Review Article

Bone metastases in non-small cell lung cancer: a narrative review

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Background and Objective: Bone metastases are common in patients with non-small cell lung cancer (NSCLC) and remain a significant source of morbidity, mortality, and diminished quality of life, despite the considerable progress made in the overall management of patients with metastatic NSCLC over the last decade. Understanding the molecular pathogenesis of bone metastases is critical to improving survival, preserving function, and managing symptoms in this patient population. The objective of our review is to provide a comprehensive review of the pathophysiology, clinical presentation, management, and factors predicting the development and prognosis of patients with NSCLC with bone metastases.

Methods: An online electronic search was performed on PubMed and Google Scholar of all English-language literature using combinations of the following keywords: bone metastases, non-small cell lung cancer, pathophysiology, skeletal related events, response to therapy, predictive factors, and immunotherapy. Bibliographies of identified papers were reviewed for additional articles of interest. Observational cohort, retrospective studies, randomized controlled trials (RCTs), meta-analyses, and review articles were examined for this review.

Key Content and Findings: Bone metastases in lung cancer patients remain a common occurrence, impacting morbidity, mortality, and quality of life. Patients with skeletal related events (SREs) have worse prognosis. There is data supporting use of bisphosphonates and/or denosumab, and these should be considered in all patients with bone metastases. Novel studies comparing the genomic alterations of skeletal metastases and primary tumors are needed. As therapy for patients with advanced disease evolves, more studies are needed to evaluate the interplay between immunotherapy and bone metastases, and in determining the response to treatment in bone.

Conclusions: Predicting development and progression of bone metastases could allow earlier and targeted therapy in patients with bone metastases. Predicting and evaluating response to conventional chemotherapy and immune checkpoint inhibitors in NSCLC patients with bone metastases remains an unmet need and merits further study.

Keywords: Bone metastases; skeletal related events (SREs); non-small cell lung cancer (NSCLC); treatment response

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Introduction

Approximately 20–30% of patients with non-small cell lung cancer (NSCLC) present with bone metastases at diagnosis, and 35–60% will develop them during their disease course (1-4). Symptoms related to bone metastases, called skeletal related events (SREs), are common and the majority of patients with bone metastases will experience significant pain during their course. While considerable progress has been made in the overall management of metastatic NSCLC, bone metastases remain a common source of morbidity, mortality, and diminished quality of life (5). Additional challenges include difficulty determining response to therapy due to lack of adequate imaging criteria in patients with bone metastases and poor outcomes in response to systemic therapies in patients with bone metastases compared to those without (6). Understanding the molecular pathogenesis of bone metastases is critical to make progress in patients with metastatic lung cancer with bone metastases. The objective of our review is to provide a comprehensive review of the pathophysiology, clinical presentation, management, and factors predicting the development and prognosis of patients with NSCLC with bone metastases. We present the following article in accordance with the Narrative Review reporting checklist (available at https://jtd.amegroups.com/article/view/10.21037/jtd-21-1502/rc).

Methods

Google Scholar and PubMed databases were searched between June 2020 and September 2021 with the following search terms to identify relevant papers for this review (*Table 1*): "bone metastases AND lung cancer AND pathophysiology", "bone metastases AND non-small cell lung cancer", "skeletal related events AND non-small cell lung cancer", "bone metastases AND lung cancer AND outcomes", "bone metastases AND lung cancer AND response to therapy", "bone metastases AND lung cancer AND immunotherapy", and "bone metastases AND lung cancer AND predictive factors". Bibliographies of identified papers were reviewed for additional articles of interest (Table S1). Published observational cohort, retrospective studies, randomized controlled trials (RCTs), meta-analysis, and review articles published from 1990–2021 were examined for this review. Manuscripts in non-English languages were not evaluated.

Discussion

Pathophysiology and molecular biology

The initial steps through which bone metastases are established are likely similar to that of metastatic colonization of other distant sites. First, there is tumor invasion of the surrounding normal tissue and new vessel formation, followed by tumor invasion into the blood vessel. Reduction of E-cadherin, normally involved in cell-to-cell adhesion, allows metastases to develop from the primary tumor (7,8). Matrix metalloproteinases (MMPs) cause the breakdown of the extracellular matrix, increasing invasion into the blood vessel (9). Once in the blood vessel, tumor cells can travel to distant sites (10,11). Chemokines, especially C-X-C motif chemokine 12 (CXCL12) and its receptor C-X-C chemokine receptor 4 (CXCR4) serve a vital role in homing of tumor cells from circulation to bone (*Figure 1*). Tumor cells express CXCR4 and undergo chemotaxis in response to CXCL12 expressed in the bone marrow and stroma (12,13).

From the blood vessel, tumor cells enter the sinusoids and then the bone marrow stroma. Here, the tumor cells must generate their own blood supply before becoming enriched in the endosteal surface of the bone. Bone sialoprotein (BSP) plays a crucial role in normal bone metabolism. BSP is expressed on NSCLC tumor cells and interacts with integrins (preferentially $\alpha_V\beta_3$ and $\alpha_V\beta_5$) (14-17) in the stroma and bone marrow. BSP expression is associated with increased invasiveness, tumor cell growth, attachment, and migration. Platelet derived growth factor receptor beta (PDGFR-β), expressed in the stroma, has also been implicated in tumor growth and invasion (18). In a lung cancer mouse model, PDGFR-β receptor inhibition with sunitinib caused growth inhibition and impaired bone metastases development (19). Discoidin domain receptor-1 (DDR1) is expressed on cancer cells and interacts with collagen in the stroma and bone marrow matrix (20). Inhibition of DDR1, both *in vitro* and in a lung cancer bone metastases model, was associated with decreased metastatic activity, cell homing, and colonization in a study by Valencia and colleagues (21). Once enriched into the bone, tumor cells can begin to stimulate osteoclast and osteoblast activity through a variety of mechanisms.

Normal bone undergoes constant remodeling involving resorption of bone via osteoclasts and formation of new bone via osteoblasts (*Figure 2*). Bone metastases

Table 1 The search strategy summary

Items	Specification
Date of search	6/1/2020–9/1/2021
Databases and other sources searched	Google Scholar, PubMed
Search terms used	Search terms included “bone metastases AND lung cancer AND pathophysiology”, “bone metastases AND non-small cell lung cancer”, “skeletal related events AND non-small cell lung cancer”, “bone metastases AND lung cancer AND outcomes”, “bone metastases AND lung cancer AND response to therapy”, “bone metastases AND lung cancer AND immunotherapy”, and “bone metastases AND lung cancer AND predictive factors”. Bibliographies of identified papers were reviewed for additional articles of interest
Timeframe	1990–2021
Inclusion and exclusion criteria	Observational cohort, retrospective studies, RCTs, meta-analysis, and review articles published from 1990–2021 were examined for this review. Manuscripts in non-English languages were excluded
Selection process	Brendan Knapp independently selected and reviewed all initial articles, with additional review by Siddhartha Devarakonda. Ultimate final article inclusion was determined by all authors

RCTs, randomized controlled trials.

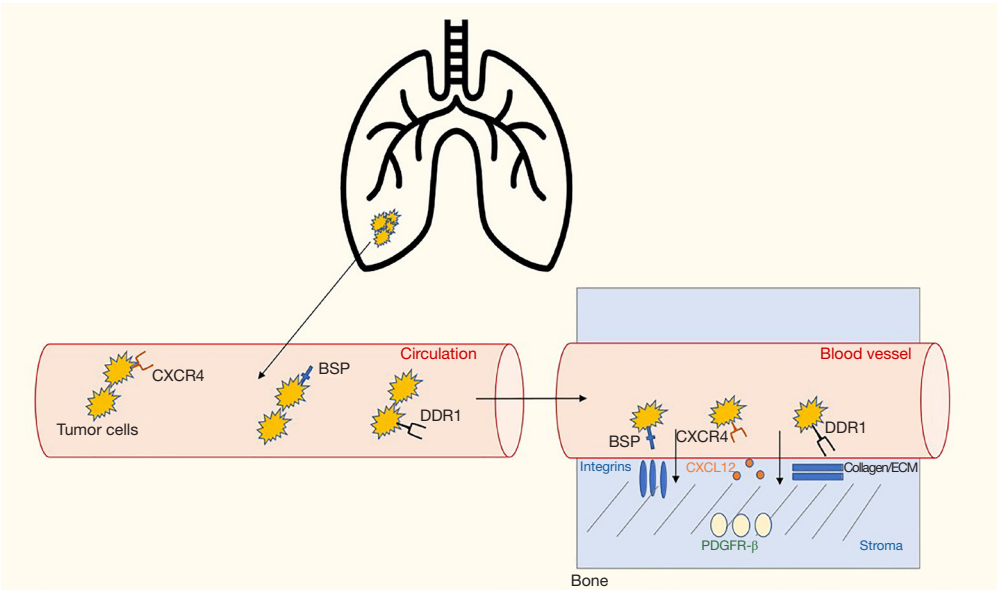

Figure 1 Invasion of tumor cells into bone. The initial steps through which bone metastases are established are likely similar to that of metastatic colonization of other distant sites. First, there is tumor invasion of the surrounding normal tissue and new vessel formation, followed by tumor invasion into the blood vessel. Once in the blood vessel, tumor cells can travel to distant sites (10,11). Chemokines, especially CXCL12 and its receptor CXCR4, serve a vital role in tumor cells via honing from circulation to bone. NSCLC cells express CXCR4 and undergo chemotaxis in response to CXCL12, which is expressed in the bone marrow stroma (12,13). BSP is expressed by NSCLC cells and interacts with integrins in the bone marrow stroma (14-17); PDGFR-β is also expressed in the stroma (18,19). Both BSP and PDGFR-β are associated with increased tumor invasiveness. DDR1, expressed on cancer cells, interacts with collagen in the stroma and bone marrow matrix and has also been associated with cell migration, homing, and colonization in bone (20,21). CXCR4, C-X-C chemokine receptor 4; BSP, bone sialoprotein; DDR1, discoidin domain receptor-1; CXCL12, C-X-C motif chemokine 12; ECM, extracellular matrix; PDGFR-β, platelet derived growth factor receptor beta; NSCLC, non-small cell lung cancer.

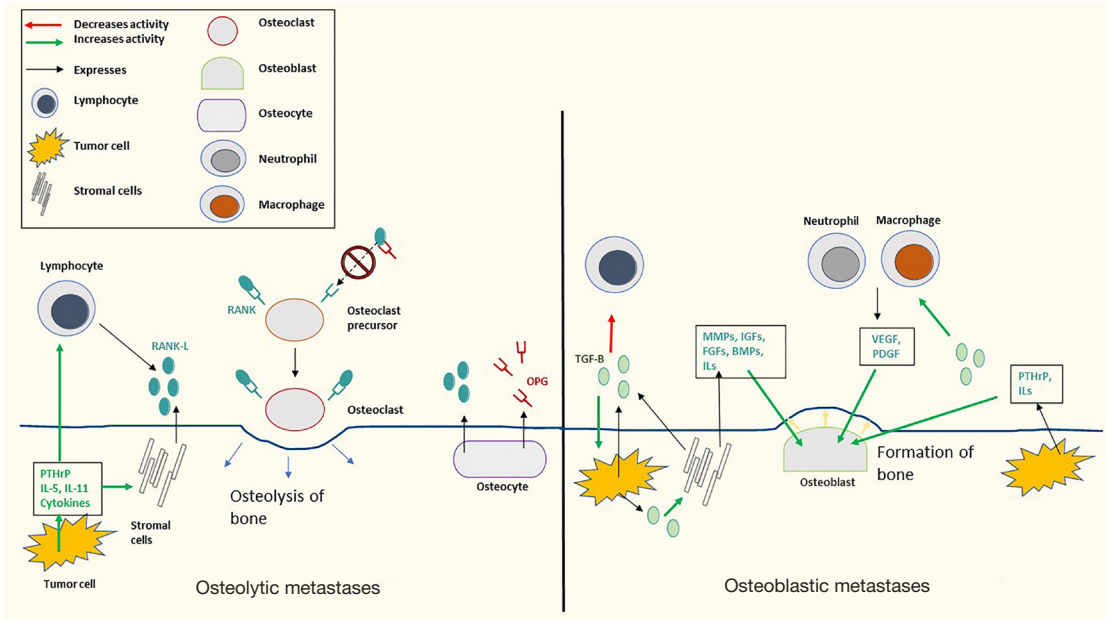

Figure 2 Simplified schema of osteolytic and osteoblastic metastases. On the left, the RANK and RANK-L interaction is described. RANK is expressed by osteoclasts, osteoclast precursor cells, and some tumor cells. RANK-L is expressed by bone marrow stromal cells, osteocytes, and T-lymphocytes. Binding of RANK to RANK-L stimulates osteoclast differentiation and activity and may increase metastatic potential of tumor cells; RANK-L expression is increased by PTHrP and ILs, among other cytokines and chemokines (11,22-25). OPG is produced by osteoblasts and osteocytes and prevents binding of RANK-L to RANK (26,27). On the right is a depiction of osteoblastic metastases, focused on TGF-β. TGF-β is a cytokine, expressed by cancer and stromal cells, that controls expression of MMPs, ILs, VEGF, and PTHrP, all of which increase bone metastases (9,28-34). TGF-β has also been implicated in inhibiting immune cell infiltration, allowing tumor growth (33,34). TGF-β induces production of VEGF and PDGF from immune cells, such as neutrophils and macrophages which increase bone metastases (29). Lung cancer cells also express PTHrP, which increases both osteoblastic and osteolytic metastases (35,36). TGF-β stimulates cancer cells to produce PTHrP, and also stimulates stromal cells to release other bone activating cytokines (such as MMPs, IGFs, FGFs, and BMPs), leading to a vicious cycle of bone osteolysis and bone formation (28,33,37,38). Most bone metastases lie on a spectrum of bone formation and bone resorption. RANK, receptor activator of nuclear factor kappa-beta; RANK-L, RANK-ligand; PTHrP, parathyroid hormone-related peptide; ILs, interleukins; OPG, osteoprotegerin; TGF-β, transforming growth factor-beta; MMPs, matrix metalloproteinases; IGFs, insulin like-growth factors; FGFs, fibroblast growth factors; BMPs, bone morphogenic proteins; VEGF, vascular endothelial growth factor; PDGF, platelet derived growth factor.

are characterized by dysregulation of the normal bone remodeling process and can be radiographically described as osteoblastic, osteolytic, or mixed. Osteolytic metastases are characterized by destruction of normal bone and are common in NSCLC. Osteoblastic metastases are characterized by new bone deposition and are classically found in small cell lung cancer. Most bone metastases have both resorptive and osteoblastic components. Cytokines and other factors more closely associated with osteolytic metastases include parathyroid hormone-related peptide (PTHrP), interleukins (ILs), and perhaps most importantly, the receptor activator of nuclear factor kappa-beta (RANK) and RANK-ligand (RANK-L) (11,22,23).

The RANK and RANK-L interaction is a major regulator of both normal and pathologic bone remodeling. RANK is a tumor necrosis factor receptor and is expressed on the surface of osteoclasts and osteoclast precursors. RANK-L is expressed by bone marrow stromal cells, osteoblasts, and osteocytes, and is secreted by activated T lymphocytes. Binding of RANK to RANK-L stimulates osteoclast differentiation, survival, and activity. Many cytokines, chemokines, and hormones induce osteolysis by increasing RANKL expression, including PTHrP, IL-5, and IL-11 produced by tumor cells (11,23,24). Osteoprotegerin (OPG), produced by osteoblasts and osteocytes, is a soluble decoy receptor of RANK-L and prevents binding of RANK

and RANK-L. The ratio of RANK-L to OPG is critical for regulating osteoclast activity. Upregulated RANK-L, RANK, and OPG has been found in NSCLC cell lines and tumor tissues with bone metastases, with an increased ratio of RANK-L:OPG found in tumor tissues with bone metastases relative to those without (26). Additionally, invasion of tumor cells has been shown to be significantly enhanced by the addition of recombinant human RANK-L and transfection of RANK-L complementary DNA (cDNA). Moreover, invasion was impaired when OPG was added to these cells (26). Similarly, in a mouse model of NSCLC, human OPG-Fc reduced development of osteolytic metastases (27). Tumor cells in the bone may cause increased RANK-L expression, and RANK-L may stimulate bone metastases via binding RANK-expressing cancer cells, leading to increased invasion and migration (25).

Factors implicated in primarily osteoblastic metastases include transforming growth factor-beta (TGF-β), bone morphogenic proteins (BMPs), insulin like-growth factors (IGFs), fibroblast growth factors (FGFs), and PDGFs (23,28,37,39-42). TGF-β is a multifunctional cytokine expressed by cancer and stromal cells (28). It controls expression of multiple genes and factors promoting bone metastases, including CXCR4, MMPs (9,29,30), IL-11, vascular endothelial growth factor (VEGF), and PTHrP (29,31-33). TGF-β has also been implicated in inhibiting immune cell infiltration, allowing tumor growth (34,43). TGF-β induces production of VEGF and PDGF from immune cells, such as neutrophils and macrophages, which increase bone metastases (29). Lung cancer cells also express PTHrP, which increases both osteoblastic and osteolytic metastases (35,36). TGF-β stimulates cancer cells to produce PTHrP and stimulates stromal cells to release other bone activating cytokines (such as MMPs, IGFs, FGFs, and BMPs), leading to a vicious cycle of bone osteolysis and formation (28,33,37,38). It is likely that based on tumor specific molecular alterations, bone metastases can either be predominantly lytic with activation of RANK and RANKL pathway, or predominantly osteoblastic due to activation of TGF-β pathway.

Clinical presentation

Symptoms related to bone metastases are described as SREs. Definitions for SREs vary among studies, but include severe bone pain, pathologic fractures, spinal cord and nerve compression syndromes, bone instability, hypercalcemia, and pain or instability requiring radiation therapy (RT) or orthopedic surgery. The most common SRE is severe pain and occurs in 80% of patients with bone metastases (1,44,45). After pain, the next most commonly reported SREs are necessity for radiotherapy (50–70% of patients), pathologic fractures (7–35%), hypercalcemia (1–20%), spinal cord compression (1–15%), and necessity for surgery (0–9%) (46-48).

Multiple metastatic lesions are more common than single sites, with multiple lesions occurring in approximately 80% of patients with bone metastases (1,44,48,49). Common sites of bone metastases include the spine (40–50%), ribs (20–27%), and pelvis (17–22%) (46-48,50). Fractures are common in the proximal portion of long bones, such as the femur or rib, as well as in the vertebrae. Sudden onset back pain and neurologic symptoms should trigger concern for cord compression in patients with vertebral metastases, of which immediate neurosurgical consultation is indicated given the poor prognosis if not addressed quickly. Cord compression has been reported to occur in 15% of patients with lung cancer and bone metastases (39,51).

Hypercalcemia is the most common metabolic complication of malignancy. In lung cancer, it generally occurs from osteolysis directly induced by tumor cells or from secreted PTHrP (52). Hypercalcemia portends a poor prognosis with a median overall survival (OS) of 10–12 weeks after its development (51,53).

SREs are associated with increased morbidity and mortality and decreased quality of life (5). They occur early in the clinical course and are often present at diagnosis. Tsuya and colleagues reported that of a cohort of 259 patients with NSCLC, 70 patients (30.4%) were found to have skeletal metastases during their course, with 35 patients having SREs. Eleven of 35 patients (31%) had SREs at the initial diagnosis of NSCLC (46). Other studies have found median time to first SRE from diagnosis of bone metastasis to be between 6 and 9.5 months (mo) (1,4,47).

Imaging and diagnosis

Bone metastases may be detected on routine imaging or with directed imaging when patients present with suspicious symptoms. Radiographs have poor sensitivity for screening at 40–50% (54), and considerable bone destruction (30–75% decrease in bone density) must be present before being evident (55). Magnetic resonance imaging (MRI) has a very high sensitivity for detection and diagnosis at approximately 95% (56,57) and is the imaging modality of choice if there is concern for cord compression (58).

Computed tomography (CT) may be more powerful than MRI for treatment planning and is especially useful for evaluating structural integrity. CT can detect osteolytic and osteoblastic metastases within the bone marrow before destruction is sufficient to be evident on radiograph. Bone scans are especially adept in patients with primarily osteoblastic metastases (56).

Once there is concern for bone metastases or at initial diagnosis of NSCLC, comprehensive skeletal evaluation is typically performed with fluorodeoxyglucose-positron emission tomography-CT (FDG-PET-CT). FDG-PET-CT is extremely sensitive (~98%) in the evaluation of bone metastases (56), and society guidelines recommend FDG-PET-CT to evaluate distant metastases of all sites in newly diagnosed patients with lung cancer (59,60). A CT of the chest and abdomen with contrast is recommended if FDG-PET is not available, and bone scans may be used as an alternative imaging modality to evaluate for bone metastases, although their sensitivity and specificity is lower compared to PET imaging (59-61). A definitive diagnosis is made by biopsy of the bone lesion. In many cases, however, biopsies are not obtained, especially if there is a known primary tumor with a characteristic skeletal lesion, and particularly if there are multiple lesions or if obtaining a biopsy would impose substantial risk to the patient. However, if there is any doubt for the diagnosis, biopsy should be considered. Indeed, in a study of 482 patients with a primary malignancy who underwent a biopsy of a suspicious bone lesion, 21% of the lesions were benign and 3% were due to a second malignancy (62).

Factors predicting development of bone metastases

Predicting the development and progression of bone metastases remains difficult, but accurate prediction could allow earlier intervention to prevent development of SRE. Predictive factors that have been evaluated include patient/tumor related factors, molecular alterations, and serum biomarkers.

Clinical characteristics

Stage at diagnosis, histologic subtype, and age have been shown to be predictive of bone metastases development in several studies. In a retrospective Italian cohort study of 661 deceased NSCLC patients with bone metastases, factors associated with a faster median time to development of bone metastases included age >65 (5 *vs.* 7 mo, P=0.046), Eastern Cooperative Oncology Group (ECOG) >2 (P=0.012), and stage IV disease at diagnosis (P=0.001) (1). On multivariate analysis of a prospective cohort study of 274 Japanese patients with stage IIIB/IV lung cancer, factors predicting bone metastases development included stage IV, ECOG >1, and increased bone alkaline phosphatase (ALP) (4). Patients with adenocarcinoma have been found to have higher risk of bone metastases relative to other histologic subtypes (63,64).

Tumor mutations

The effect of tumor mutation status on bone metastases has also been evaluated. A retrospective case-control study evaluated 189 metastatic NSCLC patients with *EGFR* (exon 19 and 21) mutations, *KRAS* mutations, and wild type *EGFR/KRAS*. There was no difference in incidence of bone metastases (60% *vs.* 52% *vs.* 50%), mean time to diagnosis of bone metastases in patients without bone metastases at diagnosis, or time to first SRE among the three groups of patients. As anticipated, median OS was longer in *EGFR* mutated patients than *KRAS* mutated or wild type patients (26.7 *vs.* 11 *vs.* 11.5 mo, P<0.0001) (65). Similarly, in a study of 209 patients at Colorado University with NSCLC with *EGFR*, *KRAS*, *ALK*, or no mutations at diagnosis, no molecular cohort was predisposed to develop to bone, brain, or lung metastases (66). However, a 2020 retrospective analysis of 570 patients with NSCLC found an increased risk of bone and lung metastases in patients with *EGFR* and *HER2* mutations compared to patients with gene fusions, RAS mutations, or mutations without an identified oncogene driver (P<0.001) (67). In a 2014 study of 277 patients with metastatic lung adenocarcinoma at a single Japanese institution, patients with *EGFR* mutations had a significantly greater number of lung, brain, and bone metastases (median 3 *vs.* 2, P=0.035) than wild type patients. Patients with *EGFR* mutations had improved OS relative to wild type patients (median 28.1 *vs.* 14.9 mo) (68). In summary, results have been conflicting, but patients with *EGFR* and *HER2* mutations may be at increased risk of bone metastases, albeit with improved OS in patients with *EGFR* mutations, likely due to the availability of effective targeted therapies for the treatment of *EGFR* mutated NSCLC.

Circulating tumor cells (CTCs) and DNA

CTCs and circulating tumor DNA (ctDNA) have been shown to have prognostic implications at diagnosis and evaluating treatment response in several solid tumors, including lung (69). Higher ctDNA and CTC quantities have been found in patients with bone metastases compared

to those without. This likely represents increased overall tumor burden irrespective of the bone metastases themselves (70-72), but some studies have found this to be specific to bone. For example, a trial of 57 patients with *EGFR* mutated NSCLC found a significant correlation between bone metastases and ctDNA detection [odds ratio (OR): 3.99; 95% confidence interval (CI): 1.027–15.45; P=0.046], but not between other locations of metastases (73). Additionally, in a study of 67 lung cancer patients with bone metastases compared to 30 patients without, CTCs were more likely to be detected in the bone metastases group than in patients without (94% *vs.* 71%). Increased CTCs were not associated with intrapulmonary or lymph node metastasis. Of patients with CTCs detected, patients with bone metastases had a significantly higher number of CTCs than bone metastases negative patients (P=0.0045) (74). To summarize, patients with bone metastases may have increased levels of ctDNA and CTCs relative to patients without, although it is more likely related to overall tumor burden rather than the bone itself.

Serum biomarkers

Several biomarkers have also been evaluated in predicting development of bone metastases. In a case-control study of 30 patients with resected NSCLC who subsequently developed bone metastases *vs.* 30 patients without any metastases *vs.* 26 patients with non-bone metastases, 10 markers were evaluated via immunohistochemistry including MMP, VEGF, and BSP. BSP was expressed in 80% of patients with bone metastases *vs.* 20% of patients without metastases and in 31% of patients with non-bone metastases. Detection of BSP was strongly associated with bone dissemination (P<0.001) and independently with worse OS in all patients (14). Zhang and colleagues also found expression of BSP to be associated with bone metastases in 180 patients with completely resected NSCLC, 40 of whom later developed bone metastases (47.5% *vs.* 22.9%, P=0.007). Two-year bone metastases free survival was increased in patients with low BSP expression (85% *vs.* 69%, P=0.01) (15). Tang *et al.* found levels of bone ALP, Tartrate-resistant acid phosphatase 5b (TRAPC5b), and type 1 collagen carboxyterminal telopeptide to be higher in 130 lung cancer patients with bone metastases *vs.* 135 patients without (75). Finally, a 2017 retrospective study of 2021 patients with lung cancer at a single institution found risk factors predictive of development of bone metastases to include elevated cancer antigen-125 (CA-125) and elevated ALP (64).

Treatment of bone metastases

In general, the treatment of bone metastases is not curative; goals of management include maximizing symptom control, preserving function, minimizing SREs, and enhancing local tumor control. In addition to pain management, therapies include osteoclast inhibitors and other bone specific therapy, systemic anti-cancer therapy, radiation, surgery, and interventional techniques. A multi-disciplinary approach is required. A majority of patients will have significant pain during their course, and most will ultimately require opioids for analgesia. Other pharmacologic approaches for pain management include acetaminophen, NSAIDs, steroids, antidepressants, and gabapentin (45,76).

Bisphosphonates

Bisphosphonates are standard of care in patients with bone metastases. Bisphosphonates attach to hydroxyapatite on exposed bone around resorbing osteoclasts and are internalized by osteoclasts, causing disruption of bone resorption and possible osteoclast apoptosis (51). They are effective for both osteolytic and sclerotic lesions. In addition, they may have a direct effect on tumor cells via GTPase modulation leading to apoptosis (77) and may stimulate anti-tumor immune mechanisms (78). Bisphosphonates as a class are well-tolerated. Common side effects include flu-like symptoms and hypocalcemia; rare jaw osteonecrosis may occur. Close monitoring must be taken in patients with renal insufficiency.

The most well studied of the bisphosphonates in malignancy is zoledronic acid (ZA). There have been several studies regarding its use in bone metastases broadly and a few specific to lung cancer. A large prospective RCT by Rosen *et al.* in 2003 evaluated 773 patients with metastatic bone disease from solid tumors (excluding breast and prostate), of whom 378 had lung cancer. ZA delayed time to first SRE (230 *vs.* 163 days, P=0.023) and reduced the risk of developing SREs in all tumor types [hazard ratio (HR): 0.73; P=0.017] (79). While the data from smaller prospective studies provides conflicting results with regard to the efficacy of ZA on pain control, SRE, progression-free survival (PFS) and OS (80,81), a 2012 systematic review and meta-analysis of 12 trials of bisphosphonates in lung cancer patients with bone metastases found that patients treated with ZA and chemotherapy had significantly fewer SREs than those treated with chemotherapy alone. Patients treated with bisphosphonates in addition to another treatment modality (chemotherapy or RT) had improved

pain control (82). ZA is typically dosed every 4 weeks, although longer intervals may be efficacious (83). Despite data supporting their use, bisphosphonates may not be as widely prescribed in lung cancer as other cancers, with percentages among both prospective and retrospective studies ranging from 6–60% (1,44,46,49,84). In summary, use of bisphosphonates in patients with known bone metastases may confer a modest benefit in terms of pain control, decreasing SRE, and perhaps improvement in PFS.

Denosumab

Denosumab is a monoclonal antibody against RANK-L, blocking binding to RANK and reducing formation, function, and survival of osteoclasts, leading to decreased bone resorption. It is considered safe in patients with impaired renal function, unlike bisphosphonates (85). Otherwise, its side effect profile is similar to bisphosphonates and is usually administered every 4 weeks. Denosumab was compared to ZA in a large phase three RCT of patients with solid tumors (excluding breast and prostate). Denosumab was shown to be non-inferior to ZA in delaying time to first-on-study SRE (primary endpoint). The OS and PFS were similar in both groups (86). An exploratory subgroup analysis of 811 lung cancer patients with bone metastases from this study was performed, with 411 patients receiving denosumab and 400 receiving ZA. Denosumab was associated with improved median OS in all lung cancer patients (8.9 *vs.* 7.7 mo in ZA; HR: 0.80; 95% CI: 0.67–0.95) and in 702 patients with NSCLC (9.5 *vs.* 8 mo; HR 0.78) (P=0.01 for each comparison) (87). The mechanism for potential improved OS in patients with bone metastases in this exploratory study is unclear. Denosumab inhibition of RANK-L may have a direct anti-neoplastic effect via apoptosis or anti-migration of tumor cells (88,89). Denosumab may also have additional immunomodulatory effects via disrupting the interaction between tumor cells and the bone microenvironment (87,90). Importantly, data is conflicting, with a recent open label RCT of 514 patients with metastatic NSCLC (275 with bone metastases) receiving chemotherapy plus denosumab *vs.* placebo showing no difference in OS in patients with or without bone metastases (91).

Radiation therapy

RT is a standard approach for symptomatic bone metastases. Short, fractionated schedules have equal effectiveness as protracted schedules (92), and pain relief typically occurs within 1–2 weeks in 50% of patients (93). A comprehensive review of radiation treatment and fractionation schedules, as well as outcomes and adverse events associated with radiotherapy, is beyond the scope of this review, and has been covered elsewhere (94-100).

Surgery and interventional techniques

Surgery is usually reserved for lesions with a complete or impending fracture, or in spinal metastases with mechanical instability or cord compression. Surgery can alleviate pain and preserve function in impending fractures in non-vertebral bones (101). However, the need for surgery portends a poor prognosis, with median OS after surgery reported to be 3 and 5.4 mo in two small retrospective analyses of NSCLC patients with operatively managed bone metastases (102,103). Presence of a fracture portended worse prognosis (3 *vs.* 6.3 mo median OS) (103). Most studies specific to non-spine metastases include patients with several types of malignancy, not limited to NSCLC. Two retrospective studies of patients with non-spine metastases found most patients had multiple bone metastases (*vs.* single metastases), with the most common location being the femur. Complete fracture was associated with worsened survival relative to those who underwent surgery for impending fracture or pain in both studies (104,105).

Surgery is indicated in patients with spinal cord compression and may be associated with improved ambulatory status compared to radiotherapy alone, as shown by a seminal 2005 study by Patchell and colleagues. In this study, 101 patients with spinal metastases (26 with lung cancer) were randomized to RT plus surgery *vs.* RT alone. Patients receiving surgery showed improved ambulatory rate (84% *vs.* 57%), maintenance of continence, functional ability, and survival (126 *vs.* 100 days) (106). Most studies specific to spinal metastases from NSCLC are observational. A recently published systematic review and meta-analysis of outcomes of surgery in patients with cord compression secondary to metastatic NSCLC included 11 observational cohort studies without controls. One mo mortality following surgery ranged from 1.4–10%, with reported median OS following surgery ranging from 2.1–12 mo. Improved ambulatory status following surgery ranged from 37% to 92% with a mean value of 59.5%. Improved OS and improved post-operative ambulatory status were noted in patients with fewer (1–2 *vs.* >2) vertebral metastases (R=0.74 for and 0.88, respectively), and fewer metastases (0 *vs.* unremovable) to major internal organs (R=0.82 and 0.81, respectively) (107).

Finally, numerous interventional techniques are available, including nerve blocks, spinal injections, ablation (cryo-, thermo-, or radiofrequency), and vertebroplasties (108), and several studies have shown good efficacy in pain control with these techniques (108-113). To summarize, a multidisciplinary approach must be taken for the management of bone metastases given the breadth of treatment options, and treatment should be individualized to each patient.

Predicting outcomes in patients with bone metastases

Several factors have been evaluated in prognosticating outcomes in patients with bone metastases from NSCLC. More aggressive interventions could be pursued in patients with poor prognostic factors.

Clinical characteristics

The presence of bone metastases is associated with worse survival and patients with SREs tend to do poorly. The median survival from diagnosis of bone metastases has been reported to be 6–7 mo in patients with lung cancer (51,53). In a Denmark cohort study, 1-year survival of lung cancer patients without bone metastases was 37% *vs.* 12.1% with bone metastases and 5.1% in patients with bone metastases and SRE (114). The presence of multiple bone metastases may portend a worse prognosis than single metastases. In a retrospective study by Sugiura *et al.* published in 2008, presence of multiple bone metastases was associated with significantly shorter OS than patients with single metastases (8.9 *vs.* 14 mo, P=0.02). Presence of fractures was also associated with worse OS compared to no fractures (6.4 *vs.* 10.2 mo, P=0.04) (48). In a retrospective cohort study of 661 deceased NSCLC patients with bone metastases, median OS after diagnosis of bone metastases was 9.5 and 7 mo after first SRE. Presence of more than 2 of 4 factors (age >65, non-adenocarcinoma histology, EGOG >2, presence of visceral and bone metastases at diagnosis) was associated with worse OS from diagnosis of bone metastases (5 *vs.* 8 mo, P<0.001). Lack of bisphosphonate use was also associated with shorter OS (1). Studies comparing survival between patients with metastatic NSCLC involving different organs have found mixed results. However, in general, these studies suggest a relatively worse prognosis in patients with liver metastases (115-117), followed by bone and brain metastases (118-120).

Tumor mutations

In general, NSCLC patients with driver mutations are known to have improved outcomes compared to those without (121), and this has been found in patients with bone metastases (65,122,123). For example, a Japanese study of 125 patients with NSCLC with bone metastases showed patients with *EGFR* mutations had significantly lower incidence of SRE (21% *vs.* 38%, P<0.05) and longer time to first SRE (13 *vs.* 6 mo, P<0.05) when treated with a tyrosine kinase inhibitor compared to *EGFR* mutation negative patients, treated mostly with chemotherapy (123). Presence of bone metastases was a significant predictor of OS in *EGFR* mutated (HR: 2.04; 95% CI: 1.17–3.64; P=0.011) and wild type (HR: 2.15; 95% CI: 1.40–3.29; P<0.001) patients, in a study of 277 Japanese patients with metastatic lung adenocarcinoma. On subgroup analysis of 116 patients with bone metastases however, the authors found no significant difference in OS in patients with *vs.* without SRE in both wild type and *EGFR* mutated patients (68).

Serum biomarkers

N-telopeptide of type 1 collagen (NTX) has been identified as a marker of bone metastases progression. In a retrospective analysis, high *vs.* normal urinary NTX correlated with a greater than two-fold increased risk of bone lesion progression and death in the placebo group of a phase three prospective RCT comparing ZA to placebo in NSCLC patients with bone metastases. Additionally, ZA reduced the relative risk of death by 35% in patients with higher baseline NTX levels compared to those with high levels receiving placebo (124). TRAPC5b is another marker of bone resorption. In a study of 141 newly diagnosed patients with stage III or IV NSCLC (72 with bone metastases), TRAPC5b activity was higher in patients with bone metastases than without (3.50±2.23 U/L, 2.09±0.72 U/L, P<0.001). A decline in TRACP5b was associated with response to treatment in patients with bone metastases (P=0.047), whereas an increase was associated with new development of bone metastases (P=0.05) (125). In a study of urinary n-telopeptide and bone ALP in 441 patients with several types of cancer (115 with NSCLC) who had bone metastases, high levels of N-telopeptide (>100 nmol/mmol creatinine) was associated with increased relative risk of death compared to patients with NSCLC who had low levels of N-telopeptide [risk ratio (RR): 3.51; 95% CI: 2.13–5.79; P<0.001] (126).

Response to chemotherapy and targeted therapy

Predicting response to therapy is critical in metastatic

Table 2 MD Anderson criteria for evaluation of response in bone metastases

Response type	Definition
Complete response	Complete fill-in or sclerosis of lytic lesion on CT or XR
	Disappearance of tumor signal on bone scan, CT, or MRI
	Normalization of osteoblastic lesion on CT or XR
Partial response	Sclerotic rim formation around initially lytic lesion on CT
	Sclerosis of lesions previously undetected on CT or XR
	Partial fill-in or sclerosis of lytic lesion on CT or XR
	Regression of measurable lesion on CT, MRI, or XR
	Regression of lesion on bone scan
	Decrease in blastic lesion on CT or XR
Stable disease	No change in measurable lesion on CT, MRI, or XR
	No change in blastic or lytic lesion or CT, MRI, or XR
	No new lesion on CT, MRI, or XR
Progressive disease	Increase in size of existing measurable lesion on CT, MRI, or XR
	New lesion on CT, MRI, bone scan, or XR
	Increase in lytic or blastic lesion on CT or XR

CT, computed tomography; XR, plain radiography; MRI, magnetic resonance imaging. Adopted with publisher permission from (129).

NSCLC. Bone metastases have been considered "unmeasurable" by the Response Evaluation Criteria in Solid Tumors (RECIST) criteria, secondary to difficulty determining response to treatment (127,128). In 2004, Hamaoka *et al.* established the "MD Anderson criteria" (*Table 2*) for bone metastases response to therapy, but this is not widely used in clinical practice (129,130). Osteosclerotic changes, considered to be a repair process of bone, appear as changes in attenuation on CT and have also been evaluated in determining response (131).

Few trials have specifically evaluated presence of bone metastases in response to therapy, and most have been of small sample sizes. One retrospective study of 25 patients with NSCLC with bone metastases treated with first line platinum-based chemotherapy with or without bevacizumab found improved bone specific response (23 *vs.* 0%, P=0.038), disease control, and median time to bone progression (13.7 *vs.* 4.3 mo, P=0.06) in patients treated with bevacizumab *vs.* without. OS was similar in both groups (132). A retrospective study of 52 NSCLC patients with bone metastases receiving platinum-based combination chemotherapy found patients with osteosclerotic changes on CT had significantly higher disease control rate (100% *vs.* 64.7% at 3 mo, P<0.001) and improved 1-year PFS than patients without osteosclerotic changes (1-year PFS: 74.9% *vs.* 30.2%, P<0.001) (133). A similarly improved response and OS in 41 lung adenocarcinoma patients treated with gefitinib was found in patients with osteosclerotic lesions *vs.* those without in a study by Yamashita *et al.* (134).

Response to immune checkpoint inhibitors

The bone is a hematopoietic organ, plays an active role in regulating the immune system, and may influence response to immunotherapy (135). However, there are relatively few trials dedicated to evaluating immunotherapy in bone metastases in NSCLC. An Italian cohort study by Landi *et al.* (6) of previously treated NSCLC patients receiving nivolumab evaluated the role of bone metastases in immunotherapy. Cohort A included 1,588 patients with non-squamous disease (39% with bone metastases) and cohort B included 371 patients with squamous cell disease (32% with bone metastases). In both cohorts, patients with bone metastases had a lower overall response rate based on RECIST (A: 12% with bone metastases *vs.* 23% without, P<0.0001; B: 13% *vs.* 22%, P<0.04), shorter PFS (A: 3 *vs.* 4 mo, P<0.0001; B: 2.7 *vs.* 5.2 mo, P<0.0001), and shorter OS (A: 7.4 *vs.* 15.3 mo, P<0.0001; B: 5.0 *vs.* 10.9 mo, P<0.0001) compared to those without bone metastases treated with nivolumab. Presence of bone metastases negatively affected outcome regardless of performance status or presence of liver metastases and was independently associated with risk of death on multivariate analysis (A: HR: 1.5; B: HR: 1.78). In both groups, there was an increased risk of death and progression within 3 mo in patients with bone metastases. Importantly, there was no info on programmed death ligand-1 (PD-L1) status in this trial, nor a control arm without immunotherapy (6).

CheckMate 227 was a RCT that evaluated nivolumab with ipilimumab *vs.* nivolumab with chemotherapy *vs.*

chemotherapy alone in metastatic NSCLC patients who had not received prior chemotherapy. Regardless of whether patients received ipilimumab and nivolumab or chemotherapy, presence of bone metastases was associated with worse OS (12.2 *vs.* 19.2 mo in ipilimumab/nivolumab group; 8.8 *vs.* 16.0 mo in chemotherapy group). There was improved OS in patients with bone metastases treated with ipilimumab/nivolumab *vs.* chemo in patients of all PD-L1 status [12.2 *vs.* 8.8 mo; HR: 0.68 (0.53–0.88)] and in those with PD-L1 expression <1% [9.5 *vs.* 7.6 mo; HR: 0.58 (0.37–0.89)], but not with PD-L1 expression >1% [13.4 *vs.* 10.0 mo; HR: 0.75 (0.55–1.03)] (136). Conversely, survival analysis of the CheckMate 057 study of nivolumab *vs.* docetaxel as second line therapy in NSCLC evaluated 161 patients with bone metastases, 86 receiving nivolumab and 75 docetaxel. At 3 mo, 26 of 86 patients in the nivolumab had died *vs.* 11 of 75 patients receiving docetaxel (P=0.019), suggesting immunotherapy may not overcome the poor overall prognosis of skeletal metastasis (137). Additionally, a retrospective study of 330 patients with metastatic NSCLC who received immune checkpoint inhibitors found significantly worse OS in patients with bone metastases than those without (5.9 *vs.* 13.4 mo, P<0.001). Patients with baseline bone metastases had a higher HR of death than those without when controlling for performance status, histology, line of therapy, and burden of disease (HR: 1.57; 95% CI: 1.19–2.08; P=0.001) (138). Conversely, a retrospective review of 201 patients with metastatic NSCLC receiving nivolumab at three Japanese centers found liver and lung metastases, but not bone, to be predictive of shorter median PFS (139). Finally, a small retrospective review of 15 NSCLC patients with bone metastases who received single agent nivolumab evaluated response of bone metastases using the MD Anderson response criteria to predict overall outcomes. Non-responders based on the MD Anderson criteria had earlier disease progression based on RECIST criteria compared to responders. Additionally, in responders according to both RECIST and MD Anderson criteria, time to response was earlier with the MD Anderson criteria (1.4–2 mo) than the RECIST criteria (2.8–3 mo) (140), suggesting the MD Anderson criteria could be used in future larger studies to evaluate the response of bone metastases.

Conclusions

Bone metastases in lung cancer patients remain a common occurrence, impacting morbidity, mortality, and quality of life. Patients with SREs have worse prognosis. There is data supporting use of bisphosphonates and/or denosumab, and these should be considered in all patients with bone metastases. Molecular profiling should be evaluated as a potential biomarker for risk of development of bone metastases and response to treatment. Additionally, next generation sequencing has revealed a high degree of heterogeneity among all tumors (141). Multiple subclones derived from the primary tumor may behave in different phenotypes and determining the role of driver mutations driving skeletal metastases could help identify patients at risk of developing bone metastases (142). Novel studies comparing the genomic alterations of skeletal metastases and primary tumors are needed. As therapy for patients with advanced disease evolves, more studies are needed to evaluate the interplay between immunotherapy and bone metastases, and determining the response to treatment in bone. One such trial, DENIVOS (NCT03669523), evaluating combination therapy with denosumab and nivolumab as a second-line treatment in patients with NSCLC and bone metastases, is currently ongoing. Future RCTs of immunotherapy should include data on presence of bone metastases, and dedicated trials regarding bone metastases and immunotherapy should be performed.

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Footnote

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