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REVIEW

Management of Long Bones Metastatic Disease: Concepts That We All Know but Not Always Remember

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Abstract: Bones are the third most common site of metastatic disease. Treatment is rarely curative; rather, it seeks to control disease progression and palliate symptoms. Imaging evaluation of a patient with symptoms of metastatic bone disease should begin with plain X-rays. Further imaging consists of a combination of (PET)-CT scan and bone scintigraphy. We recommend performing a biopsy after imaging workup has been conducted. Metastatic bone disease is managed with a combination of systemic treatment, radiotherapy (RT), and surgery. External beam RT (EBRT) is used for pain control and postoperatively after fracture stabilization. Single-fraction and multiple-fractions schemes are equally effective achieving pain control. Adequate assessment of fracture risk should guide the decision to stabilize an impending fracture. Despite low specificity, plain X-rays are the first tool to determine risk of impending fractures. CT scan offers a higher positive predictive value and can add diagnostic value. Surgical management depends on the patient's characteristics, tumor type, and location of fracture/bone stock. Fixation options include plate and screw fixation, intramedullary (IM) nailing, and endoprostheses. Despite widespread use, the need for prophylactic stabilization of the entire femur should be individually analyzed in each patient due to higher complication rates of long stems.

Keywords: bone metastasis, pathological fracture, radiotherapy, surgery

Introduction

After the lungs and the liver, the skeleton represents the third most common site of metastatic disease, with 60–84% of the metastases targeting bone.[1,2] Metastases to the long bones, those having a shaft and two ends and length/width ratio greater than 1, can severely compromise the patient functioning due to their role in locomotion and weight-bearing. With improved treatment options and prolonged survival of more patients with cancer, risk and prevalence of metastatic bone disease is increasing.[3,4] Neoplasms that metastasize to the bone include breast (70%), prostate (85%), lung (40%), kidney (40%) and thyroid (7%), with breast, lung and prostate carcinomas accounting for >80% of the cases.[5] At diagnosis, bone metastases are identified in 17%, 5% and 4% of the patients with lung, prostate, and breast carcinomas.[6]

Skeletal related events (SRE) involve severe pain, loss of function, pathological fractures, bone marrow aplasia, spinal cord compression and hypercalcemia.[5,7] SREs are major contributors to the deterioration of the quality of life of patients with cancer and may, in certain cases, initiate dependent care for many of them.[3]

Bone metastasis is considered a chronic condition as treatment requires a multidisciplinary approach, is rarely curative, and is mostly aimed at preventing disease progression and palliating symptoms.[5,7,8] The majority of metastatic bone lesions are treated with non-surgical modalities: radiation, chemotherapy, immunotherapy, hormonal therapy, bisphosphonates, etc. Surgical goals involve local tumor control and allowing immediate weight-bearing and function.

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Pathophysiology

For metastasis to occur, malignant cells from a primary tumor must undergo a series of steps to reach and proliferate in a distant organ. These steps include the formation of a pre-metastatic niche, dissemination through the circulation, and chemotactic attraction and homing of tumor cells to the metastatic site.[5] Once established in the metastatic niches, tumor cells may remain dormant for years until surrounding signals and an appropriate microenvironment trigger them to establish an overt and clinically detectable metastatic disease.[5,9]

Currently, two explanations exist for bone as a preferred site for metastases. First, slow blood flow through the highly vascular red marrow located predominantly in the axial skeleton, could support attachment of metastatic tumor cells to the endosteal bone surface.[5] However, the interaction between the molecular properties of malignant cells and the bone microenvironment appears more important to the pathophysiology of bone metastasis.[10]

Aspects of the bone microenvironment that favor tumor cell homing mainly involve the role of calcium, growth factors, and the immune system.[5,11,12] The natural process of bone remodeling releases calcium to the extracellular space, which has shown to promote tumor growth in the bone via cancer cell expression of extracellular calcium-sensing receptors. Additionally, tumor-derived calcium stimulates tumor cell migration and proliferation.[11] Furthermore, bone stores plenty of growth factors such as transforming growth factor B (TGF-B). TGF-B has also evidenced tumor growth promotion.[5] Lastly, the immune system plays a determinant role. Inhibitory and stimulatory effects on host cells within the bone facilitate metastasis and cytokines involved in bone cell activity regulation have effects on immune cells and the immune response.[12]

Despite breaking away from the primary, most migrating tumor cells are destroyed before establishing a metastatic focus.[9] Only a small fraction of these survives and are attracted to metastatic niches in the bone.[13] Osteolytic colonization is associated with bone destruction. This metastatic pattern, common in multiple myeloma, results from tumor cell secretion of osteolytic factors such as parathyroid hormone-related protein (PTHrP) and IL-11. These enhance the local production of RANK-L, thereby stimulating osteoclast formation and activation (Figure 1). Conversely, osteoblastic metastasis, common in prostate cancer, is associated with tumor production of bone-forming factors such as endothelin-1, growth differentiation factor 15 (GDF-15) and bone morphogenic proteins. Although in certain cancers the lytic or sclerotic component may predominate, both processes may coexist in "mixed lesions" like in breast cancer.[5]

Evaluation and Diagnosis

Clinical Evaluation

For an adequate diagnosis of bone metastasis, a proper medical history, physical examination and laboratory panel are necessary in addition to imaging studies. The most common symptom in these patients is bone pain. Innervation of the periosteum explains why bone pain shares similar qualities with neurogenic pain: progressive, poorly localized, of deep boring quality, and accompanied by episodes of aches, burns and stabbing discomfort.[14,15] This pain is also described as being worse at night and is not relieved by sleep, lying down or symptomatic treatment.[5,14,15]

Although bone pain is not directly associated with fracture risk, pathologic fractures initially result from micro-fractures, which cause pain.[8,14] Asking about need of assistive devices for ambulation can elucidate about the degree of mechanical instability.[15]

Bone metastases can also be accompanied by non-specific symptoms such as malaise, loss of appetite and weight loss. These are more common when the underlying diagnosis is lung cancer.[5] Physicians should also look for symptoms related to possible primary sites of disease that commonly metastasize to the bone.[15] Finally, the medical history must include current oncological status, related treatments and medications, personal and family history of malignant tumors and cancer risk factors, and dates of recent cancer screening tests.[2,3,15]

Physical examination should focus on the main symptomatic area, as well as other symptomatic sites. Local objectives include determining the extent of soft tissue tumor extension and establishing the neurovascular status of the affected area.[3] Presence of a limp or edema, muscle strength, neurologic compromise, and range of motion of adjacent joints should also be evaluated.[2,3,15] Furthermore, possible primary sites of disease must be checked.[15]

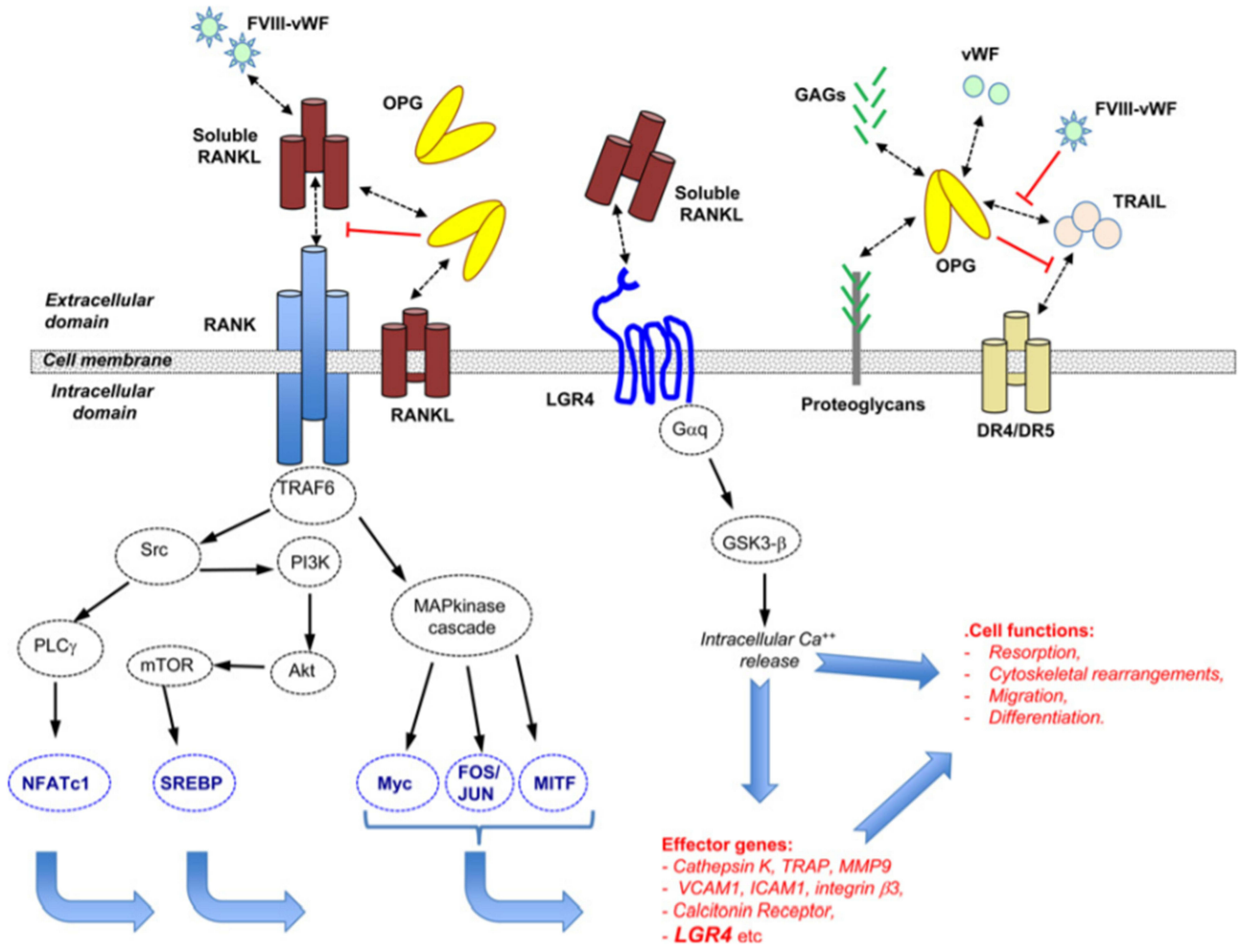

Figure 1 RANK/RANKL signaling in cancer cells.
Notes: Reprinted from Renema N, Navet B, Heymann MF, Lezot F, Heymann D. RANK-RANKL signalling in cancer. *Biosci Rep*. 2016;36(4):1–17. Copyright © 2016 The Authors. This is an open access article published by Portland Press Limited on behalf of the Biochemical Society and distributed under the Creative Commons Attribution Licence 4.0 (CC BY).[64]

Important laboratory tests for patients with bone metastasis are measurements of serum calcium to check for hypercalcemia, serum protein electrophoresis, and serum prostate-specific antigen.[2] Hypercalcemia causes non-specific signs and symptoms but can be life-threatening by inducing renal failure and cardiac arrhythmias.[3] Furthermore, infiltration of malignant cells within the bone marrow space, chemotherapy and/or immunotherapy can cause cytopenia.[5] Anemia and thrombocytopenia must be addressed prior to surgery and other future treatment modalities.[3]

Imaging and Staging

Plain radiographs are the first step in evaluation. Orthogonal planes including the affected area and the joints above and below the lesion are typically obtained. Radiographs yield valuable information about the bone tumor and help differentiate between lytic and blastic lesions.

Bone metastases are usually classified as osteolytic, osteoblastic (or sclerotic) and mixed. Osteolytic lesions are characterized by destruction of normal bone and are associated with multiple myeloma, breast cancer, renal cell carcinoma and non-small cell lung cancer, among others. Osteoblastic lesions occur due to deposition of new bone and are mainly associated with prostate cancer (Figure 2). Lesions that have both an osteolytic and osteoblastic pattern may be referred to as mixed. Mixed lesions can occur in gastrointestinal cancers, squamous cancers and breast cancers;

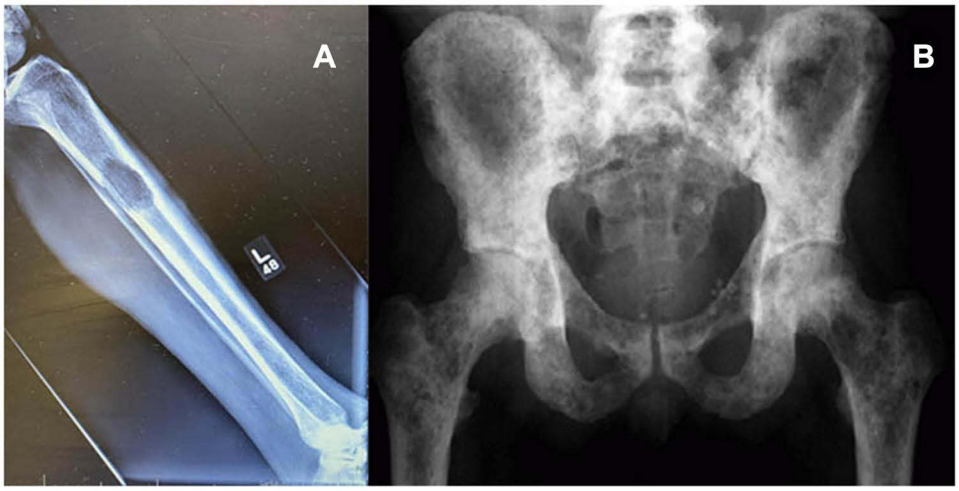

Figure 2 Anteroposterior radiographs showing: (**A**) Lytic bone lesion in tibial diaphysis. (**B**) Multiple mixed lytic and blastic/sclerotic bone lesions in pelvis.

indeed, although breast cancer most often causes osteolytic lesions, 15–20% of the women with breast cancer will present osteoblastic or mixed lesions.[7]

Further Imaging and Tumor Staging

Further assessment of the lesion often requires additional imaging. Currently, additional imaging of the bone lesion and staging of the patient is based on a combination of CT scan, positive emission tomography (PET)-CT and bone scintigraphy (bone scan).

CT scan provides additional information about the bone lesion and is additionally used to detect other distant metastases. CT scan of the area of interest can help define whether the bone lesion is contained, with intact cortical boundaries, or uncontained, extending into the surrounding soft tissue. In addition, patients with bone metastases often undergo CT scan of chest, abdomen and pelvis for staging purposes. Due to its higher sensitivity and specificity in comparison with plain CT, PET-CT is commonly performed in patients with bone metastatic disease (Figure 3). Yang HL et al reviewed all literature regarding diagnostic techniques for bone metastasis and showed that PET-CT had a much higher sensitivity than plain CT, although the specificity was slightly superior.[16] Other advanced imaging modalities, such as bone scintigraphy, are also commonly performed. A Tc-99m total body bone scan is a valuable tool to detect osteoblastic activity; however, it may not detect lytic bone lesions and could potentially yield false-negative results in the setting of bone lytic lesions, such as those caused by multiple myeloma.[15]

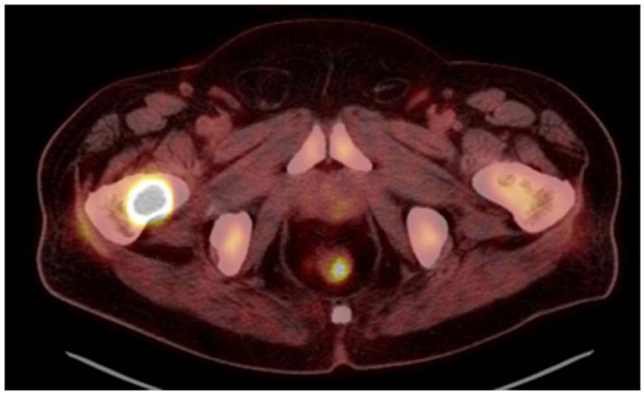

Figure 3 PET-CT scan showing radiotracer uptake of bone metastasis located on right femur. Standard uptake value (SUV) = 22.3.

Biopsy

Unless a primary bone tumor can be completely excluded, bone biopsy is necessary to obtain a diagnosis. Timing of the biopsy may vary since it can be performed as a separate procedure or simultaneously with the operative management of the bone lesion. The main modalities of biopsy in bone lesions are image-guided percutaneous biopsy and open biopsy.

Percutaneous biopsies provide a less invasive alternative with a high accuracy rate. Skrzynski et al prospectively analyzed diagnostic accuracy of percutaneous needle biopsies and found that 84% of the samples arrived at the diagnosis.[17] This method provides several advantages, including lower risk of soft-tissue contamination and significantly lower procedural cost. However, insufficient tissue obtained, especially in the setting of soft tissue component, often leads to inability to differentiate between benign and malignant lesions.

We recommend performing a staging workup prior to biopsy, as it allows the treating physician to (1) determine optimal biopsy site, (2) assess the need for preoperative embolization, and (3) avoid biopsy in patients with disseminated metastatic disease and an already identified primary tumor.[2,18]

Although in many cases, a biopsy might be avoided in patients with bone lesions and an already diagnosed extraosseous primary tumor with metastatic spread, primary bone tumors cannot be completely ruled out (Figure 4). Therefore, a high index of suspicion for primary bone tumors should always be held both preoperative and during surgery.

Prompt diagnosis of primary bone tumors is of utmost importance since inadequate surgical treatment may lead to amputation and related morbidity, as described by Adams et al in which six out of eight patients underwent amputation as definitive treatment after inadvertent nailing of primary bone sarcomas.[19] It is important that general orthopedic surgeons always consider the possibility of metastatic bone disease or primary bone tumors in patients with pathological fracture or impending fracture; adequate workup staging and biopsy are necessary to allow for prompt referral to an orthopedic oncology service and avoid unnecessary procedures.

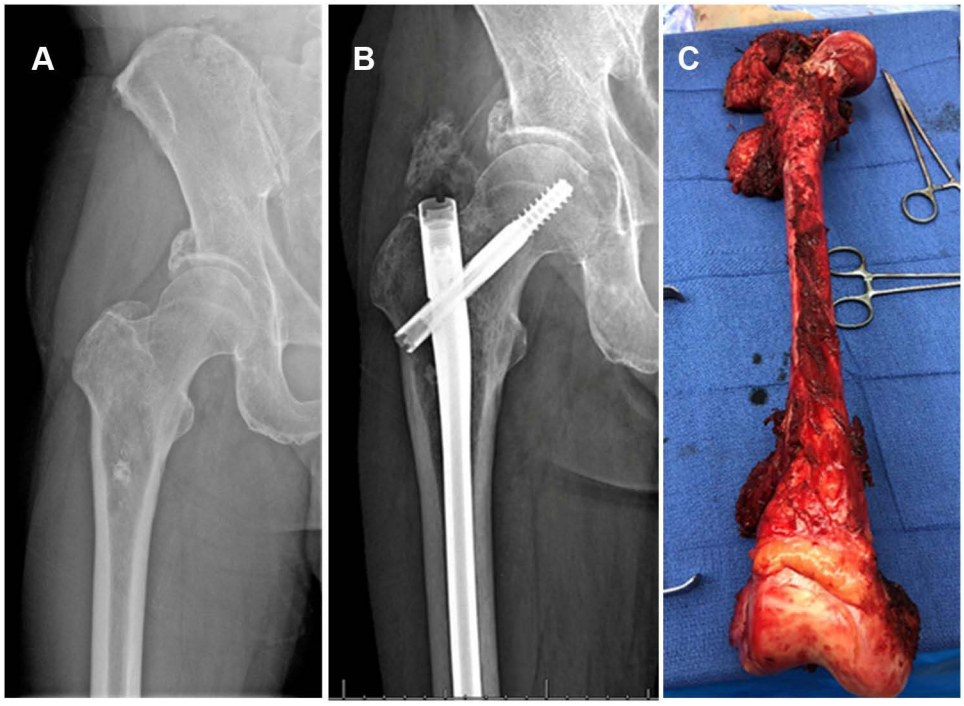

Figure 4 Patient with metastatic prostate cancer who complained of right Hip pain with weight-bearing. Staging workup revealed multiple pulmonary nodules and blastic metastases in T3, left acetabulum and ischium. **(A)** Plain radiograph of right femur showed a lytic bone lesion with calcification. **(B)** The patient initially underwent surgical stabilization with an intramedullary nail due to high risk of impending fracture with suspicion of metastatic disease; however, final histopathological analysis of intraoperative reamings revealed a chondrosarcoma. **(C)** The patient finally underwent a complete femur resection and modular endoprosthesis reconstruction once his metastatic prostate cancer was stable.

Management

Management of bone metastatic disease involves a multimodal approach involving the use of systemic treatment, radiotherapy and, if necessary, surgical treatment.

Systemic Treatment

Systemic treatment for bone metastases consists of a combination of inhibitors of bone resorption (bisphosphonates and denosumab) and systemic antitumor therapy. Systemic antitumor treatment depends mainly on pathological type of tumor. Chemotherapy, immunotherapy and hormonal therapy have shown clinical benefits in several carcinomas.[20,21] Optimizing systemic treatment, either with a palliative intent in patients with multiple metastases or to prolong life expectancy in those with solitary bone metastasis, is an important focus of the multidisciplinary care. Furthermore, in the setting of increasing survival rates in metastatic disease due to newer and more effective compounds, the main focus of both medical and surgical treatment should be preserving patient function and maximizing quality of life. A full discussion of systemic therapy goes beyond the scope of this review article.

Radiotherapy

External beam radiotherapy (EBRT) for metastatic bone disease is typically used for pain control rather than primary treatment of the disease. Conventionally, multiple-fraction (MF) strategies include 20 Gy in 5 fractions, 24 Gy in 6 fractions and 30 Gy in 10 fractions for previously unirradiated painful bone metastases is used. Alternatively, a single-fraction (SF) dose of 8 Gy is used to provide relief from bone metastases with equal efficacy to MF schemes, but higher retreatment rates.[22,23]

EBRT for painful bone metastasis has been proven to be effective, with an overall response rate of 60%, depending on the type of tumor. Chow et al conducted a meta-analysis of all randomized controlled trials published until 2010 and found a similar overall response rate between SF and MF schemes.[22] Despite conclusive evidence of equal efficacy between SF and MF schemes, retreatment rates are higher in patients who receive single-fraction EBRT.[24] Van der Linden et al retrospectively reviewed data from the Dutch Bone Metastasis Study and found that with or without the effect of retreatment, SF and MF radiotherapy provided equal palliation for painful bone metastasis.[23] These results show that physicians are more likely to retreat patients after an SF of 8 Gy because of the lower combined radiation exposure, compared to MF.

Fracture Risk After Radiotherapy

The effect of radiotherapy on the bone remains an area of extensive research and not yet completely elucidated; indeed, although radiotherapy is commonly used after surgical stabilization of a fracture and has been shown to decrease the rates of implant failure, it also increases the risk of pathological fractures. Radiation-associated fractures of metastatic bone lesions commonly occur after high doses of radiation (>50 Gy)[25] and early after radiation; for metastatic femoral bone lesions, Shimoyama et al reported that 87.8% (29/33) of post-irradiation fractures occurred within a year.[26] On the contrary, radiation-associated fractures in primary bone tumors usually occur >3 years after radiation.[27,28] Treatment of radiation-associated fractures is difficult, with a high rate of nonunion (Figure 5). Lin et al reported that out of 9 patients with pathological fractures after radiotherapy, only 3 of the 9 fractures successfully united.[29] Due to the high nonunion rate of this type of fractures and the associated morbidity for the patients, prophylactic internal fixation after combined surgical excision and radiotherapy may be considered.[25,27]

Radiotherapy After Fracture Stabilization

Postoperative EBRT after fracture stabilization plays a critical role in management of painful bone metastasis. Multiple studies have shown improved postoperative functional status, lower number of orthopedic secondary surgical interventions at the same site, and longer survival.[30,31] Townsend et al retrospectively reviewed 64 stabilization procedures in patients with pathological or impending fractures that were managed with either surgery alone or surgery and radiotherapy, and found that patients managed with a combination of surgery and radiation had an improved functional status

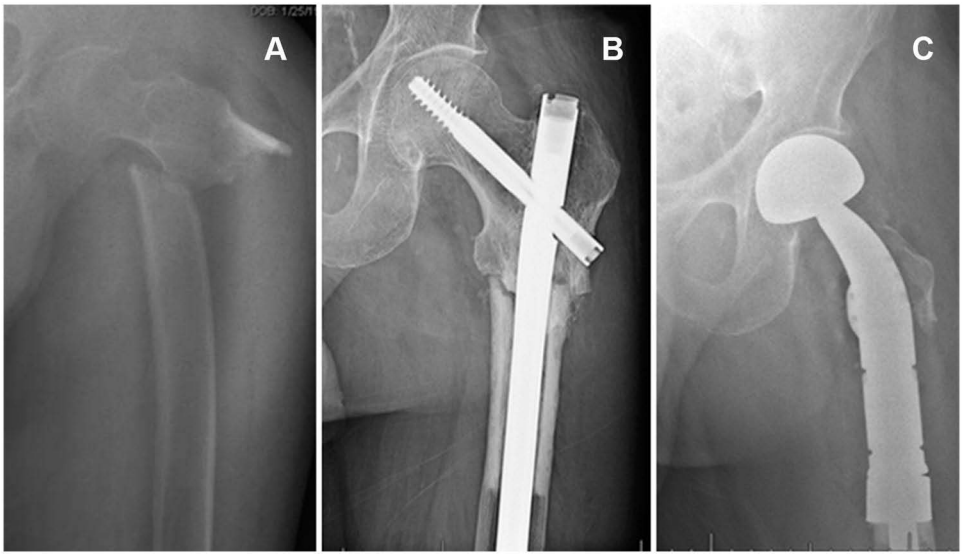

Figure 5 (A) Plain radiograph showing pathological fracture of proximal femur after radiation. **(B)** Initial stabilization of fracture with IM nail. **(C)** Fracture nonunion lead to final management with proximal femur resection and reconstruction with megaprosthesis.

(53% vs 11.5%), lower number of orthopedic second procedures, and longer survival (12.4 months vs 3.3 months); they found all data to be statistically significant.[30] Wolanczyk et al revised stabilization procedures in 72 patients with impending or pathological fractures that were posteriorly treated with radiotherapy, bisphosphonates, or both. They found significantly lower rates of local tumor progression in patients treated with radiotherapy or radiotherapy and bisphosphonates (9% and 7% vs 44%).[31]

Despite lack of overwhelming evidence, postoperative EBRT is currently recommended based on retrospective studies citing its benefits. However, recommendations regarding this practice are not evidence-based and further prospective research is needed to determine its overall effectiveness.

Alternatives to Radiotherapy for Regional Control

EBRT is a well-established technique to relieve pain refractory to medical management. Still, about 30–40% of the patients show partial or no response and retreatment can present numerous challenges including the risks associated with cumulative doses of radiation and the elevated fracture risk.[22] Interventional radiology techniques such as cryoablation or percutaneous injection of acrylic surgical cement have been described with moderate efficacy but are invasive procedures with a higher risk of complications.[32,33]

Magnetic resonance-guided high-intensity focused ultrasound (MR-HIFU) is a non-invasive treatment approach with excellent results and sparing the complications associated with EBRT.[34,35] In a Phase III trial of 147 patients with painful bone metastases, with 112 receiving MR-HIFU and 35 placebo, response rate for the primary outcome (improvement in self-reported pain score without increase of pain medication 3 months after treatment) was achieved in 64.3% and 20% of the patients, respectively ($p < 0.001$).[34] Likewise, Bongiovanni et al reported a 50% complete response of current pain and 50% partial response in 12 patients with painful bone metastases of solid tumors.[35] In addition to pain relief, MR-HIFU has been reported to be an effective treatment for tumor control, with a radiographic response rate of 33.3–67.7% according to MD Anderson criteria.[36,37]

Role of Bisphosphonates and RANK-L Inhibitors

Bisphosphonates are widely used in the management of metastatic bone lesions and have evidence-based indications for use in the following settings: (1) hypercalcemia, (2) non-mechanical metastatic bone pain, and (3) prevention of SRE. Although radiotherapy remains the treatment of choice for localized bone pain, bisphosphonates have been shown to be very effective in the treatment of diffuse, non-localized bone pain.

Contrary to the main mechanism of action of bisphosphonates, which is inhibiting osteoclast bone resorption and stabilizing bone architecture, bisphosphonates can paradoxically cause atypical fractures, and its risk is increased with longer duration of bisphosphonate use, with treatment for ≥8 years being associated with 44 times greater risk of developing atypical fractures compared to treatment for 3 months or less (Hazard ratio 43.41).[38]

Regarding SRE, current American Society of Clinical Oncology (ASCO) guidelines recommend starting bisphosphonates as soon as bone metastases are definitely diagnosed to delay the first SRE and reduce complications associated with metastatic bone disease.[39]

Denosumab, a monoclonal antibody with high affinity for the RANK ligand, is an effective alternative to treat bone pain and prevent SRE in metastatic bone disease. Benefits of denosumab include the possibility to be used in renal failure, reversibility of its effect after treatment discontinuation and superior suppression of bone turnover markers in prostate and breast cancer.[40,41] However, limitations of its potential use include an increased infection rate in patients with osteoporosis and breast cancer, a short post-marketing surveillance time, scarce, and increased costs.[42] Due to scarce or unavailable data on its effectiveness in certain cancer types, denosumab is often used as a second-line option when bisphosphonates are not effective or contraindicated.

Surgical Management of Metastatic Bone Disease

Principles of Surgical Treatment

Orthopedic surgeons should consider each patient's background independently and establish case by case whether the patient is suitable for surgery and what surgical approach is best.

Management of metastatic disease should be based on 3 pillars: (1) Patient's characteristics, (2) Tumor type, and (3) Location of fracture/bone stock. Physicians should not consider each pillar as an independent entity, rather, as a component of a decision-making process (Figure 6).

Patient's Characteristics

Determining the patient's degree of functional impairment before deciding on the optimal surgical approach is imperative, as performance status prior to the disease significantly impacts prognosis. Crooks et al observed that the Karnofsky Performance Scale (KPS) was an effective proxy score for a patient's overall health and was also a significant predictor of hospitalizations and survival time.[43] Therefore, independent assessment of the patient's functional status will help determine the course of action, considering the different durability and complication rates of each procedure. Furthermore, metastatic status at diagnosis must also be considered part of the patient's characteristics, as it significantly affects prognosis and thus, management.[44] To adequately estimate overall survival in patients with metastatic bone, we recommend the use of clinical decision-support tools such as PATHFx, available at www.pathfx.org, an already externally validated calculator that uses machine-learning to provide an estimate of each patient's overall survival.[45,46]

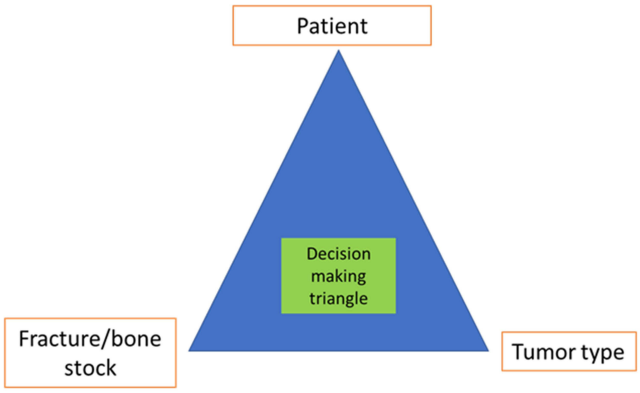

Figure 6 Decision-making triangle illustrating the 3 main pillars of surgical management.

Tumor Type

Physicians should also consider the primary tumor type and its associated prognosis and response to non-surgical options such as systemic therapies and radiation therapy. Factors such as histopathological diagnosis, differentiation status and metastatic spread of the primary tumor influence prognosis and overall survival.[6] Correctly determining each patient's prognosis when deciding on treatment approach is key to decrease patient-related morbidity and improve pre-treatment functional status.

Location of Fracture/Bone Stock

Assessment of the type of fracture and bone stock allows the physician to establish the best surgical approach that minimizes risk of nonunion and postoperative complications. A CT scan is an important aid in the assessment of bone stock, as it shows the degree of bone destruction which will determine surgical management. Extensive bone destruction (lack of bone stock) is generally an indication for endoprosthetic reconstruction, while IM nailing may be employed primarily in patients with limited bone loss in addition to cementation,[47] and trochanteric or subtrochanteric lesions.

Impending Fractures

While current recommendations agree on the need for surgical stabilization of impending fractures, to date there is no consensus on the threshold parameters to define "substantial risk of impending fracture" and subsequently stabilize the bone.

Plain Radiographs

Orthopedic surgeons commonly attribute a higher risk of fracture to lytic lesions in comparison to blastic ones; indeed, widely used scoring systems such as the one developed by Mirels et al attribute a higher score to lytic lesions.[48]

Harrington et al described the concept of impending fracture due to lytic lesions as (1) a lesion 2.5 cm or larger involving the femur, (2) lytic destruction of 50% or more of the cortex of the long bone, and (3) persistent pain with weight-bearing, despite local radiotherapy.[49] However, Harrington's definition of impending fracture was very limited in scope since it did not consider the risk of fracture of blastic lesions and did not consider anatomic location as a risk-modifying parameter.

In 1985, Mirels et al scoring system provided a simple method to assess the risk of fracture based on 4 parameters: site of lesion, radiographic appearance, bone width, and pain (Table 1).[48] Bone lesions with a score of 8 should be considered for surgical stabilization due to 15% probability of fracture; lesions with scores ≥9 should be always prophylactically fixated due to at least >33% probability of fracture. However, all these factors are based on retrospective studies and the level of evidence is low. Despite the widespread use of scoring systems based on clinical and radiographic parameters, treating physicians should be aware that conventional risk factors significantly overestimate the risk occurrence of pathological fractures and clinical assessment always plays an important role.[50]

CT Scan

Although widely used to determine risk of impending fractures, X-rays cannot determine total volume of the lesion. CT-based analysis, including PET-CT, provides a better view of the lesion and can assess total surface area of cortical involvement, a parameter associated with risk of fracture. Tatar et al prospectively analyzed femoral metastases with CT and impending fractures were then monitored to assess fracture occurrence. Circumferential cortical involvement >30% was the only predictive parameter for pathologic fracture; in contrast to the Mirels score, this threshold was found to be both highly sensitive and specific, with a positive predictive value of 71%.[51] In addition, machine learning algorithms based on radiological (CT scan) and clinical data have been developed to predict the risk of fracture. Oh et al retrospectively

Table 1 Mirels Scoring System for Diagnosing Impending Pathologic fractures[49]

Score (Points)	Site	Radiographic Appearance	Lesion Size (Bone Width Involvement)	Pain
1	Upper limb	Blastic	<1/3	Mild
2	Lower limb	Mixed (blastic-lytic)	1/3 – 2/3	Moderate
3	Peritrochanteric	Lytic	>2/3	Functional

reviewed 84 patients with metastatic lung cancer and femur lesions and found an area under the receiver operating characteristic curve of 0.80 to detect pathologic fractures through gradient boosting algorithm.[52] Although further prospective research is required to compare X-ray and CT-based assessments, broader use of CT analysis to determine risk of fracture in metastatic bone disease could significantly reduce the number of unnecessary surgical fixations.

MRI

This advanced imaging study is not commonly used to assess the risk of pathological fracture. This modality is less accurate for evaluation of bone stock in comparison to a plain radiographs or CT scan. The utility of this imaging study is based on the fact that these lesions can have a soft tissue component and can contribute to surgical planning.[53]

Surgical Treatment

The goal of surgical treatment in metastatic bone disease is rarely curative; rather, it seeks to relieve pain, improve functional status, and restore skeletal stability. Patients should ideally be able to restore function and bear weight immediately after surgery. Depending on the procedure, different degrees of intraoperative blood loss can occur. We recommend that hypervascular bone metastases due to renal cell carcinoma and thyroid cancer undergo pre-operative embolization to reduce blood loss during the procedure.[54]

Surgeons must be aware that fixation techniques of traumatic fractures in healthy bone might not be applicable in pathological bone. There are still controversial anatomical locations such as the acetabulum and femoral neck; in these cases, choice of treatment might depend on a combination of factors including life expectancy of the patient, degree of bone destruction, and each surgeon's preference. Fixation options may be classified into 3 broad categories: plate and screw fixation with or without cement, intramedullary (IM) nailing with or without cement, and endoprostheses.

Open reduction and internal fixation (ORIF) offers good visualization of the bone and allows curettage and resection when tumor debulking is required. Tumor debulking is important in metastatic tumors that are not radiosensitive, such as renal cell carcinoma. Nonetheless, ORIF has a much higher rate of revision surgery compared to IM nailing or prosthetic replacement, mainly due to failure of fixation.[55]

IM nailing is widely used in radiosensitive and chemosensitive tumors and provides whole-bone fixation with a relatively small dissection. All IM nails need distal locking to avoid rotation within the medullary cavity and subsequent failure of fixation in cases of displaced pathological fractures.[56] In the femur, antegrade nails can be proximally fixed with interlocking screws to provide additional stabilization to the femoral neck and head. IM nails allow for immediate stability and early restore of mobility; however, they are also associated with a higher rate of revision surgeries for failure of fixation compared to prosthesis.[55] Furthermore, use of IM nails requires adequate bone stock in the sites of the locking screws.

Prosthetic reconstructions include segmental- and endoprosthesis, and hemi- and total arthroplasty. They are the treatment choice in tumors with extensive bone destruction and provide immediate stability that does not depend on fracture healing (Figure 7). Arthroplasties are the treatment of choice for femoral neck lesions due to high biomechanical stress in this anatomical site, which limits the use of cannulated screws. However, prosthetic reconstruction is associated with multiple complications that limit its widespread use. Need for extensive surgeries may lead to increased blood loss, and detachment of all surrounding tissue from the bone and reattachment to the prosthesis relates to a deficit in functional strength and/or range of motion and increased rates of joint dislocation. Revision surgeries commonly occur, mostly due to deep infections.

Janssen et al compared complications for 3 different surgical approaches, intramedullary (IM) nailing, endoprosthetic reconstruction, and ORIF in 417 patients with proximal femoral fractures due to metastatic disease. Probability of revision for failure of fixation at 3 months was 0.47%, 0%, and 5.4% for IM nailing, endoprosthetic reconstruction, and ORIF, respectively. In contrast, the probability of revision for deep infection at 3 months was 1.1%, 6.8%, and 0% for IM nailing, endoprosthetic reconstruction, and ORIF, respectively.[55] Likewise, treating orthopedic surgeons should bear in mind each patient's expected survival when determining the optimal surgical approach.

Currently, it is common practice to prophylactically stabilize the entire femur using either a long femoral stem during a hip arthroplasty or adjacent cephalomedullary nail during stabilization with IM nails. Recent studies have demonstrated the low rates of new bone metastases after surgical stabilization.[57–59] We recommend that physicians analyze case-by-case

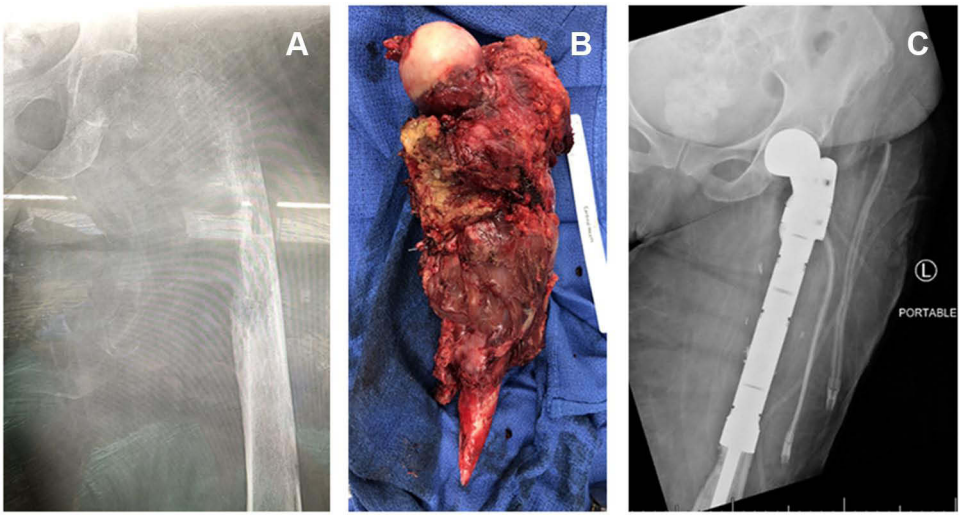

Figure 7 Patient with metastatic breast cancer presented complaining of left Hip pain. **(A)** Initial plan radiographs showed diffuse proximal femoral bone destruction. **(B)** The patient underwent proximal femur resection due to invasive metastatic lesion compromising the entire proximal femur. **(C)** Plain radiographs after final management with proximal femur replacement.

the need for nails and/or use of long stems, due to probable higher cost, higher complications rates, blood loss, and radiation exposure associated with these procedures. Although literature on risk factors for complications after surgery for metastatic bone disease is scarce, a review of the literature on the topic was conducted (Table 2).

Table 2 Risk Factors for Post-Operative Complications and/or Death After Stabilization of Impending or Actual Pathologic Fractures Due to Metastatic Bone Disease

Author (Year)	Patient (n)	Common Primary Tumor(s)	Impending/ Actual Fracture	Metastatic Bone Affected	Outcome Measure	Risk Factors
Bindels at al (2020)[60]	1090	Breast (24%), lung (23%), MM (15%)	45% IF, 55% PF	Femur (70%), humerus (22%)	30-day complication rate after surgery	Rapid-growth tumor (OR=1.56), multiple BMs (OR=1.63), PF (OR=1.48), lower extremity (OR=2.24), Na^+ < 135 mmol/L (OR = 0.044), albumin < 3.5 g/dL (OR = 1.71), WBC count > 11,000/mm^3 (OR=1.65)
Janssen et al (2016)[55]	417	Breast (30%), lung (23%)	59% IF, 41% PF	Proximal femur	30-day systemic complications	Age (OR=1.06), mCMI (OR=1.22), modified Bauer score (OR=0.69)
Tsuda et al (2016)[61]	1497	Lung (19.2%), breast (16.6), prostate (10.3%)	100% PF	Proximal femur	Overall postoperative complication rate	Age ≥ 80 (OR=2.15), lung as PS (OR=2.05), breast as PS (OR=4.41), CMI ≥ 10 (OR=13.6), blood transfusion (OR=14.4)
Weiss et al (2014)[62]	391	Breast (100%)	19% IF, 81% PF	Femur (53%), spine (20%), humerus (16%), pelvis (9%)	Risk of death after surgery*	Age > 60 (OR=1.9), Hb < 110 g/L (OR=2)
Weiss et al (2012)[63]	306	Prostate (100%)	5% IF, 95% PF	Spine (54%), Femur (30%), Humerus (8%), Pelvis (8%)	Death and any complications after surgery*	Age > 70 (OR=1.3)$^{\pm}$, generalized metastases (OR=2.4)$^{\phi}$, multiple skeletalal metastases (OR=2.2) $^{\pm}$, pelvis locations (OR=2.3)$^{\phi}$

Notes: *Although the patient sample of this study included spine metastases, risk factor analysis was restricted to appendicular bone metastases. $^{\pm}$Outcome measure refers to risk of death. $^{\phi}$Outcome measure refers to risk of any complications.

Abbreviations: MM, multiple myeloma; IF, impending fracture; PF, pathologic fracture; BM, bone metastasis; Na^+, sodium; WBC, white blood cell count; mCMI, modified Charlson Comorbidity Index; PS, primary site; Hb, hemoglobin.

Conclusion

Management of impending or actual pathological fractures due to metastatic disease requires a multidisciplinary approach. The decision to undergo surgical stabilization of an impending fractures relies on radiological features, which quantify the risk of progression to a pathological fracture. Adequate quantification of the risk of fracture is paramount to choose the optimal patient for surgical treatment and avoid overtreatment. In this area, artificial intelligence algorithms that improve accuracy predicting the risk of fracture are currently under investigation.

Data Sharing Statement

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

Ethical Approval

This is a review article. As such, it did not involve human participants and therefore did not require an ethical approval.

Consent to Participate

This is a review article. As such, it did not involve human participants, and therefore no Consent to Participate was required.

Consent to Publish

This is a review article. As such, it did not involve human participants, and therefore no Consent to Publish was required.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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