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Metastatic Bone Disease: A Clinical Approach

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Background: Advances in oncological management have contributed to longer survival of patients, even in the presence of metastases. Consequently, more patients would be expected to present with symptomatic bony metastases. The major objectives of orthopaedic surgical interventions in bone metastases include stabilization of impending or actual pathological fractures, restoration of mobility and gait, with resultant reduction in the overall morbidity during the survival period of the cancer patient.
Purpose: This review was aimed at producing a synoptic material for ease of reference by students, trainees and young surgeons who come into contact with patients suffering from metastatic bone lesions.
Methods: A review of the literature on the subject of metastatic bone diseases was done. Information on epidemiology, pathophysiology and mechanisms of bone metastases, clinical problems and concept of skeletal related events (SREs), differential diagnoses, diagnostic approach, general principles and options of treatment, and prognosis was extracted and presented.
Conclusions: Metastatic lesions are the most common malignant tumours that affect the skeleton, and these malignant deposits in bones increase overall morbidity in cancer patients. Appendicular skeleton offers a large surface area for deposition of tumour cells from primary sites, including the breast, prostate, lung, kidney and thyroid, with the highest incidence coming from breast and prostate. The osseous lesions of primary malignant diseases predispose to pain, mechanical instability and fractures in the affected parts. These factors contribute to the overall morbidity and reduced survival in cancer patients.

Keywords: Clinical approach, metastases, bone, surgical guideline

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Metastatic lesions are the most common malignant tumours affecting the skeleton, but opinions are divided in literature as to whether or not the skeleton is the commonest site of metastatic disease, ahead of the lung and liver[1-4]. According to Utzschneider *et al.*,[2] and Coleman[1], the skeleton is the most common site of metastatic cancer. Teixeira *et al.*,[3] have documented that bone is the third most common site for metastatic disease, after the lung and the liver. Indeed, any malignancy can

metastasize to bone, but about 80% of these osseous metastases originate from primary diseases in the breast, prostate, lung, kidney and thyroid, with the highest incidence coming from breast and prostate according to a study by Riccio *et al*.,[5] in the United States. In Hong Kong, the lung was reported as the most common primary source for osseous metastasis[4].

Appendicular skeleton offers a large surface area for deposition of tumour cells from primary sites. These deposits, after establishing in the bones, predispose to pain, mechanical instability and fractures. These factors contribute to the overall morbidity and reduced survival in cancer patients. The risk of impending pathological fracture from lytic osseous metastases, especially in the extremity bones, is a concern to both the patient and the Surgeon and requires a decision for surgical intervention[4,5]. With recent advances in oncological management, patients are beginning to survive longer, even with metastases, and more patients would be expected to present with symptomatic bony metastases. The major objectives of orthopaedic surgical interventions in bone metastases include stabilization of impending or actual pathological fractures, restoration of mobility and gait, with resultant reduction in the overall morbidity during the survival period of the cancer patient[4,6,7].

Most metastatic bone lesions occur in adults older than 50 years. Metastatic lesions put significant economic burden on the healthcare systems of different nations. As at 2007, approximately 1.2 million new cancer cases were reportedly diagnosed each year in the United States, with the overall cancer prevalence estimated at over 4.5 million cases annually, and 5.3% of those patients had metastatic bone disease. The national cost burden for patients with metastatic bone disease in the United States at the time of that report was estimated at USD 12.6 billion, representing 17% of the USD 74 billion in total direct medical expenses allowed by the National Institutes of Health (NIH), thus leaving metastatic bone disease as a major influencer of overall oncology cost in the United States[7]. In 2007, the Hong Kong Cancer Registry showed that there were 24,000 new cases, out of which estimated 6,000 -12,000 developed metastases. In 2021, there were 38,462 new cases diagnosed with cancer in Hong Kong (https://www3.ha.org.hk/cancereg). As prolonged survival is recorded in more patients with primary malignancies following advances in oncological and surgical treatments, it is expected that the prevalence of metastatic bone diseases would also be on the increase[3,4,6]. This has been postulated to imply that the burden of the primary malignant diseases with the potentials of bone metastases would assume a chronic proportion[6].

Pathophysiology/Mechanisms of Bone Metastases

Bone metastases by a primary tumour greatly increases the morbidity and mortality of the primary disease, and the overall prognosis is considered as poor. Bone metastasis can be osteolytic or osteoblastic. The molecular mechanisms occurring between tumour cells and bone cells that promote tumour growth within the bone microenvironment, and leading to bone destruction or new bone matrix deposition have been studied by Yin *et al*.,[8] as depicted in Figure 1. The development of osteolytic and osteoblatic lesions depends on a functional interplay between tumour cells and osteoclasts or osteoblasts. Two modes of bone metastases have been suggested, namely, the Paget's fertile soil ('seed and soil') hypothesis and the Ewing circulation theory[8]. The fertile soil hypothesis conceptualizes the tumour cells as the 'seed' and the bone microenvironment as the 'soil', and tumour cells may reach the bone via the blood stream. Cellular motility is important for tumour cells to develop distant metastases, and is mediated by several factors such as growth factors, hyaluronians, matrix components, host factors, and tumour-secreted factors[9]. After tumour cells are deposited in the bone matrix, tumour-derived factors interact with the microenvironment of bone, causing either osteoclast or osteoblast stimulation. Therefore, bone metastasis can be osteoclastic, osteoblastic, or a mixture of both.

Osteolytic Bone Metastasis

This is caused by increased osteoclast stimulation, leading to increased osteoclast activity

and reduced osteoblast activity. Therefore, it is predominantly lytic and destructive, but occasional local bone formation response may be seen. It is not a result of direct effects of cancer cells on bone. Osteolytic metastasis is the most common form of bone metastasis in all cancer patients and occurs in such solid primary tumours as breast, thyroid, lung, renal and prostate cancers. The lung and renal cancers are reputed to produce a specific type of osteolytic metastasis known as cortical metastasis, in which the cortex of the bone is destroyed without any involvement of the medullary canal. The following molecular events are noted in osteolytic metastasis[8,10,11]:

a. Tumour cells produce chemokine receptors, cell adhesion molecules, and cell surface receptors that enable them to attach to the bone matrix and establish growth in the bone.
b. Tumour cells attach to the basement membrane of the vessel wall in distant sites using proteolytic enzymes such as integrins and cadherins. They disrupt the receptor site basement membrane, and then migrate into the substance of the distal host tissue. By means of chemotactic factors as well as receptor activator of nuclear factor kappa-B ligand (RANK ligand), the tumour cells stimulate osteoclast activity, causing bone resorption and leading to the formation of lytic areas in the bone in which the tumour cells grow. The RANK ligand is a soluble transmembrane protein required for the formation, function and survival of osteoclasts[4,8,10].
c. Tumour cells also produce factors that directly or indirectly stimulate osteolastic bone resorption. These include PTHrP, IL-1, IL-6, Prostaglandin E2, TNF, and CSF-1. PTHrP is particularly important in osteolytic bone metastasis of breast cancer and oat cell carcinoma[10,11]. IL-6 is important in the osteolytic bone metastasis of renal, bladder, prostate, cervical, breast and colon cancers. IL-6 stimulates osteoclast formation, and promotes the effects of PTHrP on osteoclasts.
d. The bone microenvironment is richly endowed with such growth factors as TGF-Beta, FGFs, IGFs and BMP-2. These factors are activated within the bone microenvironment by the process of bone resorption initiated by cancer cells, and they in turn promote the growth of metastatic cancer cells in the bone as well as the production and release of more bone resorbing factors (Cytokines) from tumour cells. This is a vicious cycle that promotes the process of bone metastasis[8,9].
e. Calcium is released from the bone matrix in the course of tumour induced osteoclastic bone resorption, leading to hypercalcaemia of malignancy[9].

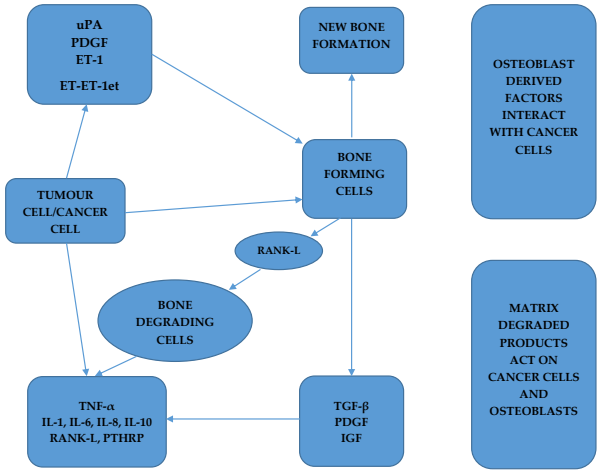

Fig. 1 Pathophysiology of Bone Metastases.

Osteoblastic Bone Metastasis

Unlike osteolytic metastasis, there is predominantly bone formation in osteoblastic metastasis. However, the quality of bone produced is poor and the patient is subject to bone pain and pathological fractures. Some mediators of osteoblastic metastasis have been identified to include Endothelin-1 (ET-1), which mediates bone formation through the Endothelin A (ET_A) receptor. ET-1 has been found to promote net bone formation by inhibiting osteoclast bone resorption and osteoclast motility. Other mediators of osteoblastic metastasis are BMP-4, 6 and 7, which have been proven to be elaborated by prostate cancer cells, and also exert paracrine effects on osteoblasts. Proteases such as urokinase-type plasminogen receptor (uPA) and Prostate Specific Antigen (PSA)

are known to activate TGF-Beta, which is also an osteoblast growth factor. PDGF is also involved in osteoblastic bone metastasis[8].

The pathophysiologic mechanisms described for metastatic dissemination of tumour cells have also been mentioned by other authors and summarized into key steps, namely, pre-metastatic niche formation by tumour cells; tumour cell dissemination through the circulation; chemotactic attraction and homing of tumour cells to the metastatic site of a target organ; and reciprocal interactions with local stromal cells and immune cells within the new microenvironment[12]. In line with this pathophysiologic pathway, researchers have documented the carcinoma of the prostate as an example of a solid tumour that follows this pathway. Prostate cancer metastasis to the bone follows at least four steps. The first step is colonization, in which circulating cancer cells enter the bone marrow niche. The next is the stage of metastatic dormancy, whereby cancer cells adapt to the bone microenvironment and remain dormant. This is followed by reactivation stage in which cancer cells switch from the dormant state to an actively proliferating state. The fourth step is reconstruction in which cancer cells disrupt the original bone structure and function[12-14].

Experimental studies show that up to 80% of tumour cells gain access into the circulation after release from the primary tumour. Out of this number, only about 2–4% initiate the growth of micro-metastases, and less than 0.01% survive in the new metastatic niche environment and give rise to macro-metastases[12,15,16]. Genetic studies of primary and metastatic tumours show that additional genetic events are required to enable metastases formation, and it has also been found that the time at which potentially metastatic cells are released from the primary tumour and arrive the secondary site may depend on the tumour type[12,17]. At the time of macro-metastases, the evolution of involved tumour cells ceases to be dependent on the primary tumour[12].

The unique vascular and cellular architecture of bone favour the entry of circulating tumour cells and eventual development of secondary deposits in the bone. The sinusoidshaped capillaries of bone, coupled with wide gaps between endothelial cells and a thin connective tissue envelope are easily permeable to tumour cells. The slow blood flow in the red bone marrow is believed to support the attachment of metastatic tumour cells to the endosteal bone surface[18]. The red bone marrow in the pelvis, sternum, cranium, ribs, vertebrae and scapulae, and to a variable extent, in the proximal ends of long bones such as the femur and humerus, constitute the major sites affected by bone metastases. Bone metastases, therefore, occur predominantly in the axial skeleton. Over 80% of patients with bone metastases show involvement of the axial skeleton, including the thoracic spine in 70%, the lumbosacral region in 20%, and the cervical vertebrae in 10%. Metastases to the pelvic bones, ribs and skull are found in 63%, 77% and 35% of cases, respectively. In the appendicular skeleton, the proximal humerus and femur are more frequently affected (53%) than the distal appendicular skeleton (1%)[12].

Common Patterns of Presentation of Metastatic Bone Disease

The common clinical presentations of bone metastasis include pain, pathological fracture, hypercalcaemia, and spinal instability with cord compression.

Pain

Bone metastases are the most common cause of cancer-related pain and the rate of pain from bone metastasis has been estimated at 35-45%. It is often insidious, poorly localised, becoming progressively more severe over a period of weeks or months. The character varies from deep, boring sensation, dull aching pain to occasional episodes of stabbing discomfort, often worse at night[9]. Pain may be spontaneous or related with activity such as weight bearing. The mechanisms of pain in patients with bone metastases are poorly understood, but a few explanations have been offered[1,9]. Pain from bone metastasis can be primary or secondary[9]. Primary bone pain is as a result of tumour-induced bone resorption, microfractures due to disruption of skeletal architecture, stretching of the periosteum by tumour expansion, nerve entrapment, and bone

collapse. Secondary bone pain occurs as a result of reactive muscle spasm, nerve root infiltration and compression by tumour, leading to neuropathic pain. There is also secondary pain from the release of chemical mediators. A variety of factors, such as bradykinin and substance P, that sensitize or directly excite primary afferent neurons to cause pain are elaborated by tumour cells[12]. The lower intracellular and extracellular pH of solid tumours is also known to activate sensory neurons, causing pain in cancer patients[9]. Tumour production of growth factors and cytokines, as well as local tissue production of endothelins, nerve growth factors and stimulation of ion channels have been documented[1,9].

Pathological Fracture

Sometimes, pathological fracture may be the first evidence of bone metastasis[19]. In a study[4], the rate of pathological fractures among Hong Kong Chinese with metastatic bone disease was found to be 34.3%. Pathological fracture occurs due to the destruction of cortical bone with attendant reduction in its load-bearing capabilities. Subsequently, there is trabecular disruption, microfractures, and complete loss of bone integrity. Pathologic fracture may occur spontaneously or following a trivial injury, especially in osteolytic metastasis. Frequent sites of election include the vertebral body, proximal ends of long bones, the pelvis, the ribs and skull. The occurrence of a fracture is a very serious event in the cancer patient. For this reason, increasing attention is advocated to predict these fractures, as well as to the use of prophylactic surgery, radiation and administration of Bisphosphonates in the management of the patients[9].

In practice, pathological fracture from tumour invasion of bone should be regarded as a spectrum, comprising actual pathological fracture on one extreme and mechanically weakened bone with impending pathological fracture on the other extreme. The radiologic criteria for predicting pathological fractures or diagnosing impending pathological fractures have been enumciated in the Mirels' scoring system.

Hypercalcaemia

Malignant hypercalcaemia occurs particularly in patients with metastasis from the lung, breast, kidney, thyroid, and haematologic malignancies such as multiple myeloma and lymphoma. It is a result of osteoclastic bone destruction from osteolytic metastasis. The pathophysiology is believed to be due to the activity of Parathyroid hormone related peptide (PTHrP) secreted by tumour cells, and to increased renal tubular reabsorption of calcium. The clinical features of hypercalcaemia such as pain, fatigue, anorexia, nausea, vomiting, dehydration, constipation, polyuria, mental disturbances and confusion are non-specific, and a high level of suspicion is needed to diagnose it. Death may occur through renal failure and cardiac arrhythmias[1,9]. The rate of hypercalcaemia has been quoted as 4.3% in a study of surgically-treated metastatic extremity bone tumours[4].

Spinal Instability with Cord Compression

Spine is the most common site of bone metastasis. Spine metastasis with spinal cord compression is the basis for the neurological compromise that may be observed in metastatic bone disease. Spinal cord compression is a medical emergency, and most patients will have weakness or paralysis. Back pain is due to spinal instability in about 10% of cases; often localised over the tumour; and is aggravated by such activities as coughing, sneezing or straining that increase intradural pressure. There may or may not be a radicular component. Pain may also be exacerbated by recumbency, straight leg raising and local pressure. Early recognition and appropriate adjunctive measures are important for a successful rehabilitation[1,9].

The Concept of Skeletal Related Events (SREs)

Skeletal related events describe the presence of pathologic fractures, spinal cord compression, hypercalcaemia, and requirement for surgery or radiotherapy to treat bone pain or impending fracture. Patients may have at least one SRE at presentation. They are difficult to treat and also diminish patients' quality of life[20]. There

seems to be a common finding among researchers indicating that mortality in metastatic bone disease may be directly proportional to the number of skeletal related events in the patients, but this relationship was not found statistically significant in a series among Hong Kong Chinese patient population, and also, the number of skeletal related events did not have any consistent effect on the mean survival duration before death in the same patient population[4].

Differential Diagnoses

Paget sarcoma, primary bone sarcoma such as malignant fibrous histiocytoma (MFH) and chondrosarcoma, benign radiolucent bone lesions such as bone cysts, malignant lymphoma, multiple myeloma, chronic osteomyelitis, osseous tuberculosis, post-radiation sarcoma, etc, are some of the clinical conditions that may very closely mimic metastatic bone lesions. Therefore, the need to consider these entities in the differential diagnosis of musculoskeletal metastasis cannot be overemphasized. Clinical diagnostic difficulty in differentiating osseous tuberculosis from metastatic bone tumours has been documented, and multifocal skeletal tuberculosis can closely mimic the distribution of multiple metastatic diseases to the central skeleton, ribs, vertebrae and pelvis[21-23]. It has also been documented that modern radiological investigations, including Flourodeoxyglucose Positron Emission Tomography/Computerized Tomography (FDG PET/CT), may also not be able to conclusively distinguish between tuberculosis and metastasis or primary malignancy, because these diseases, as well as other types of infections and inflammatory conditions, can produce areas of abnormally increased FDG activity on PET/CT. Therefore, high index of clinical suspicion as well as judicious biopsy procedures for both histopathological and microbiological examinations remains the gold standard in distinguishing these conditions[23-24].

Diagnostic Approach

In patients with known primary tumours, skeletal lesions are regarded as bone secondary until proven otherwise. In such patients, laboratory workup towards diagnosis of the bone lesion may not usually be indicated. However, when no known primary tumour exists in a patient with bone lesion mimicking metastasis, diagnostic workup is indicated for unravelling the primary tumour. Instances may exist when diagnostic search fails to suggest any primary focus. In such instances, the bone lesion may be described as metastasis of unknown primary (MUP). Generally speaking, the investigation protocol for bone lesions suspected to be metastases would include imaging techniques, laboratory tests and tissue biopsy.

Imaging Techniques

Plain radiographs (anteroposterior and lateral views) of the bone involved, and showing the joints above and below may be obtained in the first instance. It should be noted that metastatic lesion may not be obvious on plain radiograph, if significant bone destruction has not occurred. Technetium bone scan is a fairly sensitive technique for detecting bone metastases, and can detect these lesions earlier than plain radiographs. It is low in specificity because it cannot conclusively distinguish between bone metastases and other hot spots generated by such lesions as benign tumours or tumour-like conditions, infection, fracture or degenerative diseases. Computed Tomography (CT) shows bone details, including the extent of cortical destruction, but does not delineate the extent of surrounding soft tissue infiltration and medullary canal involvement. Magnetic resonance imaging (MRI) defines the extent of surrounding soft tissue infiltration and medullary canal involvement by the tumour, as well as locates metastases prior to their appearance on radiographs and CT. Positron emission computerised tomography (PET/CT scan) is a prototype of advances in imaging techniques, which now make possible the early detection of osseous involvements by primary tumours. The use of dual- tracer positron emission computerised tomography (PET/CT scan), can detect lesions anywhere between the base of the skull and the sole of the feet.

Laboratory Investigations

Routine blood tests, including complete

blood count (CBC), erythrocyte sedimentation rate (ESR), renal function tests (Electrolytes, Urea and Creatinine), C- reactive protein (CRP), liver function tests and clotting profile are some of the baseline blood workup required in the initial care of patients with metastatic bone tumours. Tumour markers such as prostate specific antigen (PSA), carcinoembroynic antigen (CEA), faecal occult blood test (FOBT), and alpha fetoprotein (AFP) may give a clue to the primary lesion. Metabolic panel needs to be explored, including serum calcium, serum phosphate and serum alkaline phosphatase levels. Higher calcium levels are an indicator of osteolysis.

Tissue Biopsy

The principles guiding tissue biopsy for musculoskeletal malignancies need to be observed. In the diagnosis of metastatic bone lesions, tissue samples may be obtained by fine needle aspiration (FNAC), Core needle biopsy (CNB), image-guided biopsy or by open biopsy.

Treatment Options and Principles in Metastatic Bone Disease

The treatment for bone metastases is primarily palliative, aimed at alleviating pain and improving quality of life. Treatment decisions for bone metastases depend on tumour location, the patient's general condition and previous treatment received by the patient, and it is usually a combination of local and systemic treatments. The systemic treatment options include chemotherapy, hormonal therapy, bisphosphonate, denosumab and target therapy. Local treatment includes radiotherapy, surgery, and radiology-guided interventions such as cement augmentation and radiofrequency ablation. Based on response to non-surgical treatment, patients are classified into good responders and poor responders. In good responders, such as in multiple myeloma, regression of lytic bone lesion may occur, and pathological fracture may unite. For this category of patients, the tendency is towards non-operative treatment or more conservative surgery. In poor responders, such as in renal cell carcinoma, lytic bone lesion may progress, and healing of pathological fracture is not guaranteed. For this category of patients, the tendency is towards more aggressive surgery.

Surgical Consideration, The Role of Surgery and Surgical Treatment Guideline in Metastatic Bone Disease

The optimum surgical management for metastatic bone disease considers such indices as the indication for surgery, estimated life expectancy of the patient, expected clinical response of non-surgical treatment, surgical treatment options and associated risks, the general health status of the patient, and the anaesthetic risk. The question of whether or not surgery is indicated and the expected benefit of surgical intervention should be carefully considered. For instance, in the presence of a systemic involvement by the primary disease, survival or cure rates following surgery depends on the response to adjunctive systemic treatment. Local treatment alone usually does not improve survival, and it is mainly for palliation or local disease control. However, a few exceptions exist, such as the isolated bone metastasis of renal cell carcinoma, in which adequate surgical excision is associated with improved survival[4]. Therefore, whenever applicable, systemic treatment should always be considered along with local tumour excision.

Surgical intervention in metastatic bone disease is indicated for the purpose of fixation of pathological fractures, stabilization of impending pathological fractures, and improving survival in selected cases. Fixation of pathological fracture stabilizes the bone, restores mobility of limbs, achieves pain relief and improves quality of life (QoL). Stabilization of impending fracture augments bone to prevent a pathological fracture, achieves pain relief and maintains mobility of limbs. Surgery improves survival in selected cases, such as solitary bone metastasis in renal cell carcinoma, after wide resection of metastatic lesions. Resection surgeries with curative intents are often indicated for solitary metastases. There is lower incidence of recurrence, and evidence shows that survival rates after resections are higher than after other standard treatments[4,6]. The indications

for amputation due to cancer metastases are extremely rare[4,6].

Approach to Impending Pathological Fractures (The Mirels' Scoring System)

There are no universally accepted criteria for operative intervention in impending pathological fractures following metastatic disease in long bones. However, the Mirels' scoring system is the most popular guideline for assessment, diagnosis and surgical decision making. The original work by Mirels[25] assessing the risk of pathological fracture in metastatic disease of the long bones was published in 1989. The Mirels' system of classification is considered reproducible, valid, and more sensitive than clinical judgment across all experience levels[26]. The Mirels' scoring system takes four (4) variables into consideration, namely, site of the lesion, nature of the lesion, size of the lesion in relation to bone cortical thickness, and nature of pain. These variables are awarded risk scores ranging from a minimum of one (1) to a maximum of three (3), depending on observation of set parameters as shown in Table 1[26,26].

Table 1a Mirels' Scoring System.

Score	Site of lesion	Size of lesion	Nature of lesion	Nature of pain
1	Upper limb	Less than 1/3 of cortex	Blastic	Mild
2	Lower limb	1/3 to 2/3 of cortex	Mixed	Moderate
3	Trochanteric region	> 2/3 of cortex	Lytic	Functional

Table 1b Clinical recommendation based on Mirels' score.

Mirels' score	Clinical recommendation
< 7	Radiotherapy and observation
8	Use clinical judgement
$\geq$ 9	Prophylactic fixation

It is commonly believed that lesions in the peritrochanteric area are associated with high risk for fracture. Furthermore, it is believed that chances of pathologic fractures are greater for weight-bearing bones than for non-weight-bearing bones. However, in Mirels' original investigation, these commonly held beliefs were not confirmed and site of lesion did not independently predict a fracture[25,26]. The nature of the lesion is either blastic, mixed or lytic. In the original investigation by Mirels, the rates of fracture in the three categories were 0%, 32%, and 48%, respectively. Size of lesion is expressed as a fraction of the cortical thickness. In the original evaluation, the rate of pathologic fracture was 0% for lesions less than 1/3 the size of the cortex, 5% for lesions between 1/3 to 2/3 the size of the cortex, and 81% for lesions occupying more than 2/3 of the cortex[25,26]. Pain is the only subjective variable in this classification system. The rate of fracture was 10% among patients with mild to moderate pain. However, all the patients with functional pain progressed to a fracture. Mirels also reported an association between pain and the size of the lesion[25,26].

Based on an overall Mirels' score, a recommendation for or against prophylactic fixation of a lesion is offered. Prophylactic fixation is strongly recommended for lesions with overall scores of nine or more. A lesion with an overall score of seven or less can be managed using radiotherapy and drugs. An overall score of eight is considered a clinical dilemma. The probability of fracture is 15%, and Mirels recommended that the attending physician use clinical judgment in such cases and consider prophylactic fixation[25,26]. Elsewhere in the literature, it is recommended that surgery be done in all cases where metastases posing risks of fractures are diagnosed, and this

applies to lesions with Mirels' scores of > 7. Such prophylactic surgeries for impending pathological fractures are believed to positively impact the QoL, and perhaps the survival profile of patients with extremity metastasis[1]. According to Guzik[6], the overall treatment results are better in cases where pathological fractures have not occurred. In another series[4], the patients that had prophylactic fixations had significantly higher postoperative duration of survival than the ones operated for actual pathological fractures. This finding was statistically significant at $p < 0.05$ (Chi-square test = 13.6267; $p = 0.001$). The researchers believed that it was difficult to measure the lag in time between metastasis and fracture occurrence, and that much less complication was associated with prophylactic fixation[4]. However, the authors adduced no immediate proof for this supposition, and believed that, in the absence of such proofs, it may be argued that the higher postoperative duration of survival in those with prophylactic fixations as against those with fixation for actual pathological fractures may only be a reflection of the natural history of the disease process, rather than the effect of surgery[4].

Another method of predicting an impending pathological fracture is according to Harrington classification, which predates the Mirels' classification[26]. According to Harrington, an impending pathologic fracture is defined as a lytic bony lesion involving more than half the diameter of the bone, greater than 2.5cm in its greatest diameter, or associated with persistent pain or radiographic progression[26].

Life Expectancy as a Surgical Consideration in Patients with Metastatic Bone Disease

After major surgical intervention, recovery and rehabilitation may take up to two months. Major surgical intervention is considered worthwhile if life expectancy of the patient is more than three months. The estimated life expectancy of the patient will dictate whether surgery is worthwhile as well as the aggressiveness of such surgical intervention. Sometimes, life expectancy may be difficult to predict as patients may suddenly deteriorate. From surgical point of view, life expectancy represents the estimated survival period of the patient after surgical intervention. Current guidelines suggest that surgical treatment for bone metastases be considered, when indicated, in patients with life expectancy of more than three months[4,27]. The estimation of life expectancy is within the domains of the Oncologists using the instrument of the Kaplan-Meier survival curve, but the essence of the surgical intervention is to maximise the quality of remaining life[6,27].

Surgical Treatment Options

The treatment of bone metastases is palliative, and surgery is probably one of the most important aspects of multimodal therapies available to these patients to improve prognosis[2]. The surgical considerations take into account the fact that fracture healing is unpredictable, that patients in general are weak physically, and that local tumour may progress. Stability after surgery relies mainly on surgical construct. Surgical construct is intended to bear the physiological stress, allow simple rehabilitation, and be stable at least for the survival period of the patient. A range of surgical treatment options with varying risk, durability and stability profile are available for consideration in patients with metastatic bone disease. These options include radiological intervention such as radiofrequency ablation (RFA), cement augmentation, osteosynthesis (internal fixation), prosthetic replacement, re-enforced prosthetic replacement, and resection with skeletal reconstruction. The internal fixation for bone metastases can either be a simple internal fixation, or internal fixation with cement re-enforcement. Prosthetic replacement can be accomplished with standard prosthesis, long stem prosthesis, megaprosthesis or intercalary spacer. Re-enforced prosthetic replacement may be accomplished with cementation or the use of allograft-prosthesis composite. Wide resection is not to be embarked on, if there are no plans for reconstruction. The simpler procedures such as cement augmentation and osteosynthesis are less risky, less durable and less stable, but the more complex procedures such as wide resection and reconstruction with megaprosthesis are more risky, more durable and more stable. Such reconstruction is often strong enough

to allow immediate mobilization and simple rehabilitation of the patient.

Avoiding postoperative complications in the circumstance of bone metastasis may depend on proper patients' selection, adequacy of operative techniques and planning, and strict adherence to the surgical principles of asepsis as well as avoidance of tumour contamination of surgical fields. These surgical due diligence help to pave the way for successful rehabilitation of patients to ambulatory status. It might well be argued that any failure in rehabilitation is an indication of failure of the surgical effort[4]. It is important that the patients are followed-up in the physiotherapy and oncology clinics. The rehabilitation potentials of patients require consideration as a guide to predicting the outcome of rehabilitation measures in individual patients. With advances in oncological services and surgical techniques, it is anticipated that the overall prognosis of metastatic bone diseases will continue to improve[4].

Prognostic Factors in Metastatic Bone Disease

Bone metastasis often suggests that the disease has reached a late stage, with a poor prognosis[28], and some of the patients may not be considered fit for bony operative procedures targeted at the bone metastases[19]. Factors acting singly or in combination with others to impact on prognosis include age, the primary tumour (lung cancer carries poor prognosis compared to other solid tumours), presence of other metastasis, pathological fracture, adjuvant therapy, other complications such as the SREs, albumin level and overall nutritional status. The duration of post-operative survival in metastatic bone disease depends on a number of factors, such as age of the patient, site of primary malignancy, indication for surgery, and the option of surgery[19,23]. Apart from predicting the risk of bone metastasis from colorectal carcinoma (CRC), the tumour markers alkaline phosphatase (ALP) and carcinoembryonic antigen (CEA) are also important in its prognosis. Evidence exists in literature to suggest that elevated levels of ALP and CEA in colorectal carcinoma patients with bone metastasis are associated with poor prognosis[28,29].

CONCLUSIONS

Metastatic lesions are the most common malignant tumours that affect the skeleton, and these malignant deposits in bones increase overall morbidity in cancer patients. Appendicular skeleton offers a large surface area for deposition of tumour cells from primary sites, including the breast, prostate, lung, kidney and thyroid, with the highest incidence coming from breast and prostate. The osseous lesions of primary malignant diseases predispose to pain, mechanical instability and fractures in the affected parts. These factors contribute to the overall morbidity and reduced survival in cancer patients. The care of the patients suffering metastatic bone tumours is generally palliative. Palliative surgical intervention, when indicated, reduces associated morbidity, but should be guided by the expected life expectancy of the patient and the overall rehabilitation potential of the patient. The surgical management of bone metastasis is a key consideration in averting potentially crippling morbidity occasioned by mechanical instability arising from the deposition of cancer cells on skeleton.

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