Chapter

Perspective Chapter: Bone Metastases of Solid Tumors

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Abstract

Bone metastases are more common than primary bone cancers, especially in adults. Bone is the third most common organ affected by metastases, from many types of solid cancers but especially those arising in the breast and prostate. Besides the impact on survival, bone metastases may have a big impact on morbidity and represents a significant healthcare burden. Skeletal-related events (SREs) include pain, pathologic fracture, spinal cord compression, and hypercalcemia and can cause a deterioration of the quality of life. Detection of bone metastases is essential for accurate staging and optimal treatment; however, there is no consensus or standard approach for diagnosis, so the choice of imaging should be guided by clinical presentation. Treatment goals may consist of controlling pain and other symptoms, preserving and restoring function, minimizing the risk of SREs, stabilizing the skeleton, and enhancing local tumor control. Therapeutic options include pain management/analgesia, osteoclast inhibitors, systemic anticancer therapy, radiation therapy, bone-targeting radiopharmaceutical therapy, surgery, and/or image-guided thermal ablation. The choice of treatment is influenced by factors like symptoms, impact on quality of life, performance status, estimated life expectancy, goals of treatment, and preferences of care.

Keywords: bone metastases, cancer pain, osteoclast inhibitors, bisphosphonates, denosumab

1. Introduction

Bone metastases are more common than primary bone cancers, especially in adults [1]. Bone is the third most common organ affected by metastases, from many types of solid cancers but especially those arising in the breast and prostate [1–3]. The most common locations for metastatic disease are the vertebral column, sacrum, pelvis, and proximal femurs [4].

The overall incidence of bone metastases is not known [1, 2]. It is estimated to have an incidence in about 70% of patients with breast and prostate cancer, which are the two most common cancers worldwide, but bone metastases can occur in a wide range of malignancies, described in **Table 1** [2, 3, 5].

In terms of prognosis, survival varies according to the tumor type, with the median survival of patients with breast and prostate cancer reaching years and of patients with lung cancer being measured in months, and it is also influenced

Primary tumor	Incidence of bone metastases (%)
Breast cancer	65–75
Prostate cancer	65–75
Thyroid cancer	40–60
Bladder cancer	40
Lung cancer	30–40
Renal cell carcinoma	20–35
Melanoma	15–45
Gastrointestinal cancer	5

Table 1.
Incidence of bone metastases in different cancers.

by coexisting non-osseous metastatic disease, which ends up being important in determining the prognosis [3]. However, bone metastases may have a big impact on morbidity and represents a significant healthcare burden [3, 6].

2. Mechanism of bone metastases

During metastatic dissemination, cancer cells from the primary tumor must first undergo epithelial-to-mesenchymal transition (EMT) to invade the surrounding tissue and enter the microvasculature (intravasation) of the blood and/or lymphatic systems. Once in the bloodstream, cancer cells may disseminate to distant organs, exit from blood vessels (extravasation), and settle in the foreign microenvironment, where they enter a dormant state or proliferate to subsequently form macroscopic secondary tumors (metastases) [7].

In the skeleton, the process of metastasis development begins with colonization, when circulating tumor cells enter the bone marrow and engage in specialized microenvironments or niches. Then, the colonizing tumor cells adapt to their new microenvironment, evade the immune system, and may reside in a dormant state for a long period of time until they reactivate and develop, escaping from the dormant state to actively proliferate and form micrometastases. With uncontrollable growth, the cancer cells become independent of the microenvironment and end up modifying the bone as metastases develop.

3. Type of bone metastases

In metastatic bone disease, the normal bone homeostasis that involves constant remodeling by the coordinated actions of osteoclasts and osteoblasts is disturbed [5, 7]. According to the primary mechanism of interference with normal bone remodeling, bone metastases can be classified as osteolytic, osteoblastic, or mixed [8].

Osteolytic lesions are characterized by the destruction of normal bone and are associated with high osteoclast activity and reduced osteoblast activity. Several factors secreted by tumor cells enhance osteoclast-mediated bone resorption, either directly (like interleukin-8) or indirectly [like the parathyroid hormone-related peptide (PTHrP), interleukin-6] via stimulation of the receptor activator of the nuclear

factor kappa-B (RANK) ligand (RANKL) secretion and inhibition of osteoprotegerin (OPG) production by osteoblasts. In turn, the binding of RANKL to RANK on osteoclast precursors leads to the formation of new osteoclasts, increasing their activity [7]. This type of metastasis is characteristic of prostate cancer, small cell lung cancer, carcinoid tumors, and medulloblastoma.

Osteoblastic metastases are characterized by the deposition of new bone (osteosclerosis). Several factors secreted by tumor cells directly enhance osteoblast differentiation, like endothelin-1 (ET-1) and bone morphogenetic proteins (BMPs). The stimulation of osteoblast differentiation is associated with increased OPG production, whereas RANKL secretion is decreased, and tumor-derived ET-1 directly acts on mature osteoclasts to inhibit osteoclast activity. Therefore, there is a strong imbalance between bone formation and bone resorption, leading to aberrant bone formation [7]. This pattern is usually seen in renal cell cancer, non-small-cell lung cancer, melanoma, and thyroid cancer.

If a lesion has both osteolytic and osteoblastic components, it's classified as **mixed** and is usually seen in breast cancer, gastrointestinal cancers, and squamous cancers.

4. Clinical presentation

Bone metastases may cause few or no symptoms, being diagnosed incidentally during the initial staging of the primary cancer. However, they can represent a prominent source of morbidity because of skeletal-related events (SREs), which include pain, pathologic fracture, spinal cord compression, and hypercalcemia [3, 5].

Pain is the most common symptom of bone metastases and can have a significant impact on the quality of life [3, 9]. It could be of either biologic or mechanical origin. Biologic pain is related to the local release of cytokines and chemical mediators by the tumor cells, periosteal irritation, and stimulation of intraosseous nerves. Mechanical pain is related to the pressure or mass effect of the tumor tissue within the bone, with loss of bone strength, thus turning into activity-related pain. It's usually localized, but not rarely patients can complaint of pain in more than one site, and it might become severe and refractory to analgesia [7]. Sudden severe pain may be caused by a pathologic fracture, and prompt evaluation is necessary.

Pathologic fractures occur in 10–30% of all cancer patients, with proximal parts of the long bones being the most frequent fracture site and the femur accounting for over half of all cases [10]. Pain at the fracture site is the most common symptom, but other clinical features may be present depending on the fracture location, such as the inability to bear weight, point tenderness, pain that radiates, ecchymosis or skin discoloration, soft tissue mass or swelling at the site of pain, edema or joint effusion, loss of bony or limb contour, extremity shortening, open wound and bone exposure, decreased range of motion, significantly diminished mobility, and/or sensory disturbance of the distal extremity. The presence of neurologic symptoms should be a red flag for spinal cord compression.

Spinal cord compression can be caused by pathologic spine fracture, with the bone compressing the spinal cord or by tumor extension into the epidural space. Symptoms range from pain, which is usually the first symptom, to neurologic deficits, including motor weakness and paralysis, sensory deficits, bowel and bladder dysfunction, and ataxia [3, 11]. In terms of motor symptoms, these will depend on the site of compression – if it's at or above the conus medullaris, it generally produces fairly symmetric lower extremity weakness (if compression is above the thoracic spine, upper

extremities may be affected too); if it's below the level of the conus medullaris, it may present with signs and symptoms of cauda equina syndrome, with asymmetrical and less severe weakness. Sensory findings are common and are usually present prior to the onset of weakness, with patients describing ascending numbness and paresthesia in a radicular distribution [11]. If the site of compression is above the conus medullaris, sacral dermatomes are usually spared, while in the cauda equina syndrome, a saddle sensory loss is common. Proprioceptive loss can also occur, although this is less common and usually occurs later.

Hypercalcemia is the most common metabolic complication of malignant disease, and it's usually caused by direct induction of local osteolysis by the tumor cells and generalized osteolysis by humoral factors secreted by the tumor [3, 7, 12]. Patients with mild hypercalcemia may be asymptomatic or have nonspecific symptoms, such as constipation, fatigue, and depression, while patients with higher serum calcium elevations may present polyuria, polydipsia, dehydration, anorexia, nausea, muscle weakness, and neuropsychiatric disturbances and may even lead to cardiac arrhythmias and acute renal failure [2, 7].

5. Diagnosis

Detection of bone metastases is essential for accurate staging and optimal treatment. There is no standard approach for the detection of bone metastases in patients with cancer, so the choice of imaging should be guided by the clinical presentation.

Radiographs are fast, cheap, and widely available and are recommended for the initial evaluation of symptomatic areas, particularly of the extremities [10]. The typical radiographic appearance of a lytic metastasis is a permeative lesion of the diaphysis or metadiaphysis of a proximal long bone or bone of the axial skeleton, while osteoblastic lesions are usually sclerotic in appearance, sometimes admixed with lytic elements. Although it can be specific, for a destructive lesion in trabecular bone to be recognized, it must be >1 cm in diameter with loss of approximately 50% of the bone mineral content, so the sensitivity is low [10, 13]. Therefore, if the clinical suspicion is high, then computed tomography (CT) or magnetic resonance imaging (MRI) should be done.

CT produces images with excellent tissue and contrast resolution [13]. Compared to MRI, it is superior in terms of the evaluation of structural integrity of the bone, and it can be used to diagnose bone metastases in situations in which MRI is contraindicated or not available. However, differentiation between metabolically active from inactive bone lesions cannot be made, limiting its use for the evaluation of treatment effect [13].

In general, **MRI** is more sensitive than CT to detect bone metastases, allows better delineation of the extent of tumor, and is particularly useful for patients with spine metastases to evaluate the extent of medullary and extraspinal disease [10, 14, 15]. Metastatic lesions display decreased signal on T1-weighted sequences, reflecting the replacement of normal fatty marrow with water-containing tumor, while on T2-weighted images, they usually have a higher signal than the surrounding normal bone marrow [14–16].

Whole-body skeletal evaluation with Tc-99 m **skeletal scintigraphy**, generally referred to as **bone scan**, is the most widely used method to detect bone metastases because it provides visualization of the entire skeleton [5, 15]. However, it lacks specificity, it has low sensitivity for tumors with little to no osteoblastic activity, and it is inferior to MRI on the evaluation of vertebral metastases [1, 10, 14, 15, 17].

Positron emission tomography (PET) scan is based on the preferential uptake of 18-fluorodeoxyglucose (18FDG) by tumor cells because of their increased glucose metabolism, so it detects the presence of tumor directly by quantifying the metabolic activity [5, 10, 16]. Therefore, it has high sensitivity and specificity for the diagnosis of distant metastases, including the bone, and it's use in initial staging and further evaluation for metastatic disease is increasing.

Definitive diagnosis requires histologic examination of **biopsy**. However, in patients with known cancer, a skeletal lesion with a typical appearance on imaging studies may be presumed to be metastatic, and there is no need for tissue diagnosis. For patients with bone-only disease, especially when there are few lesions or imaging tests are equivocal, histological confirmation of metastatic disease is strongly recommended [13]. The same holds true for patients with an unknown primary cancer who present with bone metastases and the initial evaluation fails to identify the primary site, where a biopsy is generally indicated to both confirm the malignant nature of the bone lesion and provide histologic information about likely primary sites. CT-guided fine needle aspiration biopsy (FNA) is easy to perform and accurate to document the presence of metastatic disease; however, it may not indicate the most likely site of the primary malignancy. Therefore, in this setting, a core biopsy may be needed, as it has higher diagnostic accuracy for determining the type, grade, and specific diagnosis of musculoskeletal tumors [18]. An open biopsy is required in a residual number of cases and may be done opportunistically in the operating room prior to possible internal fixation.

6. Treatment

Treatment goals may consist of controlling pain and other symptoms, preserving and restoring function, minimizing the risk of SREs, stabilizing the skeleton, and enhancing local tumor control. Therapeutic options include pain management/analgesia, osteoclast inhibitors, systemic anticancer therapy, radiation therapy, bone-targeting radiopharmaceutical therapy, surgery, and/or image-guided thermal ablation. The choice of treatment is influenced by factors like symptoms, impact on quality of life, performance status, estimated life expectancy, goals of treatment, and preferences of care. Optimal treatment may be complex and may require multimodality treatment strategies.

6.1 Analgesia

Patients with bone metastases will suffer from significant bone pain at some point of the disease course. Initially, for mild to moderate pain, nonopioid analgesic drugs, such as acetaminophen and nonsteroidal anti-inflammatory drugs (NSAIDs), may be used alone, but for moderate to severe pain, opioids should be the therapy of choice, according to the WHO "analgesic ladder" approach [19, 20].

Glucocorticoids may be helpful for selected patients as well as other adjuncts, like antidepressants and antiepileptics such as gabapentin [21, 22]. Actually, for patients with neurologic deficits or pain associated with spinal cord compression, high-dose glucocorticoid therapy is part of the standard treatment - a typical dose is 10 mg dexamethasone intravenously followed by 16 mg daily orally in divided doses, until definite treatment [23].

Multidisciplinary management with a palliative care specialist should be considered for patients whose pain is refractory to analgesia or who develop significant side effects.

6.2 Osteoclast inhibitors

For patients with metastatic bone disease, osteoclast inhibitors, like bisphosphonates and denosumab, may prevent SREs as they slow down or reverse the progression of skeletal metastases and may even improve pain and quality of life. For patients in whom SREs are unlikely (those with minimal bone tumor burden) or those with a limited expected survival, treatment with osteoclast inhibitors should be decided case by case.

Bisphosphonates are analogs of pyrophosphate, a natural inhibitor of bone demineralization. Bisphosphonates bind avidly to exposed bone mineral around resorbing osteoclast, and this leads to very high local concentrations of products in the resorption lacunae. Then, they are internalized by the osteoclast, causing disruption of the chemical process involved in bone resorption [2, 7, 8]. This way, bisphosphonates decrease bone resorption and increase mineralization [5].

There are two classes of bisphosphonates: nonnitrogen containing, such as etidronate, clodronate, and tiludronate, and nitrogen containing, such as pamidronate, alendronate, ibandronate, risedronate, and zoledronic acid, which are more potent osteoclast inhibitors [19]. When a bisphosphonate is chosen, zoledronic acid is suggested over other bisphosphonates.

Zoledronic acid is the most potent bisphosphonate available and has been the bisphosphonate of choice in most clinical settings and healthcare systems [7]. Trials showed zoledronic acid has effectively decreased the risk of SREs in women with bone metastases from breast cancer, men with bone metastases from castration-resistant prostate cancer, and patients with bone metastases from other solid tumors [24–29]. The approved dose and schedule of administration is 4 mg every 4 weeks, with the dose adjusted for creatinine clearance.

If zoledronic acid is not available, **pamidronate** is a reasonable alternative [25, 29]. Other bisphosphonates that have demonstrated efficacy in reducing SREs were **ibandronate** and **clodronate** [30, 31]. The dosage and interval of administration are described in **Table 2**.

In terms of tolerance, nephrotoxicity is one of the most important side effects, which is both dose and infusion time dependent [5, 32]. Other common adverse effects include acute-phase reactions (with pyrexia and flu-like symptoms), gastrointestinal effects, and the most concerning, osteonecrosis of the jaw [5, 33].

Denosumab is a monoclonal antibody that inhibits the RANKL, a key component in the pathway for osteoclast formation and activation [5, 8]. By binding to RANKL, denosumab prevents osteoclast formation, leading to decreased bone resorption and increased bone mass, thus preventing SREs [19]. Several phase III trials have shown a superiority of denosumab when compared to zoledronic acid [34–36]. A combined analysis of these three phase III trials concluded that denosumab was superior to

Bisphosphonates	Dosing	Interval
Zoledronic acid	4 mg	28/28 days
Pamidronate	90 mg	28/28 days
Ibandronate	6 mg	28/28 days
Clodronate	1600 mg	daily

Table 2.
Dosing and interval of bisphosphonates.

zoledronic acid in reducing the risk of a first SRE (hazard ratio [HR] 0.83, 95% CI 0.76–0.90) and in delaying the time to a first SRE (median 26.6 versus 19.4 months), with no difference in survival outcomes [37]. The recommended dose and schedule of administration is 120 mg every 4 weeks. Most common adverse events are similar to those of zoledronic acid, with the benefit of not requiring monitorization of renal function or dose adjustments for patients with renal insufficiency [37].

6.3 Systemic anticancer therapy

Chemotherapy, targeted therapies, and hormone therapy may contribute to pain relief by reducing tumor bulk and/or by modulating pain signaling pathways [38]. In selecting systemic anticancer treatment for metastatic bone disease, the pathological type of the tumor is the most important [2].

6.4 Radiation therapy

Radiation therapy is commonly used in the management of bone metastases, both for pain relief and for the prevention of morbidity and disease progression [5].

External beam radiation therapy (EBRT) is a standard approach for symptomatic skeletal metastases, as it can provide significant palliation of painful bone metastases in 50–80% of patients, with up to one-third of patients achieving complete pain relief at the treated site [39]. For uncomplicated bone metastases, a single fraction of 8 Gy to the involved area has been shown to provide equivalent pain palliation and may be more cost-effective and convenient compared with fractionated regimens, although retreatment is needed more frequently [13, 40].

Stereotactic body radiation therapy (SBRT) utilizes precisely targeted radiation to a tumor while minimizing radiation to adjacent normal tissue, allowing the treatment of small or moderate-sized tumors in either a single or a limited number of dose fractions. This approach should be reserved mostly for patients who have a reasonable life expectancy (superior to 6 months) and persistent or recurrent bone pain after a standard course of EBRT, which requires reirradiation [40]. Additionally, SBRT may be preferred over EBRT in the definitive treatment of patients with symptomatic bone metastases from relatively radioresistant neoplasms (such as renal cell cancer, melanoma, and sarcoma), especially in the setting of vertebral metastases with epidural extension and in patients with oligometastatic disease who have a relatively long life expectancy [41, 42].

6.5 Bone-targeting radiopharmaceutical therapy

Bone-targeted radiopharmaceuticals are radioactive bone-seeking molecules that show efficacy for pain control in patients with osteoblastic bone metastases, such as samarium-153, strontium-89, rhenium-186, and radium-223 [5].

Radium-223 is approved for the treatment of male patients with castration-resistant prostate cancer, with symptomatic bone metastases and no known visceral metastases, as it shows benefit in overall survival (median 14.9 versus 11.3 months, HR 0.70, 95% CI 0.58–0.83) and time to first symptomatic SRE (median 15.6 versus 9.8 months, HR 0.66, 95% CI 0.52–0.83) on a phase III trial, compared to placebo [43]. Its combination with systemic anticancer therapy is being studied; however, the benefit of the combination has not yet been established.

6.6 Surgery

Surgical management of bone metastases is typically reserved for lesions with a complete or impending pathologic fracture or spine metastases that cause mechanical instability or spinal cord compression [5, 44]. Nonetheless, for highly selected patients with advanced cancer who present with or develop a bone lesion as the only focus of cancer beyond the primary site, resection of the bone metastasis may optimize local tumor control, provide durable pain relief, and possibly prolong survival.

6.7 Thermal ablation

For patients who have persistent or recurrent pain due to one or a few skeletal sites with small volume disease after palliative radiation therapy, and who are not candidates for surgery or reirradiation, local thermal ablation is an important therapeutic option. Radiofrequency ablation, microwave ablation, and cryoablation are effective ablative treatments for the palliation of symptomatic skeletal metastases [45–48]. There are no randomized trials comparing these procedures, so the choice of ablation technique should take into account availability, patient preference, and local expertise.

7. Conclusion

Bone metastases are a common manifestation of distant relapse from many types of solid cancers, a significant source of morbidity, and a major contributor to the deterioration of the quality of life. Prompt diagnosis is essential for optimal treatment, which may consist of controlling pain and other symptoms, preserving and restoring function, minimizing the risk of SREs, stabilizing the skeleton, and enhancing local tumor control. This way, a multidisciplinary approach is essential to achieve the best outcome possible.

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