REVIEW

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Metastatic bone disease: Early referral for multidisciplinary care

ABSTRACT

It is estimated that more than half of all cancers develop bony metastases, exacting a substantial cost in terms of patient quality of life and healthcare expenses. Prompt diagnosis and management have been shown to reduce morbidity and costs. When a patient with a history of cancer presents with musculoskeletal pain, heightened awareness of the risk of bone metastasis should prompt immediate referral to an orthopedic specialist. A multidisciplinary approach is needed to identify an appropriate treatment plan for the patient based on the prognosis, fracture status, and extent of skeletal disease.

KEY POINTS

More than 50% of patients with cancer survive their disease for at least 10 years, making durable reconstruction in metastatic skeletal disease more important.

Most patients with metastatic bone disease present to an orthopedic team after a pathologic fracture has already occurred, increasing the likelihood of discomfort and morbidity.

Awareness of the diagnostic and therapeutic challenges associated with metastatic bone disease is essential for timely referral to an orthopedic specialist.

doi:10.3949/ccjm.89a.21062

Treatment of metastatic bone disease has evolved over the last 50 years, but a lack of awareness and recognition of symptoms continues to delay referral to specialist teams. This article highlights crucial concepts surrounding the management of patients with bone metastasis, reviews changes in therapy that have occurred over time, and clarifies the need for a multidisciplinary approach to management. It provides guidance in achieving early diagnosis and referral for patients who present with metastatic bone disease in primary care settings and offers a decision tree for assessing surgical and nonsurgical treatment options.

CONSIDERING THE NUMBERS

The estimated cost directly attributed to care of bone metastasis in the United States is greater than $12.6 billion annually, which accounts for 17% of total cancer care.[1] In 2012, Medicare paid $100 million in hospital charges to cover the cost of prophylactic internal fixation of the femur as a result of metastasis.[2]

The rate of new cases of cancer in the United States currently stands at 442.4 per 100,000 men and women per year. In January 2019, the US National Cancer Institute predicted 16.9 million cancer survivors in the United States with a projected increase to 22.2 million by 2030.[3] Similarly, in the United Kingdom, the number of people

living with cancer is rising by 3% each year, with survivorship projected to increase by 1 million per decade from 2010 to 2040.[4] In 2015, an estimated 2.5 million people were living with cancer in the United Kingdom, with a predicted rise to 4 million by 2030.[1] In the United Kingdom, 375,000 new cancer cases are diagnosed every year, or about 1,000 new cases daily.[5]

In the early 1970s, the median survival time for patients with metastatic disease was 1 year. By 2007 it was 6 years, and by 2011 it was 10 years.[6,7] Today, it is estimated that over 50% of patients survive their disease beyond 10 years.[7] With this increased longevity, the age of patients with metastatic bone disease and rates of survival are on the rise.[8,9]

Incidence of bone metastasis

Bone is the third most common organ affected by metastatic cancer after the lung and liver.[10]

Although it is difficult to fully appreciate the incidence of metastatic bone disease, it is estimated that more than 50% of all cancers develop bone metastases, with the variability in the literature ranging from 12% to 70%. In 2008, the incidence of metastatic bone disease in the United States was approximately 280,000 patients per year with an upper estimate of 322,000. This is likely to have increased significantly since then.[11]

Although almost any carcinoma can metastasize to bone, those that do so most frequently are prostate, breast, renal, lung, thyroid, and blood (multiple myeloma) in origin.[12] Some autopsy studies have demonstrated skeletal metastases in 90% of men who die of prostate cancer.[13] Bone is the most common site of metastasis in patients with breast cancer, and up to 70% of women with metastatic breast cancer have some form of skeletal involvement.[14]

Quality of life

The quality of life in patients with skeletal metastases is compromised by skeletal-related events, ie, intractable pain, forced immobilization, hypercalcemia, spinal cord compression, and pathologic fractures. Bony metastasis is often the most symptomatic and disabling manifestation of secondary cancer.[12] Approximately 68% of patients with skeletal metastasis have pain, and 10% to 20% of those with long-bone metastases eventually sustain pathologic fractures.[15,16] Pathologic fracture may be the first sign of disease and the index finding leading to the diagnosis of cancer. In 3% to 4% of patients who present with pathologic fracture, the primary site is not discovered.[17] In most cancer types, the morbidity rate in patients with multiple skeletal-related events is higher than in patients with single events. Additionally, the presence of extraosseous disease in the context of skeletal-related events is a powerful predictor of poor outcomes.[18]

Bone metastasis typically occurs via hematogenous spread and therefore tends to seed in more heavily vascularized parts of the skeleton.[15] The most frequent sites for metastases are the spine, pelvis, proximal femur, proximal humerus, skull, and ribs,[19] and involvement of any of these sites can significantly affect activities of daily living, quality of life, functional status, and overall prognosis.[15]

Healthcare costs

The management of patients with skeletal events due to bone metastasis has important implications for healthcare costs. Early intervention for patients with metastatic bone disease has been shown to reduce patient morbidity as well as overall cost.[20] A prompt, proactive response has been shown to reduce complication rates, length of stay, need for community care, and overall treatment costs, and this is specifically true of pathologic fracture.[20] A prophylactic approach has shown to be safer and much more cost-effective compared with traditional management, or acute fixation, after a completed fracture.[21]

Patients are living longer with advances in systemic therapy, targeted therapy, and radiotherapy treatments, thus making durable reconstruction of a metastatic skeletal location more important. The appropriate surgical approach and choice of implant have the potential to reduce healthcare costs.[12]

EARLY RECOGNITION OF BONE METASTASIS: CHALLENGES AND CONSIDERATIONS

Patients with metastatic bone disease commonly present to orthopedic surgeons in 1 of 3 ways: an oncologist refers the patient after noting disease during a routine investigation; the patient is admitted with a pathologic or impending pathologic fracture; or a primary care physician refers the patient for evaluation of musculoskeletal pain.[12]

Unfortunately, most patients have already sustained a pathologic fracture by the time they present to an orthopedic team[21] and thus have a greater likelihood of severe discomfort and increased morbidity during the treatment process. A fracture event may create complexity that limits treatment options. Heightened awareness in the primary care setting of possible metastatic bone disease is essential in patients who present with musculoskeletal pain and a history of cancer or previous radiotherapy.

Bone cancer pain

The primary symptom often described by patients is pain, and this is especially relevant in a patient with cancer.[10]

Bone cancer pain can be very complex and has an associated intricate pathogenesis.[22] It is often described as a dull ache that is deep and intense in nature, exacerbated by weight-bearing, and often worse at night. Red flags for bone metastasis include a chronic dull ache that continues to worsen over time, pain associated with weight-bearing, night pain, pain on direct palpation, and unexplained localized pain in a patient over age 45. A sudden change to more intense or severe pain usually indicates a pathologic fracture, particularly in the context of minimal trauma.

Patients who live with cancer ultimately deal with considerable suffering and pain; therefore, sudden changes in the quality or quantity of pain should be acted on swiftly.[12,22] Significant symptoms that accompany pain include unexplained weight loss, night sweats, and any red flag symptoms of back pain (eg, nighttime pain during movement, band-like bilateral nerve root pain or radiculopathy, unsteady gait, progressive weakness of limbs, bowel and bladder symptoms).

Time to metastasis

Few epidemiologic studies establish the median time from primary cancer diagnosis to bone metastasis. The results vary by country, ethnicity, primary cancer type, patient age, and initial treatment received. In broad terms, the highest risk of metastatic bone disease is within the first 3 to 5 years of the initial diagnosis, before the cancer reaches a stable state, ie, no increase or decrease in severity or extent.[9,23] However, bony metastasis can present as late as 20 years after the primary diagnosis, so a history of cancer at any stage is important.[24]

Progression to fracture

Patients with known cancer involving the skeleton or those who have had previous radiotherapy to skeletal metastatic deposits are at particular risk of pathologic fracture. Several landmark studies have suggested that the risk of pathologic fracture after radiotherapy can range from 13% to 41%.[25,26] One study suggested that after radiotherapy, 26% of patients develop disease progression at the bony site,[27] and another study noted that 35% of fractures develop at just 6 months after radiotherapy.[28] For this reason, patients who receive radiotherapy for bony metastasis should be assessed by an appropriate specialist to determine the need for further stabilization or surgical treatment.

Evaluation

Patients who present in a primary care or hospital setting with suspected metastatic bone disease need preliminary investigations in addition to an initial thorough examination. Certain blood tests (eg, alkaline phosphatase, lactate dehydrogenase, calcium, blood cell count, basic tumor markers) and plain radiographs can supplement the history and physical examination.[12] Although no blood test is specific for bone metastasis, increased calcium and alkaline phosphatase levels can supplement the clinical picture of metastatic bone disease.

Because bone lesions may not become apparent on radiography until 50% to 70% of the bone has been destroyed, initial radiographs may not show an obvious abnormality. A patient with bony lesions may experience symptoms related to hypercalcemia such as nausea, vomiting, polyuria, muscle weakness, constipation, and confusion, and metastasis to the spine may cause neurologic compromise. Urgent referral to an oncologist, orthopedic surgeon, or neurosurgeon is warranted if cauda equina syndrome is suspected.[29] Delays in appropriate treatment can lead to increased morbidity, complications, and challenges that would not have been present earlier in the disease process such as changes in bony anatomy with wider destruction, increased frailty of the patient, and missed opportunity for less-invasive treatment options.

NEXT STEPS: STOP, THINK, STAGE

When bone metastasis is suspected or confirmed, the next step is to establish the origin and nature of the lesion, the degree of disease dissemination, the patient's overall health and prognosis, and the effect of the lesion on the bone.[30] Analysis of this information requires a multidisciplinary effort to allow for effective decision-making as to the most appropriate management (**Figure 1**).

The multidisciplinary team

Management of metastatic bone disease requires input from a team of specialists to determine the best treatment options for the individual patient. The team should consist of a medical oncologist, radiation oncologist, radiologist, pathologist, orthopedic surgeon with an interest in bone metastasis, anesthesiologist, palliative care specialist, rehabilitation specialist, cancer nurse specialist, and, most important, the patient and family.[15]

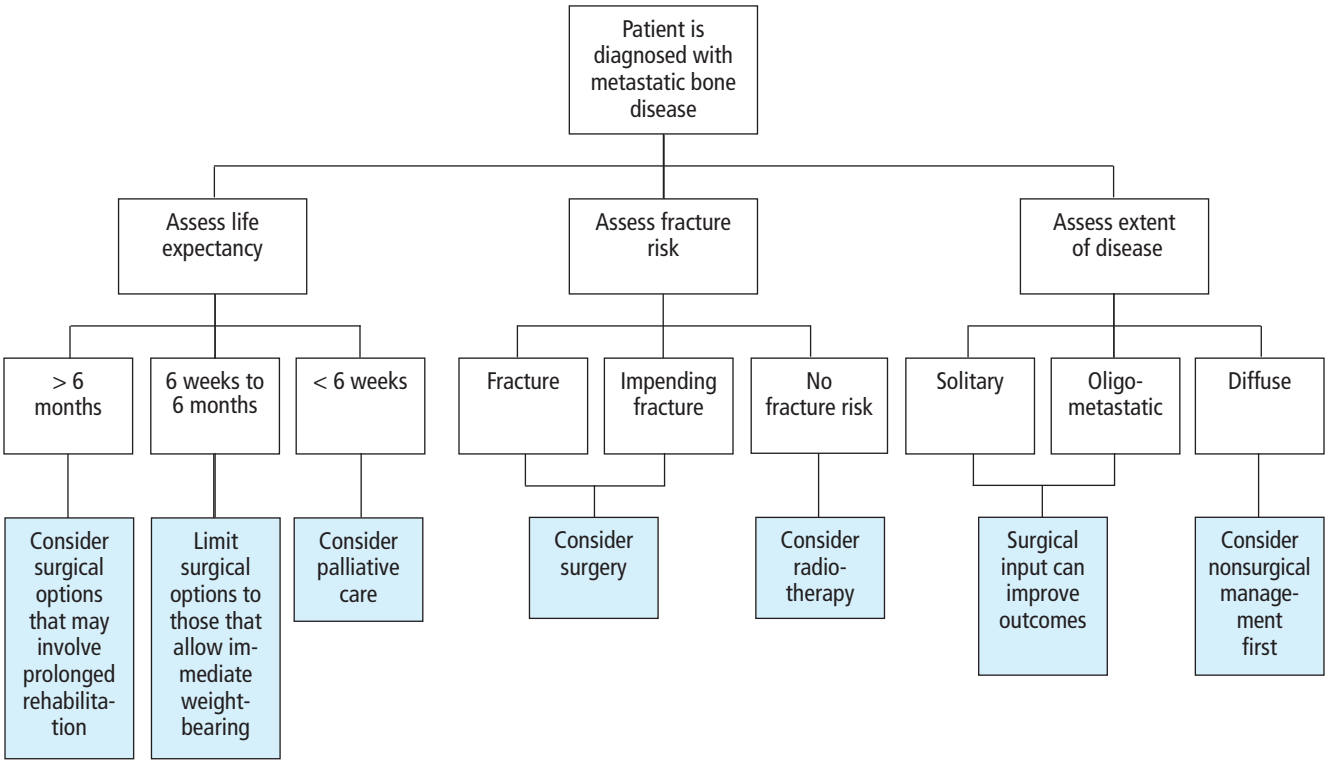

Figure 1. An overview of team management of metastatic bone disease.

Origin and nature of the bone lesion

The origin and nature of a bone lesion plays a key role in the decision-making process. All bony lesions are treated as primary bone tumors, or sarcoma, until proven otherwise. Applying this principle ensures that no primary bone tumor receives delayed or inappropriate treatment.[30]

Initial investigation: Imaging and biopsy

The initial investigation includes a computed tomography (chest, abdomen, pelvis), whole-body nuclear bone scan, positron emission tomography, and magnetic resonance imaging of the affected area. Biopsy is becoming a more important and better recognized diagnostic step. Today, most patients who present with a bone lesion should be considered for biopsy in order to obtain a histologic diagnosis, regardless of whether metastatic bone disease is suspected. Biopsy has been reported to reveal a benign diagnosis, infection, a different primary cancer, or change of immunophenotype between the primary disease and the metastasis.[12]

Bone scan, positron emission tomography, and computed tomography are increasing in use, are readily available, and can determine the degree of disease dissemination. This is important because metastatic bone disease can range from a solitary lesion to widespread bone involvement.[31]

Prognosis

Estimating a patient's life expectancy and overall prognosis will significantly frame the support and input the patient requires. As a general rule, a patient should have a life expectancy greater than 6 weeks if surgical management is to be considered. With this prognosis, the surgical procedure must permit immediate weight-bearing. If the procedure requires partial weight-bearing or no weight-bearing postoperatively, the minimum prognosis must be at least 3 to 6 months. A life expectancy greater than 6 months justifies and requires comprehensive surgery (**Figure 1**).[12,29]

THE HOLISTIC APPROACH TO MANAGEMENT

The key principles of management of metastatic bone disease are to control pain, maintain or improve quality of life, allow early mobilization, create a durable orthopedic construct to replace or augment bone, and prevent disease progression if possible.[32]

Painless, smaller lesions

It is generally accepted that painless, smaller lesions with little risk of fracture respond well to radiotherapy alone, but a pathologic fracture will likely require some form of surgical stabilization. A delicate balance is required to avoid overtreatment and undertreatment of these lesions, especially with procedures that have longer recovery times or incur greater morbidity. The clear benefit of operating on early impending fractures must be weighed against the risks of surgery, anticipated prognosis, and overall benefit to the patient.[33]

The primary aim of treating asymptomatic small lesions is disease control and prevention of skeletal-related events. The mainstay of treatment is systemic control such as hormonal therapy, immunotherapy or targeted therapies, chemotherapy, or agents that improve bone strength combined with potential radiotherapy for local control. For smaller symptomatic lesions and at more difficult surgical locations, percutaneous ablation techniques with interventional radiology have been shown to be effective.[34]

Larger, symptomatic lesions

For lesions that are larger and more symptomatic, the aim of treatment is not only to control disease but also to maintain mobility and improve pain.[32] The need for surgical intervention must be considered in addition to local radiotherapy and systemic medical control of the disease.

Although postoperative radiotherapy has played a role in management, evidence supporting its use is weak, and the associated risks are quite high (eg, wound infection, skin irritation, osteoporosis, and failure of metalwork). Because radiotherapy itself is a risk factor for propagating pathologic fractures, its use needs to be weighed against the potential benefits.[35]

NONSURGICAL MANAGEMENT

Antiresorptive drugs are the mainstay of nonsurgical treatment of bone metastasis, and bisphosphonates and denosumab are the most commonly used.

Bisphosphonates and denosumab

Bisphosphonates affect osteoclast activity and survival.[36] Zoledronate is approved for use in solid tumors and multiple myeloma, and pamidronate is approved for bone metastases from breast cancer and multiple myeloma. Ibandronate is effective in breast cancer patients. Zoledronate is particularly useful in hypercalcemia associated with bony metastasis. Monitoring is required for complications such as kidney failure, hypocalcemia, and osteonecrosis of the jaw.

Denosumab reduces osteoclast activity and is generally well tolerated. It can be used in patients with renal failure since it is not nephrotoxic. It has been shown to prolong the time to first skeletal-related event in patients with metastatic breast and prostate cancer.[37]

Radiotherapy

Radiotherapy is used primarily for pain management, spinal cord compression, and pathologic fractures. Pain relief is achieved within the first 2 weeks and is almost complete in 50% of patients. The dose, technique, and schedule depend on several factors. Short courses of treatment are often used in Europe and Canada, while longer courses are preferred in the United States.[37]

Other methods

Other methods of pain relief should follow the World Health Organization analgesic ladder[38] and range from anti-inflammatory drugs to opiate-based treatment. Guidelines for more detailed pain management options in cancer patients have been published[39] and may require input from specialized pain services.

SURGICAL MANAGEMENT

When surgical intervention is necessary, the intervention should be a single procedure that will last the patient's life span while allowing immediate weight-bearing and mobility.[17] Pathologic fractures caused by metastatic bone disease will not heal, even with radiotherapy. The surgical intervention must be appropriate for the stage of disease, condition of the patient, and the patient's preferences and wishes. In general, surgical options include the use of intramedullary nails, ridged plate and screws, bone cement supplementation, and endoprostheses, or a combination of these.[11,17,31]

Current research favors early diagnosis and a prophylactic surgical approach in managing bony metastases in patients with impending pathologic fractures. Many studies have shown that in appropriate patients, a prophylactic procedure (compared to a procedure performed after fracture) leads to reduced blood loss, reduced length of hospital stay, quicker return to baseline mobility, and, overall, a better 2-year survival rate.[40]

The surgical approaches have evolved with advances in technology and prosthesis design. Fixation alone may not necessarily be the most appropriate option. For example, there is a popular notion that surgical management involves only prophylactic intramedullary nail stabilization. But more recent

studies have shown that in appropriate patients, the use of massive endoprostheses for the treatment of bone metastases is a reliable method of limb reconstruction.[41] This option is associated with low complication and failure rates, can restore good function, allows for early weight-bearing, alleviates pain, and sometimes allows for complete resection of the tumor.[41]

Observational studies have shown sustained improvement in pain relief and function up to 1 year after surgery in patients with metastatic bone disease, irrespective of prognosis.[42] Studies have also indicated that patients with low-volume bony oligometastatic disease (< 5 metastases throughout the body) have enhanced survival and better disease prognosis with appropriate surgical intervention.[12,43,44] While these arguments show that the burden of disease and morbidity should not be underestimated, there still exists little awareness and appreciation in hospital and primary care settings regarding possible management options for skeletal-related events due to bone metastasis.[12]

TAKE-HOME MESSAGES

- Metastatic bone disease is associated with high rates of mortality and morbidity and has a significant impact on quality of life. A holistic, team-based approach to management is essential to providing appropriate, expeditious, and aggressive treatment. Delay in referral and treatment is associated with increased morbidity.
- Awareness of the signs of metastatic bone disease and early referral for specialist input are essential. To improve overall outcomes and quality of life for patients with cancer, treatment strategies need to be planned comprehensively and tailored to the individual patient.
- A prophylactic approach to management of metastatic bone disease leads to better pain relief and function.
- Healthcare systems need a well-defined and easily accessible platform for primary care physicians and oncologists to expeditiously refer patients for further assessment and management.

DISCLOSURES

Dr. Nystrom has disclosed consulting, teaching, and speaking for Onkos Surgical. Dr. Mesko has disclosed consulting for Bone Support, Onkos Surgical, and Stryker Orthopaedics, and teaching and speaking for KCI and Onkos Surgical. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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