



Current progress and mechanisms of bone metastasis in lung cancer: a narrative review

Shengyu Wu^{1,2#}, Yue Pan^{1,2#}, Yanyu Mao^{1,2#}, Yu Chen³, Yayi He¹

¹Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University, Shanghai, China; ²Medical School, Tongji University, Shanghai, China; ³Spine Center, Orthopedic department, Shanghai Changzheng Hospital, Shanghai, China

Contributions: (I) Conception and design: Y He, Y Chen; (II) Administrative support: Y He, Y Chen; (III) Provision of study materials or patients: S Wu, Y Pan, Y Mao; (IV) Collection and assembly of data: S Wu, Y Pan, Y Mao; (V) Data analysis and interpretation: S Wu, Y Pan, Y Mao; (VI) Manuscript writing: All authors; (VII) Final approval of manuscript: All authors.

[#]The authors contributed equally to this work.

Correspondence to: Yayi He. Department of Medical Oncology, Shanghai Pulmonary Hospital, Tongji University Medical School Cancer Institute, Tongji University School of Medicine, No. 507 Zhengmin Road, Shanghai 200433, China. Email: 2250601@qq.com; Yu Chen. Spine Center, Orthopedic department, Shanghai Changzheng Hospital, No 415, Fengyang Road, Shanghai 200433, China. Email: yugangg2003@163.com.

Abstract: Lung cancer is a kind of malignant tumor with rapid progression and poor prognosis. Distant metastasis has been the main cause of mortality among lung cancer patients. Bone is one of the most common sites. Among all lung cancer patients with bone metastasis, most of them are osteolytic metastasis. Some serious clinical consequences like bone pain, pathological fractures, spinal instability, spinal cord compression and hypercalcemia occur as well. Since the severity of bone metastasis in lung cancer, it is undoubtedly necessary to know how lung cancer spread to bone, how can we diagnose it and how can we treat it. Here, we reviewed the process, possible mechanisms, diagnosis methods and current treatment of bone metastasis in lung cancer. We divided the process of bone metastasis in lung cancer into three steps: tumor invasion, tumor cell migration and invasion in bone tissue. It may be influenced by genetic factors, microenvironment and other adhesion-related factors. Imaging examination, laboratory examination, and pathological examination are used to diagnose lung cancer metastasis to bone. Surgery, radiotherapy, targeted therapy, bisphosphonate, radiation therapy and chemotherapy are the common clinical treatment methods currently. We also found some problems remained to be solved. For example, drugs for skeletal related events mainly target on osteoclasts at present, which increase the ratio of patients in osteoporosis and fractures in the long term. In all, this review provides the direction for future research on bone metastasis in lung cancer.

Keywords: Lung cancer; bone metastasis; diagnosis methods; mechanism; treatment

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Introduction

Lung cancer is a kind of malignant tumors with rapid progression and poor prognosis, it brings difficulties to clinical treatment (1). Distant metastases have been the main cause of mortality among lung cancer patients (2). Bone is the second commonest site of lung cancer metastasis (3). According to the

characteristics of the lesions, bone metastasis can be divided into the following three types: osteolytic, osteogenic and mixed type (4). Osteolytic bone metastasis account for 70% and most lung cancer bone metastasis can be classified into this category (5). Bone metastasis can cause pain, pathological fractures, spinal instability, spinal cord compression and hypercalcemia, which impairs the structural integrity of the

bone, and often predicts a decline in the quality of life and shortened survival of patients (6).

Since the severity of bone metastasis in lung cancer, it is undoubtedly necessary to know how lung cancer spreads to the bone, how can we diagnose it and how can we treat it. We tried to review these from four different aspects: the process of bone metastasis in lung cancer, possible mechanisms, diagnosis methods and current treatment for bone metastasis.

We present the following article in accordance with the Narrative Review reporting checklist (available at <http://dx.doi.org/10.21037/tlcr-20-835>).

The process of bone metastasis in lung cancer

The process of bone metastasis in lung cancer could be roughly segmented into three steps: tumor invasion, tumor cell migration and invasion in bone tissue (*Figure 1*). At first, with the influence of some factors such as protein-protein interactions (7,8) and signaling events (9,10), in particular, the decrease of E-cadherin (11,12) and some proteinases like matrix metalloproteinases (MMPs) (13-15), the status of lung cancer cells are changed. Intercellular adhesion and crosslinking are decreased as well. Thus, tumor cells invade and have a trend of migration. Then, lung cancer cells enter into the circulatory system and are named as circulating tumor cells (CTCs) (16-18). The location of bone metastasis is associated with the red bone marrow (RBM) content (19). The common metastasis sites are spine (20,21), pelvis (19), ribs (22) and so on. This is tumor cell migration. Finally, when the tumor cells reach the surface of the bone, they start to invade. Certain adhesion molecules, for instance, vascular cell adhesion protein-1 (23), play an important role. They promote lung cancer cells joining with the bone cells, beginning to change the bone microenvironment (24).

Types of bone metastasis in lung cancer

Osteoblast and osteoclast regulate bone changes. They function opposite and maintain relative balance in normal bone shaping and bone homeostasis. The maintenance of bone metabolic balance requires the dynamic balance and coupling between osteoclast-induced bone resorption and osteoblast induced bone formation (25,26). Tumor cells can lead to the imbalance of osteoblasts and osteoclasts, thus interrupting bone reconstruction (27). There are two different types of bone metastasis in lung cancer: osteolytic metastasis and osteogenic metastasis. Among all cases, most

lung cancer metastases are osteolytic metastasis caused by osteoclasts.

Osteolytic metastasis

Evidences showed that lung cancer cells cannot directly cause osteolytic by the secretion of proteolytic enzymes to local tissues (28). Instead, the microenvironment between lung cancer cells and bone tissue played an important role by activating osteoclasts. As a result, osteoclasts destroy the bone and lead to osteolytic lesion (29).

Most studies suggested that osteoblasts were primarily secretory cells that release molecules that regulate osteoclast formation and tumor progression (30). Tumor related factors like bone morphogenetic proteins (BMPs), semaphorin 3A (Sema3A), vascular endothelial growth factor (VEGF), macrophage chemotaxis and activating factor-1 (MCP-1) and interleukin-6 (IL-6) (31-33), have been shown to promote osteoblast differentiation. Besides, miR-139-5p was proved to positively regulate the osteogenic differentiation in mesenchymal stem cells (MSCs) (27). Through the JAK/STAT pathway, leptin can potentiate BMP9-induced osteogenic differentiation of MSCs (34). However, hypoxia inducible factor-1 α (HIF-1 α) is engaged in bone metastasis of lung cancer through promoting the expression and secretion of Sema4D to inhibit osteogenic differentiation (35). Besides, dickkopf-related protein 1 (DKK1) (36) and tumor necrosis factor- α (TNF- α) (37) have been proved to be involved in inhibiting osteoblast differentiation.

Osteoclasts are the main effector cells in bone resorption. They are derived from hematopoietic progenitor cells in the mononuclear-macrophage family (38,39). Lung cancer cells derived circulating miR-21 promotes the differentiation of monocytes into osteoclasts (40). Myeloid-derived suppressor cells (MDSCs), as osteoclast progenitors, can not only differentiate directly into osteoclasts but also produce reactive oxygen species (ROS) and cytokines to inhibit the immune response of host CD4 and CD8 T cells and promote the progress of tumor (41). MiR-34a inhibits osteoclast differentiation and osteoclastic bone metastasis by targeting the inhibition of Tgif2 (42). IL-7 produced by lung cancer cells can up-regulate T cell-derived cytokines such as receptor activator of nuclear factor- κ B ligand (RANKL) and TNF- α to promote osteoclast production (43). Hepatocyte growth factor (HGF)-MET can activate the RANKL/receptor activator of nuclear factor- κ B (RANK) signaling pathway in the bone microenvironment, induce osteoclasts

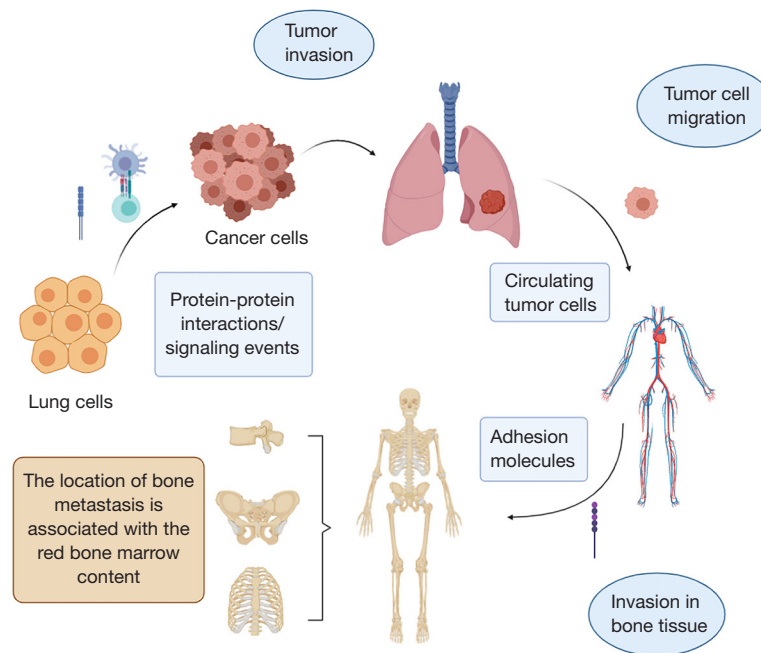


Figure 1 The process of bone metastasis in lung cancer.

activation, and eventually lead to the occurrence of osteolytic metastasis (44).

Osteogenic metastasis bone-resident osteocalcin-expressing (OCN⁺) osteoblastic cells are myeloid cells derived from bone marrow. Evidence shows that lung cancer can remotely activate OCN⁺ osteoblasts in bone even in absence of metastasis. Meanwhile, SiglecF^{high} neutrophils are provided by these OCN⁺ osteoblasts, thus promoting the development of cancer (45). Therefore, Camilla Engblom and his team revealed that osteoblasts play a remote regulatory role in lung cancer progression but whether osteoblasts are connected with tumor metastasis is pending further discussion.

Compared with osteolytic metastasis, osteoblastic metastasis of lung cancer is rare and if there are unique mechanisms is still unknown. This phenomenon may be linked to some lung cancer-derived factors. For example, Wnt/ β -catenin signaling and DKK1 cause lung cancer metastasis, especially to bone. However, high expression of DKK1 determines the activity of alkaline phosphatase (ALP) and secretion of osteocalcin, having an impact on differentiation of osteoblast (46).

Overall, the bone metastasis of lung cancer is mostly based on osteolytic metastasis.

Possible mechanisms (Figure 2)

Genetic factors

Recently, more and more studies focus on gene regulation to metastasis in lung cancer, especially about miRNA. The miRNA secreted by cancer cells is absorbed by surrounding cells in the form of exosomes and functions. For example, miR-192 overexpressed in lung cancer cells can target vascular endothelial cells through exosomes, inhibit angiogenesis by down-regulating the expression of IL-8, intercellular adhesion molecule (ICAM) and chemokine (C-X-C motif) ligand 1 (CXCL1), thereby reducing the ability of bone metastasis (47,48). It was reported that miRNA-144 targets cyclin E1 (CCNE1) and cyclin E2 (CCNE2) to inhibit non-small cell lung cancer (NSCLC) bone metastases (49). By targeting tripartite motif-containing 44 (TRIM44), miR-192-5p inhibits lung cancer bone metastasis (50). Exosome miRNAs derived from hypoxic bone marrow mesenchymal stem cells (BMSCs) also evidenced to promote metastasis of lung cancer cells through epithelial-mesenchymal transition (EMT) induced by signal transducers and activators of transcription 3 (STAT3) (51). MiR-335 via insulin-like growth factor-I

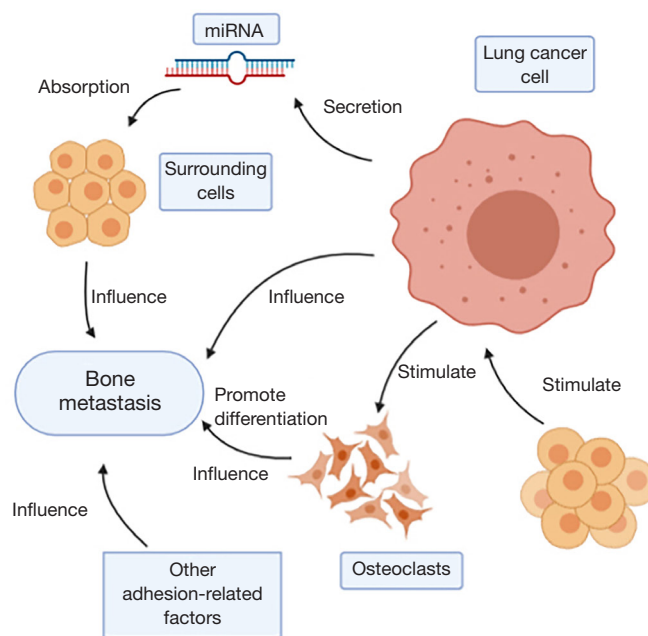


Figure 2 Possible mechanisms.

receptor (IGF-IR) and RANKL pathways inhibited the bone metastases of small cell lung cancer (SCLC) (52). Hsv2-miR-H9-5p is strongly expressed in bone metastasis, which is closely related to the pathology and metastasis of lung cancer (53). Besides, miR-29c is used as a tumor metastasis suppressor, which can directly inhibit the integrin b1 and MMP2 expression, and further reduce the enzyme activity of MMP2, so as to suppress the adhesion of lung cancer cells to extracellular matrix (ECM) and metastasis (54).

Furthermore, DNA is of great significance. For example, by upregulating miR-660-5p and targeted SWItch/Sucrose Non-Fermentable (SWI/SNF) related, matrix associated, actin-dependent regulator of chromatin, subfamily A, member 5 (SMARCA5), Nm23-H1 causes inhibition of bone-specific metastasis (55).

Additionally, mRNA also plays an important role in it. In lung cancer patients, the activation of epidermal growth factor receptor (EGFR) signaling pathway up-regulated angiogenic factors such as VEGF-A and VEGF receptor-1 (VEGFR1) to induce the formation of tumor blood vessels and promote the invasion and metastasis of tumor cells (56). Inversely, down-regulation of *CnaA* gene

expression can reduce the speed of proliferation and colony formation, inhibit the progress of cell cycle, reduce cell migration and invasion, and inhibit cell adhesion to bone matrix (57).

Microenvironment

Microenvironment plays a fateful role in bone metastasis. Plenty of microenvironmental factors participate in the bone metastasis. BMSCs are guided to tumor cells and help to form a cancer microenvironment (58). Besides, mast cells release tryptase, which can promote tumor cell metastasis through the extracellular body (59). The extracellular CUB2 domain of CUB domain-containing protein 1 (CDCP1) also has a function of promoting cancer cell migration through Src family kinases (SFK) activation on the plasma membrane (60). What's more, the immune cells and natural killer cells (NK cells) in microenvironment work through complex reactions (61). Besides, some mechanisms have been shown to be specific to osteolytic or osteogenic metastasis.

The bone marrow microenvironment plays a key role in osteoclast generation. Leptin can induce cancer cells to secrete soluble ICAMs and induce osteoclast-

like cell formation (62). Macrophage colony-stimulating factor (M-CSF) secreted by bone marrow stromal cells or osteoblasts can induce osteoclast generation and differentiation (63). Moreover, the RANKL/RANK pathway may be an important link in mediating osteolytic bone destruction in bone metastasis of lung cancer (64). Thromboxane enhances the production of RANKL dependent osteoclasts and promotes bone metastasis of lung cancer (65).

Parathyroid hormone-related protein (PTHrP) is considered to be one of the main regulatory factors in the process of osteolytic bone metastasis in lung cancer, and lung cancer with positive expression is more likely to develop bone metastasis (66). The PTHrP secreted by lung cancer cells binds to the PTH/ PTHrP receptor on the surface of osteoblasts (67), enhancing the expression of RANKL gene on the surface of osteoblasts and decreasing the synthesis of osteoprotegerin (OPG) (68). RANKL binds to RANK on the surface of the precursor cells of osteoclasts, which facilitates the differentiation and maturation of osteoclasts, enhances osteoclasts activities and results in osteolytic bone destruction (69). Repeated intravenous injection of PTHrP neutralizing antibody significantly inhibited the formation of bone metastases in a dose-dependent manner but had no significant effect on metastasis to the internal organs (lung, liver, kidney, lymph nodes) (70). These results suggest that PTHrP is closely related to osteolytic bone metastasis in lung cancer, but has no significant effect on the metastasis of other organs in lung cancer (71).

Growth factors are also a kind of factor contribute to osteolytic metastasis. During osteolytic bone resorption, a large amount of TGF- β is released from the bone matrix, which can stimulate disseminated tumor cells (DTCs) to produce more PTHrP, and further up-regulate the expression of RANKL on the surface of bone fine cell and bone basal fine cell, thus exacerbating the formation of osteolytic metastasis (72-74). Inflammatory factor IL-1 β may promote the proliferation and migration of lung cancer cells through the COX2-miR-93-Lin28B-let-7 cascade pathway (42).

Furthermore, chemokines also affect bone metastases in the microenvironment. From microarray analysis and validation by a real-time polymerase chain reaction confirmed that CX3C chemokine ligand 1 (CX3CL1) can be a potential chemokine widely involved in spinal metastases (75). Activation of the KRAS signaling pathway promotes the secretion of chemokine ligand 12 (CCL12)

by tumor cells, and the binding of CCL12 to the receptor CXCR4 is conducive to the homing of tumor cells to the target organ (76).

Enzymes participate in the impact of bone metastases as well. Cathepsin A knockout decreases the proliferation and invasion of A549 lung adenocarcinoma cells (77).

Other adhesion-related factors

Any change of adhesion-related factors may affect the bone metastasis of lung cancer. For example, high expression of lumican in lung cancer cells promotes bone metastasis through the autocrine mechanism (78). The expression of HIF-1 α (79) and LIGHT/TNFSF14 (80) are high in advanced NSCLC. The β 3-integrin down-regulated cells significantly reduced cell adhesion, migration and invasion (81). Conversely, BMP7 significantly reduces cellular motility of lung cancer cell line, SK-MES1, and its adhesion to Matrigel. RhBMP7 is also able to significantly reduce the invasion of lung cancer cells (82).

Diagnosis methods

There are many technologies or methods to support the diagnosis. Emission computed tomography (ECT) and positron emission tomography (PET)/computed tomography (CT) are the main methods for screening bone metastases. ECT is currently the screening method of choice for bone metastasis (83). ¹⁸F-FDG PET/CT is most sensitive to osteolytic and bone marrow metastasis and can be used as the first choice for patients with bone metastasis of unknown origin (BMUO) (84,85). X-ray, CT and magnetic resonance imaging (MRI) are common examination methods (86).

Besides all these imaging examinations above, there are some biochemical examinations. The patients with bone metastasis have higher concentrations of cell-free DNA, whose survival outcomes are poorer. So, use of cell-free DNA can provide clinical prognosis management for patients (87). Urinary markers [decrease of circulating tumor DNA (ctDNA) means better overall survival outcome] (88), lactate dehydrogenase values, bone metabolism markers in osteoclasts and osteoblasts, serum level of ALP have the diagnosis significance as well. Apart from that, serological markers like carbohydrate antigen 125 (CA125), carcinoembryonic antigen (CEA), neuron specific enolase (NSE), and squamous cell carcinoma antigen (SCCA) and serum carboxy-terminal telopeptide of

type I collagen (ICTP) (89) are applied for diagnosis of lung cancer bone metastasis.

The pathological examination is the golden standard (90). In general, imaging examination, laboratory examination, and pathological examination are used to diagnose lung cancer metastasis to bone.

Due to the poor prognosis of lung cancer bone metastasis, early diagnosis of bone metastasis is particularly necessary. Recently, the serological molecular model logit (p) has been proven to have the function of early diagnosis and progression monitoring (91).

Current treatment

Surgery

Patients with clinical N0–1 NSCLC with simultaneous bone metastasis may obtain a longer survival rate after primary lung tumor resection. The radically curative-intent surgical resection of the primary lung tumor includes pneumonectomy, systemic decomposition of hilar and mediastinal lymph node dissection (92,93).

Radiotherapy

Radiotherapy has been shown to improve survival in patients with extensive-stage small cell lung cancer (ES-SCLC) with bone metastases, and also significantly decreased the local recurrence rate, especially in patients with only one metastatic site (94,95).

Targeted therapy

Molecular targeted therapy for lung cancer is a new type of biotherapy model that targets the driving genes that may cause cell canceration and blocks tumor signaling pathways at the molecular level, thereby inhibiting tumor cell growth, inducing apoptosis, and even causing it to completely disappear (5). According to the target of drugs, targeting drugs commonly used in lung cancer are shown in *Table 1*.

EGFR-tyrosine kinase inhibitor (TKI) inhibitors

EGFR-TKI can be used as a first-line therapeutic regime option for patients with bone metastases from NSCLC who have a sensitive mutation in the *EGFR* gene, and can prolong the survival of patients (96,97). Osimertinib is recommended for patients who have progressed after EGFR-TKI treatment and are T790M positive (98).

Phosphoinositol 3 kinase (PI3K) inhibitors: buparlisib

Metastasis of NSCLC results in pathological fracture. Sustained signal transduction by PI3K increases the PI3K dependence and the growth potential of osteoclasts, leading to the continuous growth of NSCLC. Buparlisib, a PI3K inhibitor, inhibited osteoclast formation presenting anti-tumor activity, so that targeting PI3K pathway may be a potential therapeutic strategy (99).

Statins as inhibitors: fluvastatin

It is known that long-term use of statins can reduce the risk of various cancers. Statins can directly inhibit osteoclastogenesis and the proliferation of cancer cells by blocking the post-translational modifications of RhoA and Ras (100). Statins such as fluvastatin have been reported to inhibit tumor progression and greatly reduce the ability of tumor cells to migrate and invade. In addition, fluvastatin induces p53 which activate autophagy of cancer cells. The induction of autophagy can exert an anti-cancer effect in an immune-dependent or independent manner (101).

Denosumab

Denosumab is a monoclonal antibody against RANK ligand specifically, which can significantly improve the survival rate without bone metastasis, and has the best therapeutic effect on advanced high-risk population (102). Denosumab does not require kidney monitoring or dose adjustment, because of the convenience of it with subcutaneous drug delivery (103,104).

Cabozantinib

Cabozantinib is a multi-target, small-molecule inhibitor of MET and VEGFR2 that can be taken orally (105). Cabozantinib's clinical activity is manifested in the introduction of bone cell blockage and osteolytic lesions into the process to reduce soft tissue lesions, improve progression-free survival (PFS), reduce the resolution of bone scan and reduce bone turnover markers (106).

Latest progress

The matricellular glycoprotein thrombospondin (TSP-2) promotes osteoclastogenesis through RANKL pathway and changes the RANKL:OPG ratio in differentiation of osteoblasts. It has been proved that TSP-2 gene knockout inhibits osteolytic metastasis of lung cancer *in vivo* so it may be the possible target for treatment in the future (65).

Ribosomal protein lateral stalk subunit P2 (RPLP2), enolase 1 (ENO1) and NME/NM23 nucleoside diphosphate

Table 1 Targeting drugs commonly used in lung cancer

Experimental drugs	Year	Experiment name
EGFR-TKI	2008	Efficacy of EGFR-TKI
PI3K inhibitors: buparlisib	2019	The effects of a PI3K inhibitor on NSCLC growth in bone and osteoclast formation
Statins as inhibitors: fluvastatin	2017	p53 in both fluvastatin-induced autophagy and suppression of lung adenocarcinoma bone metastasis
Denosumab	2012	The phase 3 trial of denosumab versus zoledronic acid (ZA) in the treatment of bone metastases from solid tumors (except breast or prostate) or multiple myeloma
Cabozantinib	2013	Cabozantinib in patients with advanced prostate cancer: results of a phase II randomized discontinuation trial

EGFR, epidermal growth factor receptor; TKI, tyrosine kinase inhibitor.

kinase 2 (NME1-NME2) express high in bone metastasis patients with poor prognosis. They are also identified as therapeutic targets for bone metastasis in lung cancer (107).

Tumor-microenvironment in lung cancer-metastasis also works and provides some drug targets. For instance, tests in rat models found that reduced L1CAM-expression to has relations with the lower rate of bone metastasis. This represents a potentially targetable regulating factor.

Bisphosphonate

Some bisphosphonates have direct anti-tumor effects and can be used in combination with conventional anti-tumor therapy to treat bone metastases from lung cancer, which can reduce skeletal related events (SREs), improve pain control, and show a trend of increased survival (5,108). Nitrogen-containing bisphosphonates can delay the growth of bone tumors by inhibiting bone destruction mediated by osteoclasts and preventing the release of cytokines and growth factors that destroy bones. It can also inhibit the function of tumor cells by inhibiting farnesyl diphosphate synthases (FPPS), such as the adhesion, migration, invasion, and proliferation of tumor cells and the adhesion of bone matrix, thus induces apoptosis of tumor cells (109). One of the most well-known bisphosphonate drugs is zoledronic acid. Its treatment is well tolerated, significantly reducing the incidence of bone-related events and increasing the time for the first occurrence of bone-related events (110).

Radiation therapy

Radiation therapy is one of the effective methods to treat bone metastasis of lung cancer, including external radiation therapy and radionuclide therapy. Through

this treatment, a series of symptoms can be alleviated or eliminated, pathologic fractures can be alleviated, spinal cord compression can be reduced, quality of life can be improved, and survival period can be extended (5).

Chemotherapy

Chemotherapy is widely used in the therapy of bone metastases in lung cancer, where cancer drugs are used to ease the pain. But the general anti-tumor chemotherapeutic drugs have some side effects, such as toxic reaction, bone marrow suppression and so on. Therefore, anti-tumor chemotherapeutic drugs should be carefully selected in the clinical application (111). For example, paclitaxel and kanglaite are common anticancer drugs in cancer chemotherapy. Paclitaxel has reliable anticancer activity. Kanglaite, an effective component extracted from semen coicis, can inhibit cancer cell growth and improve the patient's immune capacity. Paclitaxel and kanglaite are commonly used in chemotherapy for bone metastasis of lung cancer. In accordance with research, paclitaxel combined with kanglaite is more effective than paclitaxel or kanglaite alone in improving bone metastasis of lung cancer, which is of great help in the clinical treatment (111).

In summary, surgery, radiotherapy, targeted therapy, bisphosphonate and chemotherapy are the current treatment methods. They can be used alone or in combination.

Methods

When it comes to research selection, literature search was applied in PubMed (112). MedLine, PreMedline and other electronic publications were included. Considering the timeliness of the literature, most of the cited references are

within 3 years. They were all English literature. We chose “lung cancer”, “bone metastasis” and so on as keywords to search for the appropriate references for this review.

Summary

After tumor invasion, tumor cell migration and invasion in bone tissue, lung cancer finishes the process of bone metastasis. This process is a combined action of genetic factors, microenvironment and other adhesion related factors. We can diagnose it by many technologies, mainly imaging examinations, biochemical examinations and pathological examination, which is the golden standard. Surgery, radiotherapy, targeted therapy and bisphosphonate are the current treatment.

Because the review quoted the latest literature, we may have neglected to describe the results of earlier studies on bone metastases in lung cancer. Moreover, our review may not be the whole literature collection. But it is still a detailed review from the aspect of process, mechanism, diagnosis methods and current treatment in lung cancer metastasis.

However, lots of issues remain the focus of future research. Bone metastasis of lung cancer involves a wide range of mechanisms and any change in any step may accelerate tumor metastasis. What's more, the osteoblastic metastasis of lung cancer is rare, so whether it exists remains to be confirmed. SRE is also a problem related to tumor metastasis. Though we choose bisphosphonate to prevent it, its value in fracture prevention is uncertain at present. Other drugs like denosumab, a monoclonal antibody targeting RANKL (113), also have side effects on bone destruction like medication-related osteonecrosis of the jaw (MRONJ) (114). Enzalutamide was proved to significantly delay the first-time SREs in patients with metastatic castrated prostate cancer who received chemotherapy (115) but the effect has not been confirmed in lung cancer yet. Evidence shows that radiotherapy combined with zoledronate can reduce SREs in renal cell carcinoma (116). Drugs for SREs mentioned above mainly target on osteoclasts, increasing the probability of osteoporosis and fractures. Other treatments have no good therapeutic effect on fracture as well. Fractures caused by drugs for SREs in lung cancer is one of the problems remain to be solved in bone metastasis of lung cancer. This is also what our team will focus on in the future.

Therefore, this review summarized the current situation in bone metastasis of lung cancer to provide new direction

for future treatment.

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Footnote

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Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. This research was approved by the Ethics Committee of the Shanghai Pulmonary Hospital, Tongji University.

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