Management of metastatic bone disease in the appendicular skeleton

INTRODUCTION

The number of new cases of metastatic bone disease is spiralling. In the United States alone, there are approximately 280 000 new cases per annum, and this is expected to rise. The most likely reason for this is that patients are living longer with their illness.[1,2] The health economic and funding implications are significant, and are estimated at $12.6 billion per annum in the United States, accounting for 17% of the total annual cost of cancer treatments.[3] Bone metastases occur most frequently within the spine, pelvis, and proximal femur. Post-mortem studies have shown that approximately 70% of all patients with breast and prostate cancer, and 35% to 42% of those with lung, thyroid, and renal cancer, have developed metastatic spread to bone.[4] Bone metastasis can be associated with debilitating complications including pain, hypercalcaemia, restricted mobility, fracture, and spinal cord compression. These severely impact on the patient's quality of life and affect the treatment of their primary tumour.[5,6]

There has been a recent shift in treatment strategy towards limb salvage and reconstructive procedures alongside the improvement in systemic therapies in orthopaedic oncology. This has resulted in improved prognosis and allows for better function and better palliative surgical management. Furthermore, there is evidence that resection *en bloc* of a solitary metastasis may improve overall survival.[7] The Scandinavian Sarcoma Group (SSG) have established a prospective, multicentre, skeletal metastasis registry to evaluate treatment options and prognostic factors in surgically treated, non-spinal skeletal metastasis. With ten years of data and 672 patients, they were able to show a mean significantly enhanced survival across all tumour groups of 20 months after resection *en bloc* of solitary metastatic lesions. Their evidence for solitary renal metastasis, in particular, showed a fourfold increase in survival after resection of a solitary lesion when compared with intralesional surgery. Malignant primary bone tumours are normally referred to a tertiary bone tumour centre; however, much of the management of skeletal metastases can be, and is, provided by local orthopaedic units. Tailoring treatment decisions surrounding surgical management for individual patients involves multiple factors such as the specific site of the lesion, the associated pain, the patient's performance status and comorbidities, the primary tumour, and the prognosis of the disease. Impending or current pathological fractures complicate the picture further, and any surgical management aims to relieve pain and to be robust enough to match a patient's life expectancy. The historic workhorse of surgical management has been internal

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Criteria	Score		
	1	2	3
Site	Arm	Leg	Peritrochanteric
Pain	Mild	Moderate	Functional
Lesion	Blastic	Mixed	Lytic
Size	< ⅓	⅓ to ⅔	> ⅔

Table I. The criteria used to determine Mirels' score. Lesions presenting with a score of greater than 8 should be prophylactically fixed.

fixation; however, resection and endoprosthetic replacement is becoming more widely used.[8,9]

SURVIVAL

A systematic review by Kirkinis et al[10] reports the one-year survival of patients presenting with metastatic bone disease as varying between 17% and 69.5%. However, this review specifically highlights two articles, involving large numbers of patients, from the same tumour registry (The Scandinavian Sarcoma Group), giving survival rates at one year of 39%[11] and 41%.[12] Interestingly, these two studies also focused primarily on appendicular skeletal metastasis. In renal cell carcinoma, the one-year survival rate following orthopaedic intervention ranged from 47% to 84%.[13,14] When focusing on breast cancer exclusively, two studies gave a survival rate of 59%[15] and 45%,[16] whereas for prostate and lung cancer the one-year survival has been reported as 29%[17] and 13%,[18] respectively. Patient survival is multifactorial, although Hansen et al[11] found that those with myeloma, lymphoma, breast, or renal cancer had a higher survival rate at one year than those presenting with lung cancer, melanoma, and cancer of unknown primary. Further multivariate analysis showed lung cancer to be an independent negative predictor of survival with myeloma as a positive prognostic survival factor.[11] Nonetheless, other studies disagree, with Ratasvuori et al[12] asserting that breast, renal, and thyroid cancer, as well as myeloma and lymphoma, are positive prognostic indicators after multivariate analysis. This contrasts with Schneiderbauer et al,[19] who, in 2004, reviewed 299 patients having had a hip arthroplasty for metastatic bone disease and found that those with renal or lung cancer had a poorer survival. Aside from the nature of the primary lesion, another potentially important survival predictor is the presence of a complete, rather than impending, fracture. Again, though, there are contrasting views, with articles to support this variation in opinion. There are many studies showing that pathological factors lead to a poorer outcome,[11,17,18,20,21] with further multivariate analysis showing fracture to be an independent poor prognostic indicator.[11,18] However, Ratasvuori et al[12] showed that, while mean survival times differed, there was no statistically significant difference between true (7.5 months) and impending fracture (11.9 months) with regard to survival in a large study reporting the outcomes of 1107 cases.

The presence of visceral metastatic spread is a negative predictor of survival in multiple studies,[11,12,15,17,21] and a study by Lin et al[13] has shown better survival in bone than in pulmonary metastases.

SURGICAL MANAGEMENT

Patients with metastases of the appendicular skeleton often present after an acute fracture, with unexplained pain, or after referral with a known disease that has developed new symptoms or a change in their staging. The role of the orthopaedic surgeon with respect to the appendicular skeleton is: 1) biopsy to establish diagnosis (when required); 2) assess suitability for surgery; and 3) surgically treat for pain and fracture prevention and stabilization or reconstruction following fracture.[22]

A full history and examination of these patients should be performed including: relevant blood tests; radioisotope bone scans; staging CT of the thorax, abdomen, and pelvis; and a MRI scan of the lesion. Often, patients will require discussion with or referral to a tertiary bone tumour centre. Biopsy should be performed, particularly if there is any doubt as to the primary diagnosis, or when there is a solitary bone metastatic lesion, but only after discussion with, or by, the surgical team providing definitive treatment. The biopsy should be performed via the extensile approach that definitive surgery will utilize to prevent seeding of the tumour.

Orthopaedic surgeons traditionally use Mirels' score[23] to help guide them when deciding whether to treat a bony metastatic lesion surgically. This system uses four radiological and clinical risk factors and condenses them into a single score, the risk factors being the size and specific site of the lesion, the type of lesion, and the patient's pain, each with a score of 1 to 3 (Table I). The score was based on 78 long bone lesions, over six months, which had been treated with radiotherapy. Of these, 27 fractured, of which the mean score was 7. Of those that did not fracture, the mean score was 10. Mirels' recommendation was that lesions presenting with a score of greater than 8 should be prophylactically fixed, while a score of 7 or less could be treated with medical treatment and radiotherapy with minimal risk of fracture. However, patients presenting with a Mirels' score of 8 represent a clinical dilemma (the probability of fracture is 15%) and Mirels suggested, therefore, that management should be up to the clinical judgement of the surgical team. The most important risk factor is the presence of functional pain; this should be specifically assessed in the clinical history.[24] The sensitivity and specificity of this scoring system is 91% and 35%, respectively, suggesting that there is a high false positive rate; therefore, unnecessary procedures are being performed when treatment is guided by Mirels' score alone.[25] For established fractures, the surgeon should be aware that these may not unite with standard fixation and stabilization techniques, and, as such, the primary aims of surgery being pain relief and the resumption of normal function and mobilization may not come to fruition.[26]

	Subcategory
M1a	Separate tumour nodule(s) in a contralateral lobe; tumour with pleural or pericardial nodule(s) or malignant pleural or pericardial effusion
M1b	Single extra-thoracic metastasis
M1c	Multiple extra-thoracic metastases in one or more organs

Table II. Subcategories of metastasis (M) proposed by the International Association for the Study of Lung Cancer (IASLC).[41]

Orthopaedic treatment for metastatic bone disease is complex and dependent on a number of variables, such as the primary tumour, the site of bone spread, and the expected prognosis and survival of the patient. These variables help to guide the surgical strategy and implant choices. When considering the prognosis and survival of the patient, current thinking is that, if there is an impending or pathological fracture present with severe or chronic pain, and if the life expectancy is greater than six weeks, surgery should be considered.[27] It is worth noting that current evidence suggests that around 50% of patients will die within six months of surgery for their fracture or impending fracture.[28] However, the present studies that propose treatment guidelines are not comprehensive and can leave surgeons with difficult clinical decisions to make. This may result in inappropriate implant choice, as the prospect of bony union is not as favourable in metastatic bone disease.[6,29] The principles of orthopaedic treatment of metastatic bone disease are to rule out a primary tumour of the bone, to provide adequate stability, and, consequently, to allow immediate weight-bearing. The surgeon should assume that the fracture will not unite, the fixation should last the lifetime of the patient, and treatments should reflect the stage of the disease and the patient's wishes.

The British Orthopaedic Association (BOA) released their revised 'Guide to Good Practice' in 2013,[22] in which they make many surgical recommendations. For instance, in proximal femoral lesions, if the lesion is limited to the femoral neck or head, a cemented hemiarthroplasty or total hip arthroplasty should be the primary procedure. If the lesion is subtrochanteric with minimal bone loss and the life expectancy is 'limited', a cephalomedullary device with screws into the femoral head is recommended. For more extensive bone loss in patients with a better prognosis, the best option, both from a functional and longevity perspective, is primary excision and an endoprosthetic replacement that facilitates early weight-bearing. Regarding the diaphysis of the femur and tibia, intramedullary nailing is recommended by the BOA, with the use of polymethylmethacrylate (PMMA) highlighted as an option to fill defects and provide further stability. As these implants will be load-bearing rather than load-sharing devices, consideration should be made to using solid nails of a larger diameter to reduce the risks of fatigue failure. Endoprosthetic replacements are utilized when the bony destruction is large enough that intramedullary nailing will not provide stability or when there is a solitary lesion present. These allow for early weight-bearing and rapid rehabilitation, while also being associated with lower mechanical failure rates compared with intramedullary nailing.[9,30-32]

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PRIMARY SPECIFIC TREATMENT

Concerning evidence for treatments of renal cell carcinoma, Fottner et al[20] retrospectively reviewed 101 patients treated operatively for skeletal metastasis, finding that those patients with a solitary metastasis had significantly better long-term survival (44% *vs* 10% at five years) and that local recurrence was significantly lower in patients with a wide surgical excision yielding cancer-free margins. Similar findings were published by Les et al,[33] who reviewed 78 patients, all with renal cell carcinoma, and showed that those who had had a wide resection underwent fewer subsequent reoperations for local progression of the disease, as well as reporting an increased mean overall survival of 35 months *versus* 20 months in the group that had intralesional surgery. A smaller study by Szendroi et al[34] of 68 patients has reinforced these findings and found similar results, with an increase in survival following resection of the solitary lesion. Hwang et al[35] also recommend surgical resection and endoprosthetic replacement in a solitary lesion, provided there are no visceral metastases. Renal, as well as thyroid, metastases are known to be particularly vascular in nature and, as such, tend to bleed during surgery. It has become common practice to embolize these lesions at a maximum of 48 hours prior to surgery.[36,37] Aside from the surgical benefits of lower blood loss, embolization has been shown to provide benefit in the palliative setting.[27,38]

Similar, but less extensively reported, results have been found with breast cancer primaries and reported by Wegener et al[39] where, in their series, 115 consecutive patients with bone metastases from breast cancer had 132 surgical procedures. The overall survival was dependent on the site and number of metastases present. Solitary bone lesions had a median survival of 65 months, as opposed to 13 months if there was visceral spread of the disease. The authors also stated that a "wide resection and the absence of pathological fracture and visceral metastases were predictive for longer survival".

This trend of improved outcomes continues with thyroid metastasis. Although not reported as statistically significant, Satcher et al[40] retrospectively reviewed surgically treated patients with bone metastases from thyroid carcinoma over a period of 23 years in a single institution. There was a total of 43 patients. Overall, the survival probability was 72% at one year and 29% at five years. Those with a single bone metastatic lesion showed a trend for improved survival, although this was not statistically significant.

Metastatic bone disease in patients with lung cancer, however, seems to be an altogether more difficult illness to treat due to its shorter survival. The introduction of the eighth edition of the tumour, node, and metastasis (TNM) classification of lung cancer, as proposed by the International Association for the Study of Lung Cancer (IASLC), has created further subcategories that may be of interest to orthopaedic surgeons, particularly regarding the metastasis (M) category (Table II).[41]

This subdivision of distant metastasis essentially introduces the concept of oligometastatic disease to a staging system. However, research involving successful cases of excision of a solitary lung cancer bone metastasis with long-term survival is scarce and limited to

case reports at present.[42,43] When cases of an isolated bony metastasis in lung cancer are identified, they should be referred to the relevant multidisciplinary team. A symptomatic lesion may present to an orthopaedic surgeon and, although currently this would be managed according to the standard principles, there may be occasions when the multidisciplinary team suggests considering endoprosthetic replacement.

ONCOLOGICAL THERAPY

Although surgical treatments for bone metastases are important, most of these patients do not undergo a surgical intervention. Instead, they are treated with oncological therapies alone, including radiotherapy and systemic therapies such as chemotherapy and endocrine therapy.

Radiotherapy is commonly used to treat bone metastases, usually as a standalone treatment, but is also often used as an adjunct to surgery. It is normally administered as a single treatment for pain, but can be given in multiple treatments in the case of a solitary metastasis, where the aim might be to achieve local 'cure' or at least lesion control. Radiotherapy is also often used following surgical treatment of the bone.[44] A large retrospective review has reported a median survival of 6.2 months for patients receiving palliative radiotherapy to the bone and this differed by primary tumour site (breast 14.2 months, prostate 7.7 months, lung 2.2 months).[45] Incidentally, radiotherapy will not cure pain of a mechanical nature, that is to say, the pain caused by stress through the failing bone, but can ease pain from the presence of the lesion itself. Approximately 35% of fractures will unite even after radiotherapy.[26] Postoperative radiotherapy should be considered by the clinical oncologist within the context of the multidisciplinary team, and, in the case of a long bone being treated with a nail, the entire bone should be treated.[44]

Stereotactic ablative body radiotherapy (SABR) is a form of highly accurate radiotherapy that is able to deliver precise therapy, aims to give complete local control of metastasis, and can be used in the situation of a single or small number of bone metastases (oligometastases). A recent retrospective review has shown a local control rate of 92% at one year with limited toxicities.[46]

Systemic treatments also have a vital role to play in controlling cancers that have metastasized, although they are not specific to bone metastases. They include endocrine therapy, chemotherapy, and immunotherapy. A full discussion of these agents is beyond the scope of this review.

Bisphosphonates have been used for some years to help with bone pain from bone metastasis and to reduce associated complications. However, a recent review has suggested the superiority of denosumab, a monoclonal antibody that reduces bone destruction by directly inhibiting receptor activator of nuclear factor kappa-B ligand (RANKL), the prime mediator of increased osteoclast activity. Its use has been shown to have a significant impact on reducing 'skeletal-related events' as a result of bone metastases from solid tumours, with the exception of prostate cancer.[3,47]

CONCLUSION

Bone metastases are often the most disabling and quality-of-life-altering consequence of secondary cancer. As such, it is imperative that appropriate care be given by the correct clinician and in a timely manner. The patients should have a full medical assessment and be managed by a multidisciplinary team approach. Medical comorbidities should be optimized prior to surgery and consideration given to respiratory complications of cancer and the likes of myocardial toxicity secondary to chemotherapy.

In some ways, the most important role of the orthopaedic surgeon is to assess the appropriateness of a patient for surgery. To do this, the primary tumour diagnosis should be known as well as the extent of the disease. In cases of multiple bony and visceral metastases in a primary of known poor prognosis, surgery most likely would not be appropriate. In patients with a good prognosis, appropriate surgical strategies and more durable implants must be used. We would recommend that the prognosis should be a minimum of six weeks for consideration of surgery. Understandably, the prognosis of many of these cases is difficult to establish; as such, if surgery is to be considered, it should be discussed fully within the multidisciplinary team, as well as with the patient and their relatives. In instances of a solitary bony lesion, discussion with a tertiary bone tumour unit is advised as resection *en bloc* has been shown to improve outcomes for renal, breast, and thyroid cancer. Prior to surgery on lesions with a high risk of haemorrhage, such as renal and thyroid malignancies, preoperative embolization should be performed within 48 hours of the proposed surgery.

The treatment of lesions confined to the femoral neck can be best treated by a hemiarthroplasty or total hip arthroplasty. More extensive lesions, however, may require endoprosthetic replacement. Diaphyseal lesions should be treated with intramedullary fixation but consideration should be given to the implant used; a solid, larger-diameter nail will be more durable. Humeral lesions are treated in much the same way. Metaphyseal lesions should again be treated by prosthetic replacement, and diaphyseal lesions by cephalomedullary nailing. Mirels' score is an appropriate adjunct to the assessment of clinical need for surgery in the case of an impending fracture; however, the high false positive rate should be borne in mind.

The survival rates from metastatic cancer are improving, people are living longer thanks to improvements in the medical and surgical management of the primary tumour, and, consequently, the instance of metastatic bone disease is likely to increase. Further research may define further subsets of patients for whom surgery may produce a meaningful survival benefit, in addition to successful palliation of their symptoms.

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