage with either bone grafting or cementation (Fig. 10) or below knee amputation. Pathologic fractures can usually be treated in a cast with supplemental radiotherapy. Metastatic lung cancer can affect the small bones of the foot (Fig. 11) and is often rapidly destructive. Radiotherapy is the first line treatment.

Humerus

Endoprosthetic replacement of the proximal humerus (Fig. 12A and B), whilst sacrificing function, is effective at relieving pain. If the lesion is confined to the humeral head then a conventional shoulder hemiarthroplasty can be utilised. Infection and instability can be problems after proximal

Figure 10  (A) Isotope bone scan and (B) CT scan demonstrating large lytic lesion in the talus (metastatic breast cancer) treated by (C) curettage and cementing.

Figure 11  Lung metastases affecting the distal phalanx of the great toe.

Figure 12  (A) Metastatic prostatic carcinoma of the proximal humerus treated by (B) proximal humeral replacement.
humeral replacement. The main indications for prosthetic replacement are inadequate bone to stabilise a fracture or excessive bone destruction. It is important to reattach the muscles of the rotator cuff. Again we use a double purse-string reconstruction of the retained capsule to enhance stability if there is sufficient capsule. Where there is insufficient capsule we use polypropylene mesh augmentation of the cuff and capsule. Excision of a metastasis without reconstruction may be appropriate in some patients and is cosmetically more acceptable than a forequarter amputation.

Intramedullary nailing, either antegrade or retrograde can treat the majority of metastatic lesions in the humerus. The nail should provide sufficient stability for early mobilisation. Subsequently radiotherapy is utilised. If the patient has a very limited life expectancy then a humeral brace may be sufficient.

The distal humerus is more complex. Endoprosthetic replacements are available but infrequently utilised. More
commonly plating augmented with PMMA bone cement is adequate (Fig. 13).

Flexible intramedullary nailing is a technique usually reserved for children. However, in exceptional cases the technique may be used for pathological humeral fractures. If a metastatic lesion is very distal or very extensive, this may preclude both antegrade and retrograde conventional nailing. Stability can be provided by two flexible nails inserted retrograde through the epicondyles, enabling recovery of function\(^7\) (Fig. 14).

**Radius, ulna, carpus and hand**

Metastases in the forearm bones are uncommon (Fig. 15). Small lesions can be treated by curettage, cementation and conventional plating. More extensive lesions can be resected. It may simply be necessary to biopsy the lesion to establish a diagnosis and manage the fracture non-operatively in a plaster cast. Metastases affecting the small bones of the wrist and hand warranting surgery are unusual. Radiotherapy may, however, result in post-operative contractures and functional impairment.

**Risks and complications of surgery**

Patients with skeletal metastases tend to have co-morbidities increasing the general risks of surgery and anaesthesia. There are other more specific risks also worthy of consideration:

1. **Embolism:** particularly in those patients with metastases affecting the long bones and on reaming or insertion of an intramedullary nail. Tumour emboli or fat emboli can result in cardiac arrest. Trans-oesophageal echocardiography can be diagnostic.

2. **Infection:** chemotherapy and radiotherapy especially pre-operative but also post-operative can make patients susceptible to infection. We use a 6 week course of antibiotics when we implant a tumour endoprosthesis.

3. **Haemorrhage:** the risk of haemorrhage can be reduced by judicious use of pre-operative embolisation of tumours likely to be highly vascular (e.g. renal cell metastases). We try to embolise either on the morning of surgery or the preceding day.

4. **Dislocation:** tumour endoprostheses have a reputation for dislocation. Often this is because of the degree of
soft tissue sacrifice necessary to obtain tumour clearance. Usually surgery for metastatic disease is palliative and therefore such radical margins are not necessary. We try to reduce our dislocation rate by a double purse-stringing of the capsule (in the hip and shoulder) as well as retaining the hip abductors by freezing the remnant of greater trochanter with liquid nitrogen. We also utilise polypropylene mesh to augment the capsule where necessary (particularly in the shoulder).

(5) Radiotherapy-related complications: infection has already been mentioned but if the native bone remains, and is part of the radiation field, avascular necrosis can occur (Fig. 16). This can result in pathological fracture. There is a theoretical increase in the rate of stress fractures or non-union but this complication developed in only 13/136 patients in the series by Wedin. 53 Radiotherapy-induced osteonecrosis can be marked, verging on the untreatable, as illustrated in Fig. 17.

Conclusion

The management of appendicular skeletal metastases requires a multi-disciplinary approach. It is essential to exclude a primary bone tumour prior to employing osteosynthesis techniques. Impending fractures are technically easier to stabilise than displaced fractures, but prophylactic stabilisation remains somewhat controversial. Prognosis is important in determining the appropriate surgical treatment with simple measures for those with the poorest prognosis and resection and reconstruction for those expected to survive more than 1 year.

References


