Controversies in the surgical management of skeletal metastases

The management of skeletal metastatic disease has attracted increasing attention during the past decade. In orthopaedic practice there is an increased demand for reconstructive surgery for both pathological fractures and in the management of paraplegia from compression of the spinal cord. By applying surgical techniques which have been developed in joint arthroplasty, trauma surgery, degenerative spinal disease and limb-sparing surgery, the orthopaedic surgeon is well armed for the restoration of function in cancer patients who have skeletal complications.

The possibilities of treatment have not only increased in orthopaedic surgery but also in other specialties. For example, advanced management of pain can ensure freedom from pain until death, while improved techniques in radiotherapy give better analgesia with fewer complications. Home-based hospice care also allows more patients to lead an independent life. Improved knowledge of the pathophysiology of cancer-induced bone destruction has allowed the development of new drugs such as bisphosphonates, the indications for and benefits of which have not yet been fully explored.

The art of caring for the patient with bone cancer is to choose from these different treatment modalities in order to give the best palliation while minimising side-effects. A variety of treatments should be explored before embarking on an orthopaedic surgical adventure.

This paper will consider the diagnosis of bone lesions, the case for prophylactic stabilisation of an impending fracture, and the choice of reconstructive techniques after pathological fracture of the long bones or the acetabulum. The orthopaedic management of pathological fractures caused by haematological malignancy is similar to that needed for metastatic carcinoma. The former are also considered here although they do not represent true metastatic disease.

This paper is based upon the experience gained from patients who were treated at the Department of Orthopaedic Surgery at the Karolinska Hospital between 1986 and 2003. The data have been prospectively collected and now include 451 patients with an unknown primary cancer presenting with a bony lesion and 1028 who underwent surgery for fracture or impending fracture of a long bone (606) or the pelvis (73), or for spinal metastases (349) (Table I).

Diagnosis of skeletal metastases

The most common malignancies with a lesion of bone as their first presentation are myeloma, lymphoma and cancer of the lung and kidney. Cancer of the prostate and breast, although the most common origin of bony metastases, rarely present with bony metastases as the first sign of the disease. There are two different ways in which to investigate a patient with a bone lesion and without a previous history of cancer. The standard approach is to follow an algorithm of clinical examination, laboratory tests and imaging studies, and only proceed to a biopsy when these tests are negative. Most primary tumours will be diagnosed in this way although a number of examinations will be performed unnecessarily. The alternative approach is to proceed directly to a fine-needle biopsy for cytological diagnosis, which in many cases will be diagnostic.

In others, the result of the biopsy can guide the clinician as to where to look for the primary tumour (Fig. 1). In patients with an undiagnosed spinal lesion a needle biopsy should be performed primarily, except for paraplegic patients for whom urgent surgical decompression and stabilisation are indicated.

Fine-needle biopsy will be diagnostic in most myelomas and lymphomas. In an analysis of 100 patients with metastatic carcinoma, cytology correctly suggested the origin of the primary tumour in 51, allowing guided radiological studies in order to establish the primary site of the tumour. Core needle biopsy for histological diagnosis gives a similar result. An open biopsy is seldom necessary.
Patients with a solitary bony lesion must be referred to a sarcoma centre for diagnosis since a primary sarcoma must be assumed.\(^{11}\) In patients who present with a pathological fracture and without a history of cancer, needle biopsy will quickly discriminate between the many with a carcinoma or haematological malignancy and the few with a primary sarcoma. Some external splintage is sufficient to allow transport to a sarcoma centre for the needle biopsy.

**Survival for patients with pathological fracture**

For most patients a pathological fracture heralds the end-stage of their disease. Half will die within six months of surgery for pathological fracture or paraplegia and only a few will survive for several years (Fig. 2). It is of interest that the survival of patients who underwent surgery for bone complications is similar to that for cancer patients who were treated by radiotherapy for bone pain. In a large, randomised trial of radiotherapy for bone pain, the median survival was six months as compared with six months for patients operated upon for bone complications.\(^{12,13}\) The
rate of survival varies widely between operated series because of differences in patient selection. For example, the rate of survival of patients who received surgery at the Karolinska Hospital for an acetabular fracture was considerably higher than that of those operated upon for paraplegia or fracture of a long bone (Fig. 3). Patients with an acetabular fracture can be selected for surgery, whereas a fracture of the mid-femur, or a paraparesis, requires emergency surgery.

Prediction of the survival of patients with a pathological fracture has been increasingly studied in recent years. The rationale is that the reconstructive procedure for a patient who will survive for two months may not necessarily be the same as that for one who will live for two years. Several clinical variables are recognised as being prognostically significant. These include the extent of the bony metastases, the presence of soft-tissue metastases, and the type of primary lesion. In a recent prospective study, based upon the skeletal metastasis register of the Scandinavian Sarcoma Group, a pathological fracture, visceral metastases, haemoglobin < 7 mmol/l and cancer of the lung were independent, negative prognostic factors for survival for one year (Table II). Myeloma was the only positive prognostic factor. These variables can be converted into scores which provide good discrimination between those with a low or high chance of surviving for one year after surgery. There are limitations to these scoring systems since they need to be prospectively validated. The type of patient and the surgical indications differ among both institutions and countries. For example, when validating the Tokuhashi score based upon Japanese patients with spinal metastases, 3% of patients had cancer of the prostate and 65% were neurologically compromised. Meanwhile, in a series from the Karolinska Hospital, 40% of the patients had cancer of the prostate and 92% were neurologically compromised.

Consequently, a prognostic scoring system should be validated for the type of patient treated as well as for the surgical indications applied. Furthermore, patients with the same primary tumour will have a very different prognosis depending upon when in the course of their disease their pathological fracture occurs (Fig. 4).

Other clinical features which are well known in palliative care, such as weight loss, functional ability, and opiate intake may be more valid when identifying those at high risk of dying in the first months after surgery. Prognostic information would clearly be useful in this situation, for example, in deciding whether or not to stabilise the spine after spinal decompression.

Although a cure for metastatic bone disease is hardly achievable, there are some patients who will have a lengthy survival. In the series from the Karolinska Hospital, 54 (9%) patients have survived for more than five years from a

Table II. Multivariate analysis of prognostic factors for survival, based upon 460 patients operated upon for fracture or impending fracture of the acetabulum or long bones, from the skeletal metastasis register of the Scandinavian Sarcoma Group. Coefficient values are the results of the Cox proportional regression analysis

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<th>Factors</th>
<th>Coefficient</th>
<th>SD</th>
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<td>Myeloma</td>
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total of 632 patients who underwent surgery between 1986 and 1998 (Table III). Except for myeloma, the kidney was the most frequent primary site of cancer, which perhaps reflects the selective referral of kidney cancer patients with solitary metastases to a sarcoma centre. There is no reason to believe that surgical treatment influences the chance of long-term survival. Of the 54 patients who survived for five years or more, 25 had multiple skeletal or skeletal and visceral metastases. A solitary skeletal metastasis was found in 29 patients but only five of these underwent an en bloc excision.

Management of patients with an impending fracture
There has been great interest in, but few studies on the problem of identifying those patients who are at risk of fracture. The most cited study was performed by Mirels\(^\text{18}\) who, in 1989, devised a scoring system based upon pain and the site, size and radiological appearance of a lesion in order to assess the risk of subsequent fracture. The study was based upon only 38 patients, of whom two-thirds had cancer of the breast. In an assessment of Mirel’s system, the reproducibility between observers was good and the sensitivity of predicting a pathological fracture was 91%, although the specificity was only 35%.\(^\text{19}\) There are clear limitations to this system.

The principle of prophylactic surgery in patients who are thought to be at risk of fracture is questionable. Prophylactic nailing is not performed on the hips of elderly women with osteoporosis who are at risk of a fall. They may be given, however, protective braces while attempts are made to treat their underlying medical condition. Similarly, in metastatic bone disease an attempt should be made to prevent fracture, by radiotherapy and the administration of bisphosphonates, with surgery only being performed once the fracture has occurred. There are several reasons for this. First, survival curves show that if the bone does not fracture within three months, the chance of death occurring within that time is 35%. Secondly, a pathological fracture is a relatively rare event. In two trials of radiotherapy for bone pain, the rates of a long bone fracture were only 5% and 10%, respectively.\(^\text{12,20}\) Similarly, in a population-based study of patients with cancer of the breast and bony metastases, the risk of fracture of a long bone was 12%.\(^\text{21}\) Thirdly, prophylactic stabilisation is not like a vaccine. Surgical reconstruction carries the risk of complications and a reduction in the overall function of the patient, for example, by the need for hospitalisation for up to four weeks instead of remaining at home (Fig. 5).
Surgical treatment should be reserved for those who have clearly impaired function because of bony metastases. For example, if the patient cannot walk or use their arm because of pain from metastases, surgical treatment will allow the fastest restoration of function. In conclusion, the indication for surgical treatment without a clear fracture is loss of function, although functional ability, the extent of the disease and the appearance of the metastasis must be taken into account.

If this strategy is to be followed, it is important to inform the patient that a fracture may occur but that treatment will not be more difficult because of it (Fig. 1). Most orthopaedic surgeons are more experienced in operating on fractured than on unfractured bone. Indeed, there are reports that the risk of thromboembolism is higher if the bone has not fractured pre-operatively, although the survival after prophylactic stabilisation is better than that after surgery for a pathological fracture. This is not because of the surgery but more as a result of the selection of patients since those with fractures are likely to have more advanced disease than those with an impending fracture.

**Treatment of a solitary skeletal metastasis**

A controversial issue is the choice of treatment for a patient with a solitary bony metastasis but without a pathological fracture. It is tempting to remove the lesion with a wide surgical margin, as if it was a sarcoma, with the aim of curing the patient from cancer. This approach will generally disappoint both the surgeon and the patient. It is important to look at both the prognosis and options for treatment. For a patient with cancer of the lung, the prognosis is so poor that extensive surgery is contra-indicated. For those with cancer of the breast or prostate, or myeloma/lymphoma, their survival for two years is good, but there are other oncological treatments which will ensure local control.

Cancer of the kidney appears to be the only type of cancer which is relatively common, often presents with a solitary bone metastasis, is associated with good survival for two years, and for which there is no dependable oncological treatment (Table III). Its metastases account for a large proportion of the failures among patients who undergo surgery for a pathological fracture. In an analysis of the failures of treatment for pathological fractures of long bones, cancer of the kidney was the primary tumour in 15% of the patients yet accounted for 30% of the failures. Furthermore, it was the primary tumour in 40% of patients referred to the Karolinska Hospital after failure of treatment of their pathological fracture elsewhere.

Although there are no trials, there is good evidence that wide excision and reconstruction for a solitary metastasis from cancer of the kidney will ensure long-standing local control and function. At the Karolinska Hospital nine patients have been treated for a solitary metastasis from cancer of the kidney by wide or marginal excision and reconstruction. There have been no local recurrences and none has required a revision for failure of the implant. Although the rate of survival at one year was high (90%), this had reduced to 20% by five years. Cure therefore is sel-
dom achievable. In patients who present with a solitary bony metastasis at the time of the diagnosis of their primary renal tumour, both a nephrectomy and bony reconstruction are undertaken at the same time (Fig. 6). There are other rare types of cancer such as thyroid and neuroendocrine tumours, in which wide excision of a solitary bony metastasis may be indicated. Referral to a sarcoma centre should be considered for patients with such metastases and a good chance of survival for more than one year.

**Choice of reconstructive method for the proximal femur**

It is uncontroversial that pathological fractures of the femoral neck be treated by endoprosthetic replacement while fractures of the diaphysis may be managed by an interlocking nail. In trochanteric and subtrochanteric pathological fractures there is a choice between reconstruction nails with locking screws into the femoral head, or endoprostheses. There is no place for glide-screw devices. Reconstruction nails have some advantages over endoprostheses since they can be inserted by a closed technique and can stabilise the whole femur. However, nails are only load-sharing devices and will break if the fracture does not heal. They are also not as stable as a cemented endoprosthesis and may not provide the same immediate relief from pain. There are, however, no comparative controlled studies between nails and endoprostheses in these circumstances and it is questionable as to what extent retrospective analyses are valid. In an analysis of failures of 228 procedures for pathological fracture of long bones, osteosynthesis was associated with a rate of failure of 14% as compared with 2% for endoprostheses. However, when comparing interlocking nails and endoprostheses in only the trochanteric and subtrochanteric regions there was no difference, i.e. 2/20 and 0/20 failed, respectively. Whether reaming for a nail or inserting a long-stem prosthesis, the risk of cardiopulmonary complications must be taken into account, especially in patients with pulmonary disease.

A reasonable approach may be that when trochanteric destruction involves the femoral neck an endoprosthetic replacement is indicated. Furthermore, if there is a good chance of survival for more than one year an endoprosthesis is also indicated in order to avoid the problems of non-union and stress fracture. For the remaining patients closed nailing may be preferred as this does not risk dislocation and has a reduced chance of problems with wound healing. When an endoprosthetic replacement is chosen the entire trochanteric region need not be removed. Preservation of the greater trochanter, with its soft-tissue attachments, adds to the stability of the prosthesis (Fig. 1). If nailing is chosen, reaming is advisable since a nail of wider diameter may provide better stability, less pain, and may also reduce the risk of breakage of the nail or pseudarthrosis (Fig. 7). This also applies to the humerus. In diaphyseal lesions, reconstruction nails are preferred in order to reduce the risk of later fracture of the femoral neck (Fig. 8).
The choice of arthroplasty is also an important issue in reconstruction of the proximal femur. A hemiarthroplasty can be used if there is no degenerative change and no acetabular metastatic disease. In view of the poor rate of survival, few of these patients are at risk of pain from secondary degenerative change after hemiarthroplasty. A total hip arthroplasty, with a reinforcement ring, is performed if there is acetabular destruction. However, there are no data on whether a standard or long-stemmed femoral component should be used. A long stem may prevent further fracture if the destruction extends down the femur but may increase the risk of thromboembolic complications. It is clearly important that pre-operative radiographs are taken of the whole femur. At the Karolinska Hospital we choose a femoral stem which extends at least 12 cm below the area of bone destruction. When there is very extensive bony damage, or after a failed reconstruction, a modular prosthesis such as may be used in surgery for sarcoma can salvage a difficult situation (Fig. 9). In patients with solitary metastases, when an en-bloc resection is considered, pre-operative MRI is performed.

Pelvis

Although the pelvis is one of the commonest sites for metastatic involvement, surgical treatment of lesions in this area has not attracted as much attention as that for metastases in the long bones or spine. Surgical treatment is rarely required for pathological fractures of the pelvis other than for those involving the acetabulum. When the hip is involved by fracture, or the subchondral bone is destroyed by metastatic growth, pain-free function will not be restored without reconstruction of the joint. Radiotherapy may achieve local control of the tumour but will not improve the pain caused by destruction of the joint. Sometimes, destruction is the result of radiotherapy-induced bony necrosis. Irrespective of the cause of the damage reconstruction requires total hip arthroplasty with acetabular reinforcement by cement, rings and/or pins.

Most adenocarcinomatous metastases, such as those originating from the breast or prostate, are not associated with excessive bleeding. However, metastases from renal tumours often bleed profusely and fatal bleeding has been reported during surgery for spinal metastases. Angiography and embolisation are often indicated before surgery for renal metastases to the pelvis and spine. In the limbs, uncontrollable bleeding is less of a risk.

A reinforcement ring inserted after curettage of the lesion, supplemented by cement, will normally suffice to restore the acetabulum. These procedures can be performed by surgeons who are experienced in acetabular reconstruction for loosening of prostheses. If the bony destruction is extensive, threaded pins introduced through the iliac crest in a fan-like manner will augment stability. Such cases should probably be referred to a sarcoma centre with experience in the treatment of patients with primary pelvic bone tumours.
Paraplegia caused by compression of the spinal cord is a devastating complication of metastatic bone disease which can be caused by growth of an epidural tumour and/or a pathological fracture of the spine. With severe neurological deficits, an urgent decompression of the spinal cord combined with spinal stabilisation will, in many cases, restore lasting function.\textsuperscript{7,33,34}

In patients without neurological deficit, radiotherapy, chemotherapy and/or hormone treatment should be considered initially regardless of whether or not the metastasis is solitary (Fig. 10). In patients with an undiagnosed spinal lesion, there is evidence for the value of doing an initial needle biopsy except if the patient is frankly paraplegic, in which case surgical decompression and stabilisation are indicated.\textsuperscript{7} The place for surgical treatment in patients without a neurological deficit remains unclear. Vertebrectomy has attracted much attention recently although there are few indications for it. Percutaneous cementation of the vertebral body (vertebroplasty or kyphoplasty), first developed for the osteoporotic spine, is being used in the management of osteolytic destruction by myeloma or metastases but the benefits compared with radiotherapy alone are unknown (Fig. 11).\textsuperscript{35}

External beam irradiation is the treatment of choice for patients with pain from spinal metastases and without a neurological deficit. Prospective trials of radiotherapy show a rate of improvement of 60\% to 80\% and a risk of developing a severe neurological deficit of less than 10\%.\textsuperscript{12,20} For most patients, the palliative effect of radiotherapy will last until death and for those with recurrent pain, further radiotherapy will often be beneficial. Consequently, most patients with spinal metastases, and with cancer of the breast, prostate or lung, can safely be managed by radiotherapy. Nevertheless, there are patients with severe pain from spinal instability who will benefit from surgery, even without a neurological deficit being present.

The debate about prophylactic stabilisation for the prevention of pathological fractures of long bones can also be applied to spinal metastases. It is questionable whether there is an indication for surgery in order to prevent neurological complications or pathological fractures. The prognostic scoring system developed by Tokuhashi et al,\textsuperscript{15} and further developed by Tomita et al,\textsuperscript{16} which is based upon the extent and treatability of metastatic disease, can easily differentiate between long- and short-term survivors. However, such a scoring system cannot be used to dictate surgical indications. If the metastasis is confined to the vertebral body, without tumour or bone fragments compressing the neural elements, a vertebrectomy with a marginal margin is feasible, but such patients do not require surgery. There are rare examples of solitary spinal metastases in patients with a good chance of long-term survival and for whom an extensive excision of the tumour is indicated in order to achieve local control.\textsuperscript{36}

For patients with a major neurological deficit, surgical decompression of the neural elements and stabilisation is indicated. For patients with limited disease, without cardiopulmonary dysfunction, and with a gibbus deformity, anterior decompression with curettage of the vertebral body, cementation and anterior fusion may be a better choice. For the commoner situation of a patient with several metastatic
sites, posterior decompression and stabilisation are adequate (Fig. 12). There is no consensus on whether stabilisation should be performed through an anterior or posterior approach since deformity and instability can be improved by either. It is frequently stated that anterior procedures give better results, but this is probably a function of patient selection.

Irrespective of which approach is chosen, there is a major risk of wound or systemic complications. A strategy is, therefore, required in order to reduce the rate of complications and to avoid operating on those patients who will not benefit from surgery. The problem is not of identifying the patient with a good survival at two years, but of identifying the patient who will die of cancer or complications after only three weeks. It is difficult to define how short survival can be and yet still be regarded as worthwhile. If a paraplegic patient undergoes surgery without complications and regains the ability to walk for the last two months of his life, then surgery is clearly beneficial. However, if there is no functional improvement after surgery and, instead, postoperative infection and increased pain occur, the patient’s final months will have been made significantly worse. Solving this problem requires the follow-up of not only those patients who are accepted for surgery, but also those who are not. Studies are needed to follow-up neurological function, pain and survival. This also applies to those who are treated non-operatively but still have clinical or radiological signs of epidural compression.

Outcome
For the past 20 years, the assessment of the benefit of orthopaedic interventions has focused on functional outcomes, largely based upon subjective scoring schemes. It is questionable whether the assessment of functional outcome has played any part in the improved results of fracture or arthroplasty surgery. In metastatic bone disease it is even more meaningless to assess functional outcome as a means of improving results.

Assessment of outcome should instead focus on failures. A better outcome in arthroplasty has been achieved, not by analysis of hip scores, but by carefully recording breakage of the implant, infection and aseptic loosening. Similarly, patients who have undergone surgery for a pathological fracture should be followed up until they die. Even in published series of pathological fractures, many patients are lost to follow-up, making it difficult to draw conclusions. In 2000, the Scandinavian Sarcoma Group started a metastasis registry for patients who had undergone surgery for bony metastases of the pelvis or long bones. The aim was to gather information prospectively from a large data pool, collected at several institutions, as opposed to the retrospective, single-institution studies which dominate the literature.

There is a clear risk that many patients are left untreated because of the defeatist views of an oncologist or the lack of experience in advanced surgical reconstruction by the attending orthopaedic surgeon. Patients deemed inoperable may benefit from referral to centres which are specifically dedicated to palliative surgery. Perhaps the most important challenge for those orthopaedic surgeons who treat patients who suffer the skeletal complications of cancer is to disseminate and to apply the current knowledge in this complex field.
References