Am J Cancer Res 2025;15(4):1494-1516
www.ajcr.us /ISSN:2156-6976/ajcr0162638

Review Article

Targeting cancer-induced skeletal damage: a holistic approach to understanding pathophysiology, mechanisms, and management solutions

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Received December 12, 2024; Accepted April 9, 2025; Epub April 15, 2025; Published April 30, 2025

Abstract: Cancer's insidious reach extends far beyond its initial site, particularly manifesting in the skeleton, where it precipitates a spectrum of pathological conditions ranging from bone metastases and cachexia to primary bone cancers. This review highlights the critical impact of cancer on skeletal health, including the development of bone metastases, cachexia, and primary bone cancers, underscoring the importance of understanding the complex interaction between cancer and the bones. It emphasizes the global burden of cancer and its skeletal complications, which severely affect quality of life. The article reviews the prevalence of bone metastases in various cancers, such as breast, prostate, lung, renal cancers, and multiple myeloma, and stresses the need for targeted treatments. It also discusses the mechanisms behind tumor spread to bones and the systemic effects of cancer, including reduced bone mineral density and increased fracture risk, even without direct bone invasion. The challenges posed by primary bone cancers, which are rarer but highly aggressive, are also examined, highlighting the role of genetics and molecular research in treatment development. The review calls for a multidisciplinary approach to manage the severe symptoms of cancer-induced bone damage and explores the potential of personalized medicine to improve treatment outcomes. It concludes by advocating for continued research and collaboration to develop more precise and personalized therapies for cancer-related bone issues, aiming to improve the lives of those affected.

Keywords: Bone neoplasms, neoplasm metastasis, osteoporosis, cachexia, therapeutics, bone density

Introduction

Cancer, as a leading global health issue, not only represents the primary cause of death in individuals under the age of 85 but also stands as the second most common cause of death overall [1]. Cancer-induced skeletal damage encompasses a complex and multifaceted medical challenge that spans a spectrum of pathological states including bone metastases, cachexia, and primary bone cancers. These conditions not only markedly deteriorate the quality of life of affected individuals but also pose intricate therapeutic challenges necessitating comprehensive management strategies. The interplay between cancer and skeletal health is profoundly influenced by the metastatic spread of tumors to the bone, the systemic effects of cancer that contribute to muscle wasting and decreased bone mineral density (BMD), as well as the direct impact of primary bone malignancies. Collectively, these distinct yet interrelated aspects contribute to the overall burden of skeletal damage induced by cancer. The epidemiology of bone metastases reveals a significant prevalence among patients with breast, prostate, lung, and renal cancers, as well as multiple myeloma, underscoring the

https://doi.org/10.62347/QFHJ2430

imperative for targeted therapeutic interventions [2]. The pathophysiological mechanisms underlying these metastases involve intricate interactions between tumor cells and the bone microenvironment, fostering an environment conducive to tumor growth and bone destruction.

Conversely, cancers not directly metastasizing to bone can still adversely affect skeletal health, manifesting as cachexia and reduced BMD even in the absence of direct bone invasion. This underscores the systemic impact of cancer on the body's metabolic and structural integrity, leading to increased fracture risk and compromised physical function. Furthermore, the epidemiological landscape of primary bone cancers, though less common, presents a distinct set of challenges due to their aggressive nature and the subsequent high mortality rates [3-5]. Understanding the genetic and molecular basis of these cancers is crucial for the development of effective treatment strategies.

The clinical manifestations of cancer-induced skeletal damage vary widely, ranging from severe pain associated with bone metastases to the profound muscle wasting and fatigue experienced by patients with cachexia [6-8]. The diagnostic process for these conditions relies on a combination of imaging techniques, laboratory tests, and, in certain cases, biopsy procedures to confirm the presence and extent of skeletal involvement [9, 10].

Recent studies elucidate cancer-induced skeletal damage through tumor exosome-mediated osteoclast/osteoblast reprogramming (miR-21/34a) [11, 12], TGF-β-RANKL-IGF-1-driven osteolytic metastasis in breast cancer [11, 13], CD36+ adipocyte-fueled fatty acid transfer in prostate metastases [14], and MALAT1/miR-34c-Notch1 epigenetic dysregulation in myeloma [15]. Therapeutic advances include denosumab [16], SEMA4D inhibitors with dual anti-resorptive/immune effects [16], and CD36 blockade enhancing docetaxel efficacy [17], highlighting the need for precision approaches targeting tumor-bone microenvironment crosstalk.

This study aims to elucidate the epidemiological and pathophysiological characteristics of skeletal damage caused by different types of cancer, clarify clinical manifestations and diagnostic approaches, and evaluate current treatment modalities along with their associated adverse reactions. By providing a comprehensive overview of the intricate relationship between cancer and skeletal health, this article seeks to contribute to the ongoing efforts to improve patient outcomes and advance the field of oncology. Through the detailed examination of the mechanisms driving cancer-induced skeletal damage, the identification of diagnostic markers, and the evaluation of novel therapeutic strategies, this review underscores the importance of a multidisciplinary approach in managing this complex medical challenge.

Unveiling the epidemiology and pathophysiological landscape of cancer-induced skeletal damage

Cancer with bone metastasis

Epidemiology

Bone metastasis is a complex, multi-stage process requiring interdisciplinary collaboration for effective management [18]. Bone metastases are most commonly associated with specific types of cancer, including breast cancer (70%), prostate cancer (85%), lung cancer (40%), renal cancer (40%), and multiple myeloma (95%) [19]. Given the high incidence rates of breast cancer, lung cancer, and prostate cancer, these cancers account for over 80% of cases of metastatic bone disease [20]. Metastatic bone disease primarily affects the axial skeleton and often leads to complications known as skeletal-related events, including pathological fractures, radiation therapy to bones, orthopedic surgery, spinal cord compression, and hypercalcemia (although the latter may be directly induced by the tumor's paraneoplastic effects, without the need for bone metastasis) [19].

Pathophysiology

The metastasis of solid tumors to the skeleton is a complex and multi-stage process. The dissemination of tumor cells involves the formation of pre-metastatic niches, the spread of tumor cells via the circulatory system, chemotactic attraction and colonization at the metastatic site, and interactions with local stromal and immune cells within the bone microenvironment [21-24]. The unique bone cells (such

as osteoclasts, osteoblasts, and osteocytes), mineralized bone matrix, and other cell types within the bone microenvironment collectively create a conducive environment for tumor growth [25-27].

Tumor cells proliferating within the bone microenvironment can secrete a variety of cytokines and growth factors, leading to an increased production of the receptor activator of nuclear factor κB ligand (RANKL) by osteoblasts [28]. This process results in the activation of osteoclasts and disrupts the normal coupling mechanism between bone formation and bone resorption. Conversely, bone-derived growth factors released during bone resorption may stimulate the proliferation of tumor cell populations, thereby forming a self-perpetuating vicious cycle between cancer cells and the bone microenvironment [29-31].

Cancer without bone metastasis

Epidemiology

It is projected that by 2024, there will be 611,720 cancer-related deaths in the United States, averaging about 1,680 deaths per day [1]. Of particular concern is that up to 80% of cancer patients will develop cachexia [32, 33], a progressive condition characterized by weight loss (≥5%), skeletal muscle wasting, and elevated fracture risk, which significantly increases fatigue and weakness, impairs the ability of patients to perform daily life activities, reduces tolerance to treatment, and is the primary cause of death in nearly 30% of cancer patients [34]. A recent meta-analysis has revealed that the prevalence of low skeletal muscle index (SMI) among cancer patients exceeds previous understanding, involving multiple types of cancer (such as liver, gastric, pancreatic, lung, and esophageal malignancies) and highlighting the ubiquity of muscle loss in this population [35].

Although the focus has often been on metastatic bone cancer for its role in accelerating osteoporosis, emerging evidence reveals that even cancer patients without bone metastases experience reductions in BMD. For instance, studies have shown decreased BMD at critical sites such as the lumbar spine, femur, and hip in women treated for early-stage, non-metastatic breast cancer [36]. Furthermore, a meta-analysis encompassing 11 studies with 2,230 participants identified preoperative osteopenia (low BMD) as an independent prognostic factor for both recurrence-free and overall survival in patients with various digestive cancers [37]. Moreover, recent findings indicating a higher prevalence of osteopenia in pancreatic ductal adenocarcinoma patients compared to healthy controls, where osteopenia emerged as the strongest mortality predictor [38]. Additionally, the concept of osteosarcopenia, the concurrent loss of muscle and bone mass, has been recognized as an independent predictor of disease-free and overall survival in intrahepatic cholangiocarcinoma patients, underscoring the intertwined relationship between muscle and bone health [39].

The elevated fracture risk among cancer patients further underscores the vulnerability of their skeletal system. Research has shown that breast cancer patients experience a higher rate of fractures, including those without bone metastases [40]. Older patients, regardless of their type of cancer, face a nearly threefold increased risk of fractures compared to individuals without cancer [41]. Notably, cancer patients with solid tumors and hematologic cancers, especially those with multiple myeloma, lymphoma, breast, and prostate cancer, exhibit the highest fracture risk [42]. Given the compelling evidence linking low BMD, osteoporosis, and increased fracture risk with cancer, even in the absence of bone metastases, it is crucial to prioritize bone health in both preventive healthcare and cancer treatment strategies.

Pathophysiology

The integrity of bone health is maintained by the intricate interactions between bone cells and the osteokines they secrete. Cancer compounds this crisis by not only compromising bone integrity but also increasing the incidence of debilitating fractures. Pre-clinical studies employing mouse models have shed light on the mechanisms driving cancer-induced skeletal changes, which have documented significant reductions in bone mass and BMD, absent bone metastases, with alterations noted in both cancellous and cortical bone structures [43, 44]. Moreover, changes in the activity of

osteoclasts, osteoblasts, and osteocytes have been identified, revealing the intricate network of factors contributing to cancer-associated bone loss [45]. The evidence to date indicates compromised bone mechanical strength in cancer patients, underscoring the critical need for expanded research in this domain.

Cancer significantly contributes to skeletal wasting and fragility, exacerbating the health crisis associated with declining BMD, a crucial determinant of skeletal strength [46]. This decline is notably pronounced among older adults and is further aggravated by cancer, which compromises bone integrity and elevates the risk of debilitating fractures. Importantly, reductions in BMD are observed in cancer patients, even in the absence of bone metastases, underscoring the extensive impact of cancer on skeletal health [47]. Research has established that low BMD serves as an independent prognostic factor for inferior survival outcomes in patients with various digestive cancers, highlighting the imperative of integrating bone health considerations into cancer management [48-51].

Primary bone cancers

Epidemiology

Primary bone cancers, including osteosarcoma, Ewing sarcoma, and chondrosarcoma, represent a distinct group within the oncology spectrum. In terms of distribution, osteosarcoma accounts for 34.2%, chondrosarcoma for 27.2%, Ewing sarcoma for 19.3%, and other types for 19.4% [52]. These cancers have an incidence rate of approximately 9.0 per million annually in the United States [53]. Despite their relatively low frequency, primary bone cancers pose a significant mortality risk, with a 5-year relative survival rate of 53.9% for osteosarcoma, 75.2% for chondrosarcoma, and 50.6% for Ewing's sarcoma, rates that have remained relatively stable over time [54]. Ewing's sarcoma, noted for its aggressive behavior, predominantly affects children under the age of 15 [55]. Bone cancers are associated with severe complications, such as osteoporosis, fractures, hypercalcemia, and profound pain at diagnosis in 75% of cases, all of which contribute to a diminished quality of life and elevated mortality [56, 57].

Pathophysiology

The pathophysiology of primary bone cancers, particularly osteosarcoma, involves a complex interplay of genetic, cellular, and environmental factors. Osteosarcoma originates from osteoid-producing cells, often found amidst a variety of other cell types, suggesting its derivation from a multipotent mesenchymal precursor [58]. Epidemiological data support this, showing tumors frequently arise in the metaphyses of long bones during peak growth periods in children and young adults, implicating rapidly proliferating bone and cartilage-producing cells in tumorigenesis [59]. The introduction of TP53 mutations into osteogenic stem cells has generated osteosarcoma-like cells in vitro, with mouse models further supporting the role of TP53 and other mutations in the transition from mesenchymal stem cells to osteoblasts [60]. Key transcription factors, including SOX9, RUNX2, and Osterix, have been identified as regulators of osteosarcoma's osteogenic phenotype, influenced by tumor suppressor genes and oncogenes like TP53 and MYC [58].

Osteosarcoma's genomic landscape is characterized by widespread structural rearrangements and copy number alterations, predominantly losses including PTEN and CDKN2A/B, but also amplifications of MYC, VEGFA, and CCNE1 [61]. These changes, along with signs of whole-genome duplication, suggest early activation of mechanisms leading to chromosomal instability and malignant transformation. Recurrent mutations are relatively moderate, with TP53 being the most frequently altered gene, crucial for cancer cell survival given its role in apoptosis induction [62].

Ewing sarcoma and chondrosarcoma are driven by complex genetic and cellular biology events but have distinct molecular characteristics and biological behaviors. Ewing sarcoma typically involves specific chromosomal translocations, leading to the aberrant expression of ETS family transcription factor genes [63], while chondrosarcoma is characterized by the abnormal proliferation and differentiation of chondrocytes. The pathophysiology of these tumor types reflects different etiologies and therapeutic targets, underscoring the importance of developing personalized treatment strategies tailored to specific tumor types (**Figure 1**).

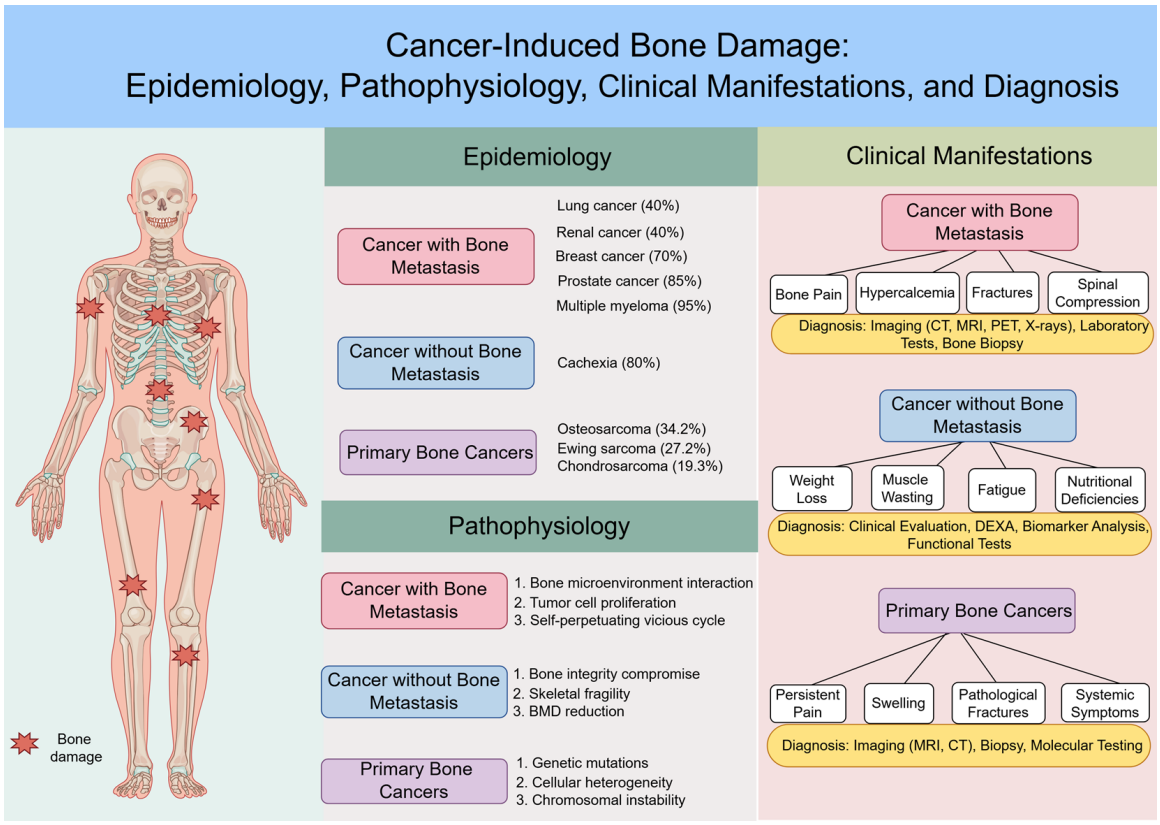

Figure 1. Cancer-induced bone damage: epidemiology, pathophysiology, clinical manifestations, and diagnosis. Created by Figdraw.com (https://www.figdraw.com).

Clinical presentation and diagnostic approaches to skeletal damage induced by cancer

Cancer with bone metastasis

Clinical presentation

In cancer patients, bone metastases manifest with a variety of clinical symptoms, primarily including cancer-induced bone pain (CIBP), malignant hypercalcemia pathological fractures, and spinal cord compression [64]. CIBP is the most common symptom, affecting 60-84% of patients with advanced cancer [65]. This pain can be categorized into inflammatory and mechanical types. The former results from cytokine release and nerve stimulation, while the latter is due to the weakening of bones and activity-related pain caused by the pressure of tumor mass [64]. The intensity of the pain does not necessarily correlate with the extent of the lesions, and pain triggered by movement adds complexity to the management of these patients. Malignant hypercalcemia, is also relatively common among cancer patients, affecting up to 44.1% of individuals, which is primarily induced by PTHrP or RANKL, leading to increased bone metastasis and osteoclast activity [66, 67]. Furthermore, pathological fractures and spinal cord compression are significant clinical manifestations of bone metastases, especially when the femur and spine are involved [68]. These conditions not only cause pain for the patient but can also lead to rapid metabolic dysregulation.

Diagnosis

The diagnosis of bone metastases relies on the integrated application of various imaging techniques and laboratory tests. Radiographic X-rays, while valuable in screening and predicting fracture risk, are limited in sensitivity and may not accurately diagnose bone metastases in all cases. CT scans are crucial for revealing bone destruction and assessing fracture risk, especially in suspected cases of spinal compression. MRI, with its high sensitivity, becomes

a key tool in diagnosing bone metastases, particularly in evaluating spinal metastases. PET scans, especially FDG-PET and FDG-PET/CT, offer highly sensitive and specific detection of distant bone metastases. Bone scans, utilizing Tc-99m bone scintigraphy, highlight areas of increased osteoblastic activity, providing a comprehensive examination of the entire skeletal system.

Beyond imaging techniques, laboratory tests play a significant role in the diagnosis of bone metastases. Elevated levels of serum alkaline phosphatase are common in cases of prostate and breast cancer, indicating increased osteoblastic activity, which aids in cancer detection and monitoring treatment [69]. Tumor markers, such as prostate-specific antigen (PSA), are crucial in identifying cancer types. Bone biopsy is considered the gold standard for confirming bone metastases, particularly when known primary tumors and typical imaging findings of skeletal lesions are present. CT-guided fine-needle aspiration biopsy (FNA) and core biopsy are highly valuable in confirming metastatic disease, especially suitable for patients with a history of cancer but no previous bone metastases [70]. In recent years, liquid biopsy based on genetic analysis has offered a minimally invasive alternative diagnostic method, providing new perspectives for the diagnosis and monitoring of bone metastases [70] (**Figure 1**).

Cancer without bone metastasis

Clinical presentation

Patients with cancer without bone metastasis exhibit a spectrum of clinical manifestations that significantly impact their quality of life and overall health. These manifestations include significant weight loss that is not ameliorated by standard dietary interventions, leading to a frail physique due to the reduction in both adipose tissue and skeletal muscle mass. Muscle wasting persists despite attempts to counteract weight loss through nutritional supplements or increased food intake, contributing to decreased physical strength and endurance. A common challenge among these patients is a decreased appetite, which exacerbates issues related to weight loss and malnutrition. Profound fatigue and a lack of energy adversely affect daily activities and the ability to engage in physical exercise, with this state of exhaustion not improving significantly with rest. The rapid weight loss and nutritional deficiencies also compromise immune function, increasing susceptibility to infections. Moreover, the psychological impact of cancer extends to feelings of depression, anxiety, and emotional instability, which can be attributed to both the disease's direct effects and the stress associated with managing a chronic condition [71, 72].

Diagnosis

In the diagnostic process for patients with cancer without bone metastasis, assessing the impact on bone health requires a multifaceted approach that incorporates detailed clinical evaluation, imaging studies, biomarker analysis, and functional testing. This comprehensive methodology ensures an accurate assessment of the patient's condition, facilitating targeted interventions to manage symptoms and improve quality of life.

The initial step involves a thorough clinical assessment, including the collection of the patient's medical history to identify weight changes, the presence of pain, alterations in mobility, and any history of fractures. A physical examination is crucial to evaluate the patient's nutritional status, muscle mass, and muscle strength, with particular attention to muscle volume and strength, such as grip and quadriceps strength, as well as any potential skeletal deformities or swelling [73].

Imaging studies play a pivotal role in this diagnostic process. Dual-energy X-ray absorptiometry (DEXA) scans serve as the gold standard for measuring bone density, crucial for diagnosing osteoporosis and assessing fracture risk. X-rays can reveal structural changes in bone quality, including osteoporosis, fractures, or bone lesions. For detailed evaluation of bone architecture and its relation to surrounding soft tissues, CT scans and MRI offer higher resolution images, particularly useful for detecting minor fractures and bone marrow changes [74].

Biomarker analysis involves blood tests to measure markers associated with bone metabolism, such as serum calcium, phosphate, alkaline phosphatase (ALP), osteocalcin, and vitamin D levels. These markers provide insights into the rates of bone resorption and formation [75]. Inflammatory markers like C-reactive pro-

tein (CRP) and white blood cell count, along with specific markers of musculoskeletal damage such as creatine kinase (CK), are also evaluated.

Functional tests, including muscle strength testing and mobility assessments like the 6-minute walk test or short physical performance battery, are conducted to evaluate the patient's muscle strength, functional status, and endurance [76]. These assessments help in diagnosing muscle wasting and determining the patient's ability to perform daily activities.

This integrated diagnostic approach not only aids in assessing the direct impact of cancer on bone health but also identifies secondary effects such as muscle wasting and decreased physical function, enabling a holistic management plan that addresses both the physical and psychological aspects of patient care (**Figure 1**).

Primary bone cancers

Clinical presentation

The common clinical manifestations of primary bone cancers include persistent and progressive pain, which often worsens at night, along with swelling and localized temperature increase in the affected area [4]. Patients with Ewing's sarcoma may exhibit systemic symptoms such as fever, fatigue, and weight loss, reflecting the systemic impact of the disease. Individuals with chondrosarcoma might report a longer duration of symptoms due to the relatively slow growth of this tumor type [77]. All these tumor types carry the potential risk of pathological fractures, especially when the tumor leads to significant bone destruction.

Diagnosis

Imaging Studies: Initial radiographic examinations are crucial for identifying the location and characteristics of the tumor. Magnetic Resonance Imaging (MRI) plays a pivotal role in delineating the extent of soft tissue involvement and bone marrow invasion, which is invaluable for surgical planning and disease staging. Computed Tomography (CT) scans are particularly useful in assessing bone destruction and screening for pulmonary metastases.

Biopsy and Pathology: Biopsy confirmation is required for the diagnosis of all primary bone cancers. Pathological evaluation reveals the tumor's cellular type and grade, which is true for osteosarcoma, Ewing's sarcoma, and chondrosarcoma. The pathological hallmark of Ewing's sarcoma includes small round cell tumor characteristics, while chondrosarcoma exhibits features of a cartilaginous matrix [78].

Molecular and Genetic Testing: Specifically, for Ewing's sarcoma, the detection of specific chromosomal translocations is critical for confirmation of the diagnosis [79]. While the molecular characteristics of osteosarcoma and chondrosarcoma are not as well-defined as those of Ewing's sarcoma, ongoing research into the genetic and molecular biology of these tumors may influence future therapeutic strategies (**Figure 1**).

Molecular mechanisms and pathways in cancer-induced skeletal alterations

Cancer with bone metastasis

Mechanism of occurrence

The development of metastatic bone cancer is heavily reliant on the intricate interactions between tumor cells and the bone microenvironment. Tumor cells influence the bone microenvironment by secreting a range of factors, including cytokines, growth factors, and enzymes. These secretions facilitate the formation of bone metastases by altering the local environment to favor tumor growth and survival. This complex interplay not only disrupts normal bone remodeling processes but also creates a conducive setting for tumor cells to thrive.

The colonization of tumor cells in the bone, often referred to as "bone metastatic niche establishment", is a multifaceted process. It encompasses the invasion and migration of tumor cells to the bone, where they must then adapt, survive, and proliferate [80, 81]. This process necessitates a coordinated interaction between the tumor cells and bone cells, including osteoblasts, which are responsible for bone formation, and osteoclasts, which are involved in bone resorption. Tumor cells can manipulate these bone cells to create a microenvironment that supports their survival and growth [82,

83]. For instance, tumor cells can stimulate osteoclasts to degrade bone tissue, releasing stored growth factors that, in turn, aid in tumor growth and proliferation [84].

Metabolic reprogramming is another critical aspect of the development and progression of metastatic bone cancer [85]. Both cancer cells and cells within the bone microenvironment undergo metabolic changes to support the energy demands and biosynthetic needs of rapidly proliferating tumor cells [86]. This reprogramming is pivotal for the survival of cancer cells in the bone microenvironment and contributes significantly to the establishment and growth of bone metastases. The altered metabolic state not only fuels tumor growth but also can lead to the suppression of the immune response, further facilitating tumor progression and colonization in the bone [87, 88].

Abnormal activation of signaling pathways

The impact of metastatic cancer on bone health involves several critical signaling pathways that regulate the activities of osteoclasts and osteoblasts, the cells responsible for bone resorption and formation, respectively. Understanding these pathways provides insights into the mechanisms of bone metastasis and potential therapeutic targets.

RANKL/RANK/OPG system: This system plays a pivotal role in regulating the activity of osteoclasts and osteoblasts. Tumor cells can promote the formation and activation of osteoclasts by increasing the expression of RANKL or decreasing the expression of Osteoprotegerin (OPG) [89, 90]. This imbalance in RANKL and OPG levels leads to enhanced osteoclast activity and subsequent bone destruction. The RANKL binds to its receptor RANK on osteoclast precursors, stimulating their differentiation and activation, while OPG acts as a decoy receptor for RANKL, preventing it from binding to RANK and thus inhibiting osteoclastogenesis.

Wnt/β-Catenin pathway: The Wnt signaling pathway is crucial for maintaining bone mass and regulating the balance between bone formation and resorption [91]. Tumor cells can disrupt this balance by modulating the activity of the Wnt pathway, thereby affecting the function of osteoblasts [92]. Activation of the Wnt pathway promotes osteoblast differentiation and activity, leading to increased bone formation [93]. Conversely, inhibition of Wnt signaling can impair osteoblast function and reduce bone formation, facilitating bone metastasis [94].

IGF and BMPs: Insulin-like Growth Factors (IGF I and II) and Bone Morphogenetic Proteins (BMPs) are growth factors that play supportive roles in the development of bone metastases [95]. Increased levels of IGF I and II in aggressive tumors enhance the activity of osteoblasts, promoting bone formation [95]. BMPs, particularly BMP-6, BMP-7, and BMP-4, not only stimulate bone formation but also promote angiogenesis, supplying nutrients to tumor cells in the bone microenvironment [96].

Endothelin-1 (ET-1) pathway: ET-1, through the activation of the Endothelin A receptor (ETAR), promotes abnormal bone formation. It activates the Wnt signaling pathway by reducing the production of the Wnt antagonist DKK1 (Dickkopf-1), further facilitating the growth of tumor cells within the bone. The ET-1 pathway is implicated in the pathogenesis of osteoblastic bone metastases, where it contributes to the formation of new bone that is often structurally weak and prone to fractures.

These signaling pathways illustrate the complex interplay between tumor cells and the bone microenvironment. Targeting these pathways offers potential therapeutic strategies for preventing or treating bone metastases, highlighting the importance of continued research in this field (**Figure 2**).

Cancer without bone metastasis

Muscle wasting and weakness

Non-metastatic cancer leads to muscle wasting primarily through the promotion of protein degradation and the inhibition of protein synthesis. This process involves the upregulation of inflammatory cytokines, such as Tumor Necrosis Factor-alpha (TNF-α) and Interleukin-1 beta (IL-1β), which activate NF-κB and FOXO transcription factors, promoting the activity of ubiquitin-proteasome and autophagy-lysosome pathways in muscles [97, 98]. Moreover, metabolic by-products produced by cancer, such as lactate, may further exacerbate muscle wasting by disrupting the intracellular pH balance.

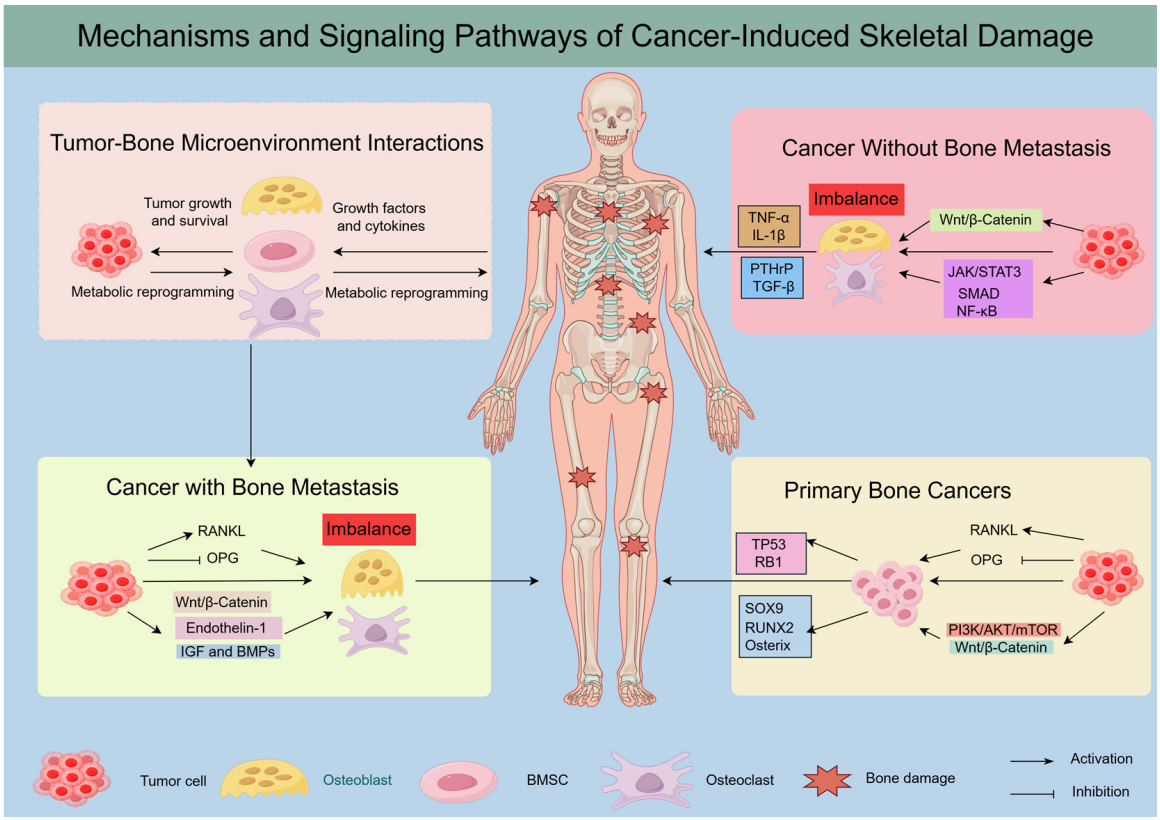

Figure 2. Mechanisms and signaling pathways of cancer-induced skeletal damage. BMPs, Bone Morphogenetic Proteins; IL-1β, Interleukin-1 beta; IGF, Insulin-like Growth Factors; OPG, osteoprotegerin; PTHrP, Parathyroid Hormone-related Protein; NF-κB, Nuclear Factor kappa-light-chain-enhancer of activated B cells; RANKL, Receptor Activator for Nuclear Factor κB Ligand; RANK, Receptor Activator for Nuclear Factor Kb; TNF-α, Tumor Necrosis Factor-alpha; TGF-β, Transforming Growth Factor-beta. Created by Figdraw.com (https://www.figdraw.com).

The increased activity of these catabolic pathways leads to a reduction in muscle mass and strength, contributing to the weakness observed in cancer patients [99].

Osteoporosis and fragility

Non-metastatic cancer contributes to bone loss and osteoporosis by activating osteoclasts and inhibiting osteoblasts. The excessive activation of osteoclasts is primarily mediated by an upregulation of RANKL and a downregulation of OPG, leading to an imbalance in the RANKL/OPG ratio [100, 101]. Concurrently, cancer-associated factors such as Parathyroid Hormone-related Protein (PTHrP) and Transforming Growth Factor-beta (TGF-β) act directly on osteoblasts, inhibiting their differentiation and function, and exacerbating the process of osteoporosis [102]. This imbalance in bone remodeling processes results in decreased bone mass and increased bone fragility, raising the risk of fractures in cancer patients.

Abnormal activation of signaling pathways

JAK/STAT3 signaling pathway: IL-6 plays a crucial role in muscle wasting and osteoporosis through the activation of the JAK/STAT3 signaling pathway [103, 104]. The activation of STAT3 promotes the expression of muscle degradation genes and inhibits the differentiation of osteoblasts, exacerbating damage to muscles and bones. This pathway highlights the importance of the inflammatory cytokine IL-6 in mediating catabolic effects in both muscle and bone tissues, linking systemic inflammation to cancer-associated cachexia and bone loss [105, 106].

Wnt/β-Catenin pathway: The suppression of Wnt signaling leads to reduced differentiation and activity of osteoblasts, resulting in osteoporosis [107, 108]. Additionally, the Wnt pathway plays a key role in muscle regeneration, and its inhibition may further exacerbate muscle wasting [109, 110]. This indicates the dual

role of the Wnt/β-catenin pathway in maintaining skeletal muscle and bone health, and its dysregulation can contribute to the musculoskeletal deterioration seen in cancer patients [111].

SMAD signaling pathway: Members of the TGF-β superfamily influence muscle and bone physiology by activating the SMAD2/3 signaling pathway. In the context of cancer, aberrant expression of factors such as TGF-β, activin A, and GDF-15 activates the SMAD signaling pathway, promoting the expression of muscle degradation genes and inhibiting the function of osteoblasts, leading to muscle wasting and osteoporosis [112, 113]. This pathway underscores the role of TGF-β superfamily members in the complex interplay between muscle and bone degradation in cancer.

NF-κB signaling pathway: The activation of the NF-κB pathway also promotes the expression of RANKL, exacerbating the formation and activation of osteoclasts, further affecting osteoporosis [114]. This pathway demonstrates the critical role of inflammation and NF-κB signaling in driving both muscle wasting and bone resorption, highlighting potential therapeutic targets for mitigating cancer-associated musculoskeletal deterioration [115, 116].

These signaling pathways illustrate the molecular mechanisms through which non-metastatic cancer can indirectly impact bone health, contributing to muscle wasting and osteoporosis. Understanding these pathways offers potential avenues for therapeutic intervention to preserve musculoskeletal integrity in cancer patients (**Figure 2**).

Primary bone cancers (taking osteosarcoma as an example)

Cell origin and genetic mutations

The origin of osteosarcoma is thought to be related to the abnormal differentiation of pluripotent mesenchymal precursor cells [117]. Mutations in the TP53 and RB1 genes are the most common genetic events in osteosarcoma [118]. These mutations lead to dysregulation of cell cycle control, promoting the transformation of immature osteoprogenitor cells into malignant cells. Moreover, the introduction of TP53 gene mutations into these partially differentiated osteoblastic precursor cells has generated osteosarcoma-like cells in vitro. This suggests that genetic alterations in key regulators of cell growth and differentiation are central to the pathogenesis of osteosarcoma, driving the transformation of normal bone-forming cells into cancerous cells that contribute to the aggressive nature of this cancer.

Role of transcription factors

Transcription factors such as SOX9, RUNX2, and Osterix are highly expressed in osteosarcoma cells and regulate the expression of genes related to osteogenesis, reflecting the osteoblastic phenotype of osteosarcoma. These transcription factors play critical roles in bone development and regeneration by promoting the differentiation of mesenchymal stem cells into osteoblasts. Their dysregulation in osteosarcoma not only contributes to the malignant transformation of osteoprogenitor cells but also to the aberrant bone formation associated with the tumor [119]. The high expression of these factors in osteosarcoma cells underscores the importance of osteoblastic differentiation pathways in the pathogenesis of this tumor, suggesting that targeting these pathways could offer therapeutic potential for osteosarcoma.

Abnormal activation of signaling pathways

Wnt-β-Catenin pathway: The Wnt-β-catenin pathway plays a central role in the initiation and progression of osteosarcoma, by regulating cell proliferation, differentiation, and apoptosis, thus influencing tumor growth [120]. This signaling pathway is crucial for normal bone development and homeostasis. In osteosarcoma, aberrant activation of the WNT-β-catenin pathway leads to uncontrolled cell growth and contributes to the malignant phenotype of the tumor cells [121]. Targeting components of this pathway offers a potential therapeutic strategy for inhibiting osteosarcoma growth and metastasis.

PI3K-AKT-mTOR pathway: Activated by IGF1 signaling, the PI3K-AKT-mTOR pathway promotes cell survival and proliferation, making it a significant therapeutic target in osteosarcoma. This signaling pathway is involved in various cellular processes, including metabolism, growth, survival, and angiogenesis. Its activa-

tion in osteosarcoma contributes to tumor growth, resistance to apoptosis, and metastasis. Inhibitors targeting the PI3K-AKT-mTOR pathway are being explored as potential treatments for osteosarcoma, aiming to reduce tumor growth and improve patient outcomes [122-124].

RANK-RANKL-OPG system: This system plays a key role in osteosarcoma bone metastasis and bone destruction. Overexpression of RANKL promotes the aggressive behavior of osteosarcoma cells towards bone, leading to increased bone resorption and osteolysis [125]. The RANK-RANKL-OPG signaling is essential for the regulation of osteoclast differentiation and activity. In the context of osteosarcoma, the balance between RANKL and its decoy receptor OPG is disrupted, favoring bone destruction and tumor progression [126]. Targeting the RANK-RANKL-OPG axis represents a promising approach to mitigate bone metastasis and destruction associated with osteosarcoma.

Single-cell RNA sequencing (scRNA-seq): Through meticulous analysis of scRNA-seq data derived from OS and healthy cancellous bone samples, this research delineated a spectrum of cell clusters and charted three distinct differentiation pathways emanating from a subset akin to cancer stem cells (CSCs). This intricate cellular cartography facilitated the groundbreaking molecular stratification of OS into three categories, each characterized by unique prognostic markers and potential vulnerabilities to specific therapeutic agents. Moreover, the investigation unveiled the distinctive molecular signatures of CSCs within OS, notably the activation of EZH2 - a pivotal factor in the advancement of the disease. These insights not only deepen our comprehension of OS at both molecular and cellular dimensions but also lay the groundwork for the formulation of precision medicine approaches. By focusing on particular cell subsets within the tumor milieu, these strategies hold promise for enhancing the efficacy of treatments and ultimately improving the clinical outcomes for individuals battling osteosarcoma [127].

These signaling pathways underscore the complexity of molecular mechanisms driving osteosarcoma growth, metastasis, and interaction with the bone microenvironment. Targeting these pathways offers hope for developing more effective therapies for primary bone cancers, aiming to improve survival rates and quality of life for affected patients (**Figure 2**).

Comprehensive management strategies and adverse reaction profiles in bone metastasis, non-metastatic cancer, and primary bone cancer

Therapeutic approaches and adverse event profiles in the management of patients with bone metastases

For patients with bone metastases, treatment strategies are primarily focused on pain relief and tumor growth control. Radiofrequency ablation (RFA) is a common method for pain relief, whose mechanism of action involves the use of high-frequency electric currents to generate heat energy that directly targets tumor tissues, thereby alleviating pain. Although RFA is significantly effective in managing pain from bone metastases, it may lead to adverse reactions such as nerve and spinal cord injuries. Therefore, detailed preoperative planning is crucial to minimize surgical risks. This technique has shown varying degrees of efficacy across different cancer types, with particular success in cancers that are more responsive to thermal ablation, such as metastases from renal cell carcinoma.

Targeted therapy and hormone therapy, aimed at specific biological markers and hormone receptors, show good effects in managing bone metastases [128, 129]. However, these treatments may accompany adverse reactions such as skin reactions, hypertension, changes in hormone levels, and sexual dysfunction. To manage these adverse reactions, measures like skin care, blood pressure monitoring, and hormone replacement therapy are necessary (**Table 1**). The effectiveness of targeted and hormone therapies varies significantly with the molecular profile of the tumor and the stage of the disease, offering improved outcomes particularly in hormone receptor-positive breast and prostate cancers.

Therapeutic approaches and adverse event profiles in the management of patients without bone metastases

The treatment goal for patients without bone metastases mainly involves reducing muscle

Table 1. Management of therapy and adverse effects in cancer-related skeletal damage

Treatment Strategy	Target/Mechanism of Action	Application/Effect	Adverse Reaction	Adverse Reaction Management Measures	Patient Group	Reference
Radiofrequency Ablation	Pain Relief	Bone Metastases	Nerve and Spinal Cord Injury	Preoperative Planning	Patients with Bone Metastases	[152]
Hormone Therapy	Management of Bone Metastases	Breast Cancer, Prostate Cancer	Hormonal Level Changes, Sexual Dysfunction	Hormone Replacement Therapy, Supportive Care	Patients with Bone Metastases	[128]
Targeted Therapy	Management of Bone Metastases	Various Cancers	Skin Reactions, Hypertension	Skin Care, Blood Pressure Management	Patients with Bone Metastases	[129]
Anti-inflammatory Treatment	Targeting IL-6, Reducing Muscle Wasting and Bone Damage	Alleviation of Cancer-induced Muscle Wasting and Bone Damage	Immune System Suppression, Increased Infection Risk	Immune Function Monitoring, Infection Prevention	Patients without Bone Metastases	[105, 130]
RANKL Inhibitor	Using Denosumab to Inhibit RANKL, Protecting Bone Health	Improved Muscle Function, Protecting Bone Health	Immune System Suppression, Increased Infection Risk	Immune Function Monitoring, Infection Prevention	Patients without Bone Metastases	[131, 132, 153]
PTHrP Neutralizing Antibody	Targeting PTHrP, Reducing Muscle Wasting and Improving Bone Health	Positive Effects in Lung Cancer Models	Endocrine and Metabolic Effects	Metabolic Status Monitoring	Patients without Bone Metastases	[154, 155]
Sclerostin Inhibitor	Promoting Bone Health and Improving Muscle Function	Promoting Bone Health	Excessive Bone Growth	Monitoring and Management of Bone Growth	Patients without Bone Metastases	[133, 134, 156]
Targeting TGF-β Family Members	Targeting TGF-β, Activin A, and GDF-15	Protecting Muscle and Bone Health	Endocrine and Metabolic Effects	Metabolic Status Monitoring	Patients without Bone Metastases	[135, 136]
CDK4/6 Inhibitor	Inhibiting CDK4/6, Blocking Cell Cycle Progression	New Treatment Strategy for Osteosarcoma, Under Clinical Trials	Not Specified, Pending Clinical Trial Results	Monitoring and Timely Treatment Adjustment	Patients with Primary Bone Cancer	[137, 138]
CDK12 Inhibitor	Interfering with Transcription and Translation Processes	Prospective Success in Osteosarcoma	Not Specified, Pending Clinical Trial Results	Monitoring and Timely Treatment Adjustment	Patients with Primary Bone Cancer	[139, 140]
IGF1 Signal Inhibition	Blocking IGF1 Receptor, Inhibiting Related Pathways	Slowing Tumor Cell Proliferation and Survival	Not Specified, Pending Clinical Trial Results	Monitoring and Timely Treatment Adjustment	Patients with Primary Bone Cancer	[141, 157]
Neoadjuvant Chemotherapy	Using Specific Drug Combinations	Improving Disease-free Survival Rate	Late Effects of Chemotherapy	Monitoring Late Effects, Timely Intervention	Patients with Primary Bone Cancer	[142-144]
Surgery	Local Surgical Management	Used in Combination with Chemotherapy, Improving Survival Rate	Loss of Major Joints, etc.	Postoperative Rehabilitation, Repeat Surgery if Necessary	Patients with Primary Bone Cancer	[142, 145, 158]
Chemotherapy Toxicity Trade-off	Chemotherapy and Tumor Control	Improved Long-term Survival Rate	Decreased Quality of Life, etc.	Balancing Quality of Life and Treatment Benefits	Patients with Primary Bone Cancer	[146, 147]
Cytokine-mediated Metastasis Inhibition	Targeting Specific Cytokines	Becoming a Treatment Target, Reducing Metastasis	Not Specified, Pending Clinical Trial Results	Monitoring and Timely Treatment Adjustment	Patients with Primary Bone Cancer	[148]
Arabinocytosineetidronate (AraC-etidronate)	P-C-P-O-P frame	Hydrolysis (Phase I NCT02673060, Phase II NCT05398861)	Not Specified	Not Specified	Patients with Primary Bone Cancer	[149, 159]
Doxorubicin-BP (12b80)	Thiourea and Hydrazone bond	pH response Phase I	Not Specified	Not Specified	Patients with Primary Bone Cancer	[150, 151]

wasting and bone damage caused by cancer. Anti-inflammatory treatment targeting cytokines like IL-6 can effectively alleviate muscle wasting and bone damage induced by cancer [105, 130]. However, this treatment may lead to immune system suppression, increasing the risk of infections. Therefore, monitoring immune function and preventing infections are essential. The impact of anti-inflammatory treatment is more pronounced in early-stage cancers, where systemic inflammation can be effectively managed to prevent cachexia and preserve muscle mass.

RANKL inhibitors (such as Denosumab) and PTHrP neutralizing antibodies work through specific molecular mechanisms to protect bone health and improve muscle function but may also cause immune system suppression and endocrine metabolic effects [131, 132]. Regular monitoring of immune and metabolic status is required to identify and address related issues promptly. These therapies demonstrate a higher efficacy in cancers with a pronounced osteolytic component, such as breast and lung cancers, by effectively reducing bone resorption and preserving bone density.

For patients without bone metastases, sclerostin inhibitors offer a promising option for improving bone health without the direct complications associated with cancer treatment [133, 134]. The benefits of sclerostin inhibitors are particularly evident in patients at an early stage of cancer with a high risk of bone loss, where they can significantly improve bone density and reduce fracture risk. This patient population, in particular, may benefit from the dual effects on bone and muscle, potentially leading to improved mobility, reduced fracture risk, and enhanced quality of life. Nonetheless, the decision to initiate sclerostin inhibitor therapy should be based on a comprehensive evaluation of individual risk factors, potential benefits, and the overarching goal of achieving a balanced and effective management of bone health.

Furthermore, an alternative therapeutic strategy emphasizes directly ameliorating bone and muscle health through modulation of the TGF-β family members, circumventing the intricacies associated with cancer treatment [135, 136]. This approach harbors considerable promise for improving the quality of life and functional capacity of patients, particularly those experiencing deterioration of bone and muscle health attributable to aging or non-malignant conditions (**Table 1**).

Therapeutic approaches and adverse event profiles in the management of patients with primary bone cancer

The treatment strategies for patients with primary bone cancer are more complex, including new drug trials, neoadjuvant chemotherapy, and surgery. The comparative effectiveness of these treatments is closely tied to the histological subtype of bone cancer and the stage at which the disease is diagnosed. New drugs like CDK4/6 inhibitors [137, 138], CDK12 inhibitors [139, 140], and IGF1 signal inhibitors [141] have shown potential in clinical trials for treating osteosarcoma, but their adverse reactions are not fully clear yet and need continuous monitoring and evaluation in clinical trials and subsequent clinical practices.

Neoadjuvant chemotherapy and surgery are traditional methods for treating primary bone cancer, significantly improving disease-free survival and overall survival rates [142-145]. These methods are particularly effective in early-stage osteosarcoma, where they can lead to a significant reduction in tumor size, making surgical resection more feasible and potentially preserving more of the limb function. However, the late effects of chemotherapy and surgical risks (such as loss of major joints) cannot be overlooked. Thus, monitoring and managing these adverse reactions (including monitoring late effects of chemotherapy, timely intervention, and postoperative rehabilitation) are key to successful treatment [146, 147].

The effectiveness of cytokine-mediated metastasis inhibition as a therapeutic target is still under investigation, with numerous clinical trials currently in progress [148]. These studies are crucial for determining the therapeutic potential of this approach, including its ability to reduce metastasis and improve the overall survival rates of patients with primary bone cancer. The anticipation of clinical trial results holds the promise of integrating cytokine targeting into a broader therapeutic arsenal against bone cancer.

Current clinical trials in bone tumors

Arabinocytosineetidronate (AraC-etidronate) utilizes a P-C-P-O-P frame to enhance circulation time and improve therapeutic efficacy by targeting bone tumors through slow hydrolysis, significantly reducing bone metastases and increasing bone mineral density in models of breast cancer bone metastasis and multiple myeloma. Notably, in its phase I clinical trial involving patients with advanced cancers and bone metastases, AraC-etidronate demonstrated a significant reduction in cancer cell activity in bone lesions with minimal hematological or cardiac toxicity. The treatment, now in phase II clinical trials (NCT02673060, Phase II NCT05398861), showed promising results by achieving a significant decrease in bone metastases incidence and improving survival times, with a maximum tolerated dose of 5 mg/kg, highlighting its potential as a safer, bone-targeting therapy [149].

David et al. and colleagues [150, 151] developed a bone-targeting doxorubicin (DOX) conjugate, 12b80, featuring an acidic cleavage linker designed for pH-responsive release in the bone resorption environment, typically around pH 4.0. Despite its slow release, with only about 11% of DOX released after three days, 12b80 demonstrated significant tumor suppression in an osteosarcoma model. It has successfully completed a phase I clinical trial in dogs with naturally occurring osteosarcoma, establishing a maximum tolerated dose of 8 mg/kg. This study highlights 12b80's promising safety profile and its preliminary clinical antitumor efficacy.

The treatment strategies for bone tumors must consider the nature of the tumor, the specific situation of the patient, and the potential risks and benefits of the treatment. Effective management of adverse reactions is crucial for improving the patient's quality of life and treatment outcomes. Future research should focus on developing safer and more effective treatment methods and optimizing existing treatment strategies to achieve the best possible outcomes for patients with bone tumors (**Table 1**).

In summary, the mechanisms and clinical manifestations of bone damage caused by different types of cancer vary significantly, necessitating corresponding adjustments in treatment strategies. Bone metastatic cancer primarily accelerates bone resorption through the interaction between tumor cells and the bone microenvironment. In contrast, non-bone metastatic cancers influence bone metabolism through systemic inflammation and cachexia. Primary bone cancer directly disrupts bone structure and interferes with the bone remodeling process. A summary of the mechanisms, clinical presentations, and targeted treatment strategies is presented in **Table 2**.

Future prospects

In a comprehensive analysis of bone metastases, non-bone metastases, and primary bone tumors, we observe significant challenges as well as hopeful prospects for the future across these domains. The treatment of bone metastases is progressing towards alleviating pain and controlling tumor growth, particularly through Radiofrequency Ablation (RFA) and targeted therapy. The systemic impact of non-bone metastases on bone health highlights the need for anti-inflammatory treatments, RANKL inhibitors, and PTHrP neutralizing antibodies to mitigate muscle wasting and bone damage. Advances in the treatment of primary bone tumors, such as osteosarcoma, are reliant on a multifaceted approach involving new drug trials, neoadjuvant chemotherapy, and surgery, with emerging medications like CDK4/6 inhibitors showing potential.

Future therapeutic strategies necessitate a deeper understanding of the interactions between cancer, the bone microenvironment, and the immune system. Particularly, the management of bone metastases will increasingly depend on immunotherapy, such as the integration of checkpoint inhibitors, marking a significant paradigm shift in treatment modalities. Meanwhile, progress in treating primary bone tumors requires a profound comprehension of disease biology and guidance through patient-derived xenograft models and targeted immunotherapies against tumor cell surface antigens.

Overall, future research and therapeutic strategies will require interdisciplinary collaboration to develop safer, more effective approaches and optimize existing treatment protocols, aiming for optimal outcomes in patients with bone

Table 2. Summary of cancer-induced skeletal damage: mechanisms and management strategies

Cancer Type	Mechanism of Skeletal Damage	Clinical Manifestations	Treatment Strategies
Bone Metastasis (Breast, Prostate, Lung, Renal Cancer, Multiple Myeloma)	Tumor cells interact with bone microenvironment, increasing osteoclast activity via RANKL pathway, creating a vicious cycle of bone resorption and tumor growth	Bone pain, pathological fractures, hypercalcemia, spinal cord compression, decreased quality of life	Anti-resorptive agents (bisphosphonates, denosumab), SEMA4D inhibitors, CD36 blockade, targeted radiation therapy, surgery, multidisciplinary care
Cancer without Bone Metastasis (e.g., Pancreatic, Gastric, Esophageal, Liver, Breast cancers without direct bone involvement)	Systemic effects of cancer (cachexia, inflammation, cytokine release) leading to muscle wasting, reduced bone mineral density, osteoporosis, and increased fracture risk	Muscle wasting (cachexia), osteoporosis, increased fracture risk, fatigue, reduced physical function	Nutritional support, physical rehabilitation, anti-cachexia therapies, osteoporosis management (calcium, vitamin D, bisphosphonates, denosumab), comprehensive metabolic monitoring
Primary Bone Cancer (Osteosarcoma, Ewing Sarcoma, Chondrosarcoma)	Aggressive tumor growth directly destroys bone structure, disrupts bone remodeling, and causes local and systemic metabolic changes	Severe localized bone pain, pathological fractures, hypercalcemia, aggressive disease course, high mortality	Surgery, neoadjuvant and adjuvant chemotherapy, targeted therapies (CDK4/6 inhibitors, CDK12 inhibitors, IGF1 signaling inhibitors), cytokine-targeted therapies, novel drug conjugates (AraC-etidronate, Doxorubicin-BP), multidisciplinary management

Abbreviations: RANKL, receptor activator of nuclear factor κB ligand; SEMA4D, semaphorin 4D; CDK, cyclin-dependent kinase; IGF1, insulin-like growth factor 1; AraC-etidronate, arabinocytosine-etidronate conjugate; Doxorubicin-BP, doxorubicin-bisphosphonate conjugate.

tumors. By integrating findings from basic and clinical research, developing targeted therapies, and addressing challenges posed by immune escape mechanisms, we can move towards more effective management strategies, ultimately improving patient outcomes. As research continues to evolve, these insights will guide the development of more precise, effective, and personalized cancer treatment methods, offering new hope to patients with bone metastases, non-bone metastases, and primary bone tumors.

Conclusion

This review delves into the intricate relationship between cancer and bone health, emphasizing the significant challenges posed by bone metastases, the systemic impact of non-metastatic cancers on bone, and the unique challenges of primary bone cancers. The prevalence of bone metastasis in certain cancers necessitates targeted therapeutic interventions based on a deep understanding of tumor cell interactions with the bone microenvironment. Similarly, the systemic effects of cancer, such as cachexia and reduced bone mineral density, along with the aggressive nature and high mortality associated with primary bone cancers, call for advancements in genetics and molecular research to develop effective strategies.

The management of cancer-induced bone damage requires a multidisciplinary approach that integrates new diagnostic markers, evaluates innovative treatment strategies, and considers the adverse effects of current treatments. Future research should focus on expanding our understanding of the pathophysiological mechanisms behind cancer-induced bone damage, identifying biomarkers for early diagnosis, and developing targeted therapies that mitigate bone loss, alleviate pain, and prevent fractures. Additionally, the review highlights the potential of personalized medicine in tailoring interventions to individual patient characteristics, thereby enhancing the efficacy of treatment regimens.

In conclusion, advancing the field of oncology in the context of cancer-induced bone damage and improving patient outcomes necessitate the collective efforts of researchers, clinicians, and healthcare providers. Through ongoing research, innovation, and collaboration, we can move closer to developing more precise, effective, and personalized treatment modalities that address the complex interplay between cancer and bone health, bringing new hope to those facing these challenges.

Acknowledgements

We acknowledge all the authors involved in the design and literature analysis of this paper.

Disclosure of conflict of interest

None.

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