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Review

When tumors break bones; emerging paradigms in the pathogenesis and prevention of oncologic skeletal fractures

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Abstract

Oncologic skeletal fractures or pathologic fractures resulting from tumor-induced bone destruction represent a devastating complication of both primary bone cancers and metastatic disease, profoundly impairing patient quality of life and survival. Traditionally viewed as mechanical failures secondary to osteolytic or osteoblastic lesions, emerging paradigms now recognize these fractures as the culmination of complex, dynamic interactions between tumor cells and the bone microenvironment. Recent advances highlight the role of tumor-secreted factors, which dysregulate normal bone remodeling by takeover of osteoclast and osteoblast activity, leading to structural weakening long before radiographic changes appear. Moreover, the concept of the vicious cycle between tumor growth and bone resorption has been expanded to include immune modulation, angiogenesis, and neural signaling within the skeletal niche. Novel imaging modalities and biomechanical modeling now enable earlier detection of at-risk bone, while biomarkers offer promise for risk stratification. Therapeutically, beyond bisphosphonates and denosumab, emerging strategies target specific molecular pathways like TGF-β, Wnt, CXCR4 to disrupt tumor-bone crosstalk and preserve skeletal integrity. Additionally, prophylactic stabilization guided by fracture risk assessment tools is increasingly personalized. Meanwhile, prevention, rather than reaction, is becoming the cornerstone of management, emphasizing collaboration among oncologists, orthopedic surgeons, radiologists, and bone biologists.

Keywords: Neoplasm, Bone fractures, Pathologic, Bone neoplasm, Bone remodeling, Osteolysis, Bone density conservation, Bone resorption

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Introduction

Tumors frequently interact with bone tissue, promoting excessive bone formation or leading to significant bone resorption, both of which weaken the bone and increasing the risk of fractures. These fractures, known as pathological fractures, occur when a bone breaks due to a weakened state rather than typical trauma (1). The process of cancer spreading to bone, known as bone metastasis, is a complex, multi-stage event that can become evident in later stages of tumor progression (2). Bone metastases are a more frequent complication of malignancy than primary bone tumors, appearing in up to 70% of advanced breast and prostate cancer cases (3). The presence of skeletal metastases significantly increases the risk for skeletal-related events, including pathological fractures, spinal cord compression, and the need for palliative radiation therapy or surgery. Pathological fractures are a serious issue in the clinical course of tumor diseases due to their frequent occurrence and severe clinical presentation (4). These fractures can result from even minor injuries that would not normally cause significant damage to healthy bones. Bones that are typically strong and resistant to breaking, such as those in the arms and legs, can fracture easily if weakened by an underlying health condition like cancer (5). Pain in the bone can even precede a fracture, indicating an impending pathological fracture. While almost all types of cancer can metastasize to the bones, some, like breast cancer and prostate cancer, are particularly prone to metastasis (3). Bone metastasis can occur in any bone; however, is most commonly found in the spine, pelvis,

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Implication for health policy/practice/research/medical education

According to the tumor type, bone metastases are osteolytic, osteoblastic, or mixed. Osteolytic metastases, common in breast cancer, involve increased osteoclast activation stimulated by tumor-secreted factors such as RANKL, PTHrP, IL-6, IL-11, and others. These factors promote bone resorption, releasing growth factors stored in the bone matrix like transforming growth factor-beta, which further stimulate tumor growth, creating a vicious cycle of bone destruction and tumor expansion. Osteolytic lesions lead to significant bone weakening and fracture susceptibility..

and thigh (6). In some cases, bone metastasis can be the initial sign of cancer, or it may appear years after initial cancer treatment. The underlying mechanism of bone weakening by cancer involves a disruption of the natural bone remodeling process (3). Healthy bone is constantly repairing and renewing itself through the balanced activity of osteoblasts, which form new bone, and osteoclasts, which break down old bone. Cancer cells can accelerate or block the actions of these cells, leading to either too much bone formation or too much bone breakdown, both of which compromise bone strength and can lead to fractures or hypercalcemia (7). Then, the physiological remodeling process of bone is disrupted by malignant cells using the same molecular mechanisms employed by native bone cells. This process involves molecular crosstalk amongst osteocytes, osteoblasts, and osteoclasts (8). Several studies demonstrated that the molecular crosstalk between tumor cells and bone cells contains numerous signaling pathways and regulatory proteins, including osteoprotegerin, sclerostin, and Dickkopf-1 (DKK1), which modulate the Wnt signaling pathway essential for bone cell function (9). It is postulated that tumor cells manipulate this signaling network to favor a microenvironment conducive to their survival and expansion. Small RNAs such as microRNAs also modulate gene expression in tumor and bone cells, influencing metastatic potential and bone destruction (10).

Search strategy

For this narrative review, we conducted a literature search across multiple databases, including PubMed, Google Scholar, the Directory of Open Access Journals (DOAJ), Web of Science, EBSCO, Scopus, and Embase, using a variety of relevant keywords like; Neoplasm, bone fractures, pathologic, bone neoplasm, bone remodeling, osteolysis, bone density conservation, bone resorption.

Mechanistic impact of bone destruction following tumor metastasis

Under normal conditions, a balanced coupling of osteoclast-mediated resorption and osteoblast-mediated formation preserves structural integrity and repairs microdamage (11). Tumor cells that colonize bone either directly or by systemic factors hijack this coupling to favor net bone loss or aberrant bone formation, depending on tumor type and molecular phenotype (12). Breast, lung, kidney, and thyroid carcinomas frequently produce osteolytic metastases characterized by heightened osteoclast activation, increased local production of proteolytic enzymes and acid, and suppression of osteoblast differentiation, leading to trabecular thinning, cortical porosity, and focal collapse (3). Multiple myeloma represents a prototypical marrow-based malignancy where malignant plasma cells secrete osteoclast-activating cytokines and concomitantly produce powerful inhibitors of osteoblastogenesis, producing diffuse osteolysis and high risk of collapse even with small tumor volumes (13). Prostate cancer often takes the opposite histologic appearance on imaging, osteoblastic or sclerotic lesions, but these are structurally abnormal bone deposits that are brittle, poorly organized, and paradoxically at risk for fracture as the new bone lacks the biomechanical properties of healthy lamellar bone (14). Central to these divergent phenotypes is the tumor's capacity to manipulate key molecular pathways, including RANK/RANKL/OPG, Wnt/β-catenin signaling, TGF-β release from bone matrix, PTHrP production, and a host of inflammatory and proteolytic mediators that reshape the microenvironment and alter both the quantity and quality of bone matrix (15). It should be remembered that the vicious cycle hypothesis has long dominated the conceptual framework for bone metastasis and fracture pathogenesis. Tumor cells release soluble factors such as parathyroid hormone-related peptide (PTHrP), interleukins, and prostaglandins that upregulate the expression of receptor activator of nuclear factor-kappaB ligand (RANKL) by osteoblasts and marrow stromal cells (16). RANKL, in turn, stimulates the differentiation and activity of osteoclasts, the principal mediators of bone resorption. As osteoclasts degrade bone, they release sequestered growth factors, most prominently TGF-β (transforming growth factor-beta) and insulin-like growth factors (IGFs), from the bone matrix, further fueling tumor proliferation and metastasis (16). In lytic lesions, this self-amplifying loop leads to profound bone loss, microarchitectural disruption, and fracture (17).

Types of bone metastasis

Bone metastases are generally categorized as osteoblastic, where new bone is formed, or osteolytic, where bone is broken down, although most cancers exhibit a spectrum between these two extremes (3). Osteolytic bone metastasis, which is frequently detected in breast malignancy is considered by increased osteoclast differentiation and function and reduced osteoblast function. Likewise, tumor cells exploit factors released by bone tissue resorption, creating a vicious cycle that stimulates metastasis (8). In contrast, osteoblastic metastasis, commonly associated with prostate cancer, involves promoted osteoblast function and differentiation and reduced osteoclast activity, resulting in a net gain of poor-quality bone tissue (18). The molecular mechanisms

involving parathyroid hormone-related protein (PTHrP) and transforming growth factor-β (TGF-β) play a role in osteolytic metastasis, with increased local PTHrP concentration leading to increased RANKL expression and subsequent osteoclast activation (19). Endothelin-1 (ET-1) and dickkopf homolog-1 (DKK-1), produced by tumors, are involved in osteoblastic metastasis, with DKK-1 being a central regulator of osteoblastic activity (20). The main cause of bone tissue resorption is strengthened osteoclast activity, but tumor cells also diminish osteoblast activity by secreting factors and utilizing bone tissue mechanisms for their progression, to establish a positive feedback system. This disruption of the communication among osteoblasts and osteoclasts, mediated by Ephrin (Eph) B2 and EphB4 membrane receptors, reduces the contact between bone tissue cells (21). In osteoblastic metastasis, primarily seen in prostate malignancy, tumor cells secrete factors that increase osteoblast count and activity (22). Furthermore, platelet-derived growth factor induces osteoblast differentiation and activity. Fibroblast growth factors and vascular endothelial growth factor also increase osteoblast activity (23). Bone morphogenetic proteins (BMPs), particularly BMPs 6, 7, and 4, secreted by tumor cells, stimulate bone formation and angiogenesis (24). Meanwhile, prostate cancer cells expressing Wnt 3a, 7b, and 10b modulate Wnt signaling pathways, influencing osteoblast differentiation and proliferation (25). Endothelin 1 secreted by tumor cells also stimulates osteoblast activity (26). Prostate cancer bone metastases are also characterized by PTHrP secretion, which may interact with endothelin receptors after protein modification. Urokinase plasminogen activator and prostate-specific antigen secreted by prostate cancer cells enhance osteoblast activity and the release of active growth factors (27). In the preliminary stages of metastatic disease in bone, tumor cells secrete substances that stimulate osteoblast activity, leading to new bone tissue formation. However, this is not a self-limiting process, as increased osteoblast activity also strengthens osteoclast activity, and bone matrix degradation releases growth factors, creating a positive feedback loop (8).

Focus on the inflammation milieu

Inflammation and the immune milieu are central to the pathogenesis of tumor-associated bone destruction and are promising targets for prevention (28). Tumor-derived TNF-α, IL-1, IL-6, and other cytokines amplify osteoclastogenesis and suppress osteoblasts (29); while immune cells within the bone microenvironment macrophages, T cells, and neutrophils, can be co-opted to support tumor growth and bone resorption (30). The recognition that immune and skeletal systems are deeply interwoven suggests opportunities to leverage immunomodulatory strategies to protect bone. For instance, therapies that inhibit key inflammatory mediators or reposition macrophage phenotypes could reduce osteoclast activation and preserve bone formation (31). Likewise, interventions that block the release or activity of latent growth factors stored in bone matrix, such as TGF-β released during resorption, may interrupt feed-forward cycles that enhance tumor progression and bone degradation (32).

Role of RANKL in osteoclast stimulation by tumor cells

A key player in humoral stimulation of osteoclast function by tumor cells is RANKL, whose activity is mediated by RANK on osteoclast precursors (33). RANKL binding to RANK initiates an intracellular cascade that activates multiple TNF receptor-associated factors and downstream signaling pathways, leading to the transcription of effectors that promote bone resorption (16). Osteoprotegerin, secreted by osteoblasts and bone marrow stromal cells, binds to RANKL to impair its interaction with RANK, thus influencing the extent of bone resorption. PTHrP secretion increases RANKL secretion, and its action is mediated by the PTH receptor (PTHR1) (34). Increased secretion of IL-1, IL-6, IL-8, and IL-18 also promotes the differentiation of osteoclast precursors into osteoclasts. Additionally, macrophage inflammatory protein 1α acts as a chemotactic factor for osteoclast precursors and induces osteoclast differentiation through a RANKL-independent mechanism (35). Cyclooxygenase type 2 expression in osteoblasts, induced by MAP kinase activity, leads to increased PGE2 concentration, which in turn enhances RANKL production and osteoclast differentiation (36). TNF-α, secreted by tumor cells and bone marrow stromal cells, plays a dual role by promoting osteoclast differentiation and inhibiting osteoblast function (37).

Role of DKK1in osteolytic bone metastases

DKK1, an inhibitor of the Wnt/β-catenin signaling pathway, plays a role in osteolytic bone metastases, particularly in multiple myeloma, by reducing RUNX2 expression (a key transcription factor in osteoblast differentiation) and stimulating osteoclast activity through reduced osteoprotegerin expression and enhanced RANKL expression (38). Other Wnt inhibitors like sclerostin and sFRP2, along with IL-7 and TNF-α, also inhibit osteoblast function (39). Tumor cells exploit the communication pathways between osteoblasts and osteoclasts, leading to bone resorption that releases factors stimulating tumor cells, thus establishing a positive feedback mechanism that spreads bone metastatic disease (7). Growth factors such as TGF-β, IGF-1, BMPs, INF-γ, and various ILs, released from the bone matrix during osteoclast activity, stimulate tumor cell growth (40). Tumor cells also respond to calcium ions released during bone resorption (41).

Impact of tumor-associated macrophages

The role of the immune system in cancer-induced bone disease is also gaining attention. Tumor-associated macrophages and myeloid-derived suppressor cells not

only promote tumor growth and immune evasion but also secrete pro-osteoclastogenic cytokines (42). In this regard, immune checkpoint inhibitors, while revolutionizing cancer treatment, can have paradoxical effects on bone; since some studies suggest immune checkpoint inhibitors may enhance anti-tumor immunity within the bone marrow (43); while others report increased fracture risk, possibly due to immune-mediated inflammation or accelerated tumor lysis in bone (44).

Impact of cancer therapy on skeletal integrity

Beyond direct tumor–bone interactions, systemic cancer therapies have emerged as major determinants of skeletal integrity (45). Endocrine therapies used in breast and prostate cancer, such as aromatase inhibitors and androgen deprivation therapy, remove critical sex-hormone support for bone, accelerating trabecular thinning and cortical thinning that elevates fracture risk over months to years (46). Cytotoxic chemotherapy may induce hypogonadism, accelerate senescence of osteoprogenitor cells, and impair microvascular supply that supports bone remodeling (47, 48). Radiation therapy, while local and often curative, causes dose-dependent damage to bone cells and vasculature, increases marrow adiposity, and fosters local fibrosis and osteonecrosis that predispose to pathologic fractures within the irradiated field (49). Newer targeted agents and immune therapies carry their own skeletal effects; for example, agents that modulate the PI3K/AKT/mTOR axis or VEGF pathways can influence osteoblast function and bone repair, and immune checkpoint blockade may alter inflammatory networks relevant to bone turnover (50). The interplay between tumor control and skeletal toxicity demands that oncologists weigh fracture risk as an integral part of long-term survivorship planning rather than an afterthought once fractures occur (51).

Prevention of oncologic fractures

Fractures in cancer patients are associated with increased morbidity, mortality, and reduced quality of life (5). Risk factors include tumor-induced bone destruction, treatment-related bone loss, comorbidities such as osteoporosis and diabetes, malnutrition, and increased incidence of falls (5). The anatomical distribution of metastases frequently involves the spine, pelvis, ribs, and long bones, sites prone to pathological fractures (52, 53). Accurate fracture risk assessment in cancer patients involves clinical history, bone mineral density measurement by dual-energy X-ray absorptiometry (DXA), imaging modalities including X-rays, CT, MRI, PET/CT, and laboratory evaluation of bone turnover markers (54). Specific scoring systems such as Mirel's Score and the Spinal Instability Neoplastic Score (SINS) assist in predicting fracture risk and guiding management (55). Strategies to prevent oncologic fractures encompass lifestyle modifications like adequate calcium and vitamin D intake, and weight-bearing exercise to improve bone strength (56). Pharmacologic therapies include bisphosphonates, which induce osteoclast apoptosis, and denosumab, a monoclonal antibody that inhibits RANKL, effectively reducing skeletal-related events and delaying fracture onset (57). Novel therapeutic agents targeting molecular pathways involved in tumor-bone interactions, such as mTOR inhibitors, cathepsin K inhibitors, and monoclonal antibodies against sclerostin and DKK1, are under investigation (48). Minimally invasive interventional techniques like percutaneous ablation, cement augmentation, and stabilization procedures provide effective pain relief and structural support in patients with metastatic bone disease, improving functionality and fracture prevention (58). Radiation therapy, both external beam and radionuclide-based, alleviates symptoms and reduces tumor burden in bone (59). In spite of advances, therapeutic options remain limited given the complexity of tumor-bone interactions and incomplete understanding of cancer cell dormancy mechanisms. Early detection of disseminated tumor cells and interventions targeting dormancy and metastatic niche disruption may offer future avenues for preventing skeletal complications (60).

Conclusion

In summary, oncologic skeletal fractures result from the complex interplay between metastatic tumor cells and the bone microenvironment, disrupting normal remodeling and compromising bone integrity. Prevention requires a multi-modal approach involving fracture risk assessment, supportive care, pharmacological intervention, and targeted therapies founded on emerging molecular insights into the pathogenesis of bone metastases.

Authors' contribution

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Writing–review and editing: All authors.

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Ethical issues (including plagiarism, data fabrication, and double publication) have been completely observed by the authors.

Declaration of generative AI and AI-assisted technologies in the writing process

During the preparation of this work, the authors utilized Perplexity to refine grammar points and language style in writing. Subsequently, the authors thoroughly reviewed and edited the content as necessary, assuming full responsibility for the publication's content.

Conflicts of interest

The authors declare that they have no competing interests.

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