RESEARCH ARTICLE

Bone metastases in lung cancer

Authors
Bocchi MB[1,2] , Cianni L[1,2] , Greco T[1,2] , Maccauro G[1,2] , Perisano C[1]

Affiliations
[1]Division of Orthopaedics and Traumatology, Department of Aging, Neurological, Orthopaedic and Head-Neck Studies, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, 00168, Rome, Italy.
[2] Università Cattolica del Sacro Cuore, Largo Francesco Vito 1, 00168, Rome, Italy.

Correspondnce
Perisano Carlo, MD
Email: carlo.perisano@policlinicogemelli.it

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Abstract
As lung cancer is the most common neoplasm worldwide, bone is one of the most metastatic sites of advanced malignant tumors in general. Nearly 50% of patients with advanced lung cancer develop bone metastases. A literature review on this matter was performed.
As in recent years the life expectancy of patients with lung cancer increased, symptoms control measures are gaining importance. The early detection of bone metastases is crucial due to prevent skeletal-related events (SREs). The bone metastases management should be discussed in a multidisciplinary setting given the numerous therapeutic options. Treatment is either pharmacological (analgesics, diphosphonates, monoclonal antibodies), non-pharmacological (radiotherapy, interventional radiological techniques, surgery) or even a combination of both. Orthopedic surgery shall be assessed in case of pathological/impending fractures. The orthopedic surgeon challenge is indeed to detect those patients who will take advantage from surgery given the substantial risk of complications. Treatment goal should be to obtain SREs prevention and control to guarantee patients a decent QoL. Unfortunately, bone metastases in lung cancer are still poor prognosis indicator.

Key Words: lung cancer, NSCLC, bone metastases, BM, skeletal-related events, SREs, pathological fracture, impending fracture, pain, pain control, hypercalcemia, spinal cord compression, SCC, Denosumab, Bisphosphonates, Zoledronate, radiotherapy, RT, prosthetic reconstruction, megaprosthesis, intramedullary nailing, PMMA, cementoplasty, vertebroplasty, kyphoplasty.

1. Background

According to GLOBOCAN estimates, 2.2 million are the new diagnoses of lung cancer in 2020 worldwide, 14.3% and 8.4% of all new 2020 cancer diagnosis among men and women respectively. [1] Lung cancer remains a major cause of deaths in industrialized countries, the estimated number of deaths in 2020 worldwide is 1.7 million,[1] while in Europe still represent the leading cause of cancer deaths in males and the second for women, accounting for 24.2% in males and 14.6% in females, respectively.[2]

Lung cancer is a heterogeneous disease comprising several subtypes with pathologic and clinical relevance: non-small cell lung cancer (NSCLC) accounts for 85% of lung cancers, while small cell lung cancer (SCLC) (15%) has been decreasing in frequency over the past two decades.[3]

Tobacco smoking remains the main cause of lung cancer. [4–9]

Despite advances in early detection and standard treatment, the survival is adversely affected from the fact that it goes undiagnosed until advanced stages, with an overall 5-year survival rate of 10% to 15%,[10] in fact nearly 40% of lung cancer new diagnosis are already at advanced stages and have metastases. The diagnostic evaluation of patients with suspected lung cancer includes histological diagnosis, a complete staging work-up including evaluation of metastases and last but not least the functional patient evaluation.

Changes in the therapeutic scenario in the last 20 years have emphasized the need of a multidisciplinary approach in lung cancer.

In the last decades the introduction of platinum-based chemotherapy,[11] of third-generation cytotoxic drugs (such as gemcitabine, vinorelbine, docetaxel and pemetrexed), of monoclonal antibodies (such as Bevacizumab), and of novel targeted therapies has radically modified the treatment of advanced NSCLC.[12–20] Consequently, median overall survival for patients with advanced lung cancer has increased from approximately 6 months to 12 months, and is longer for patients with driver mutations treated with targeted therapies. As the life expectancy of individuals with lung cancer increases, symptoms control measures become crucial. Therefore, an increased awareness concerning bone metastases and the need for their early management in order to prevent potentially debilitating skeletal complications is required.

The aim of this Literature review is to assess clinical features and treatment options of bone metastases in NSCLC.

2.Epidemiology

Bone is one of the most metastatic sites of advanced malignant tumors in general; NSCLC is the third most common cause of bone metastases following breast and prostate cancer.

Bone metastases (BM) occur in 30%-40% of patients with NSCLC during the disease course[21] and the primary tumor histology and the disease advanced stages represent the major risk factors.[22]

Metastases evident at post-mortem in up to 36% of patients have been observed and bone marrow micrometastases[23] have been found in 22%–60% of individuals.[24]

3.Mechanism of metastases

Three mechanisms have been described by which a cancer can disseminate in the body: direct seeding of body cavities or surfaces, through lymphatic spread and finally haematogenous spread.[25] The most important dissemination method to bone is via the circulatory system, in particular the venous system. Lungs for example drain their blood through pulmonary veins to the left side of the heart, which can therefore disseminate lung cancer cells to all parts of the

body. Certain cancers show an organ-specific pattern of spread. In order to explain this propensity of some tumors to metastasize to specific organs, Paget in 1889 described the 'seed and soil' hypothesis.[26] Paget suggested that secondary growth spread does not happen by chance, but exists a relation between cancer cells (referred to as 'seed') and host cells (referred to as 'soil') which would explain why some tumors metastasize to specific organs.[27] It is shown in fact that lung cancer cells find a favorable soil in the bone microenvironment due to the wealth of growth factors and cytokines released by the bone matrix and the resident immune system cells.[28]

In particular the lung tumor cells migrating via the blood circulation proliferate mainly in the bones of the trunk which are rich in red bone marrow, rather than in the bones of limbs which are rich in yellow bone marrow.

4.Clinical presentation

Bone metastases in NSCLC are more frequently multiple and osteolytic, determining brittle bones and affecting any segment of the skeleton, mainly the chest (65%) followed by the spine (43%), the pelvis (25%), long bones (27%) and the skull (16%).

Lung cancer is also the most common primary cancer to give rise to acrometastases, which are extremely rare metastases located distal to the elbow and knee.[29–31]

They determine major complications such as severe bone pain, pathological fractures, bone instability, spinal cord compression (SCC) and hypercalcemia known as skeletal-related events (SREs) responsible for significant morbidity that severely alter the patient's quality of life (QoL) and performance status (PS) from the earliest times.[32,33]

SREs indeed have a huge medico-economic impact requiring frequent hospitalization and outpatient visits.[34,35]

4.1 Pain

Clinical data showed that pain is the most observed symptom, affecting most of the patients at the moment of BM diagnosis, and almost all patients during the clinical course of the disease.[36]

In fact, as described by Berruti A. et al. overall patients with lung cancer BM are united by a significant painful symptomatology considerably more often than patients with breast and prostate cancer.[37] However one out of four patients experiencing BM has no symptoms, thus in such cases making the early diagnosis and therefore the early treatment is even more a difficult challenge.

4.2 Pathological fractures

Metastatic lesions affect the strength of bone reducing stress transmission and the ability to absorb energy.[38–40] A pathological fracture is a fracture that develops through an area of bone affected, however when the pathologic bone extension is such that a fracture is imminent but not complete is defined as impending fracture. Proximal long bones are involved more commonly than distal bones; consequently, 50% of pathologic fractures occur in the femur and 15% occur in the humerus. Pathological fractures usually occur 5 months after a diagnosis of BMs and the median overall survival time after the first event in lung cancer is 5 months.[41] These represent a serious complication in cancer patients by reducing dramatically the patient's QoL and their prognosis. This is the reason why the early detection of BM at risk of impending fracture could allow prophylactic fixation which is preferable due to shorter operative time, decreased morbidity and quicker recovery.

4.3 Spinal Cord Compression

Vertebral fractures produce neck and back pain, with or without neurological complications secondary to the epidural extension.[42] Motor dysfunction is the second most commonly found clinical manifestation in patients with spinal metastasis,[43] affecting 35-75% of patients.[44] This happens as the result of direct compression of nerves and nerve roots by tumor or fragments of bones resulting from pathological fracture,[45] causing myelopathy, radiculopathy or sometimes a combination of both, which clinically manifests itself as a weakness of muscles. Metastatic spinal cord compression (MSCC) is the most serious complication that can occur in patients with spinal metastasis, defined as compression of the dural sac and its contents (spinal cord and/or cauda equina) by an extradural tumor mass.[46]

4.4 Hypercalcemia

Because of the osseous metabolism alteration caused by the metastases presence, the calcium contained in the bones structure is released into the bloodstream determining high serum level.

Lung-cancer-associated hypercalcemia shows low incidence rate but poor prognosis[47] with approximately 50% of mortality within 30 days.[48]

5. Diagnosis

Bone metastases management should be by a multidisciplinary approach in order to aim for an early detection in view of the various therapeutic options thus increasing the patient's survival rate.[49]

The systematic detection of bone metastases should be included in the initial staging of lung cancer in order to begin their management at an early stage and thus improve the prognosis.

Conventional projectional radiography still plays an important role in the diagnostic evaluation of bone metastases.[50] Lung cancer BM are typically osteolytic, however, osteolytic changes can be seen on plain films only if 50% or more of the bone substance has been destroyed.[51,52] The diagnostic utility of plain films of the skull, spine, and pelvis is limited by superposition effects due to the low sensitivity (approximately 44–50%),[51] therefore they're not suitable for use as a screening test. Nevertheless classic radiograms in two planes still play an important role in the study of bone pain and impending/pathological fractures.[53]

Multislice spiral Computed Tomography (CT) allows for imaging of the skeleton in toto without superposition effects and is thus more suitable than radiographs for metastases even in anatomically difficult areas detection, such as the thoracic spine.[50] Furthermore CT is used to assess the stability of bony structures affected by BM in order to obtain better structural definition of abnormal findings seen on scintigraphy or MRI. However, despite its high specificity (95% according to Yang et al.)[54] and sensitivity for osteolytic bone lesions involving the cortical, CT is of limited use as a screening test for BM because of its low capacity in detecting lesions restricted to the marrow space.[55] For most types of cancer, CT is still the modality of choice for staging in the chest and abdomen and for serial follow-up imaging.

Skeletal scintigraphy with labeled phosphonates enables visualization of local bone metabolism (turnover), which is activated in an early phase of some types of cancer. The latter has a relatively low sensitivity for tumors that cause a reactive osteolysis or isolated bone-marrow infiltration such as lung cancer.[56]

Magnetic resonance imaging (MRI), with its high soft tissue contrast and high spatial resolution, reveals metastases in the bone marrow spaces precociously, before any changes in internal bone structure that could be detected by CT arise. MRI

may complement or improve the diagnostic staging accuracy, particularly in assessing vertebral invasion and is also effective for identification of distant soft tissue secondarisms.[57,58]

Since 2003, the hybrid PET/CT using ^{18}F-FDG as tracer has emerged as the most important cross-sectional imaging modality for whole-body staging of patients with non–small cell lung cancer (NSCLC).[59–62] Thus ^{18}F-FDG PET/CT assumes a prominent role in the presurgical evaluation for metastatic disease for its higher diagnostic value (sensitivity and specificity) than any other imaging methods.[53,63]

6.Treatment

The BM treatment aims to pain relief, mobility and function preservation, prevention of future complications, skeletal integrity maintenance and to reduce hospitalization due to optimize the quality of life (QoL) of these oncological patients.

By definition, all patients with lung cancer and BM have a poor prognosis, the median survival rate hovers around 6-7 months, therefore they are intended mostly for palliative treatments.[62]

The majority of metastatic bone disease can be managed adequately with nonoperative modalities including the systemic approach and radiotherapy (RT).

6.1 The systemic approach

The systemic approach to BM includes analgesic drugs and bone targeting agents (BTA), among which anti-resorptive drugs represent the mainstay of BM management.

Treatment of BM should take into consideration the use of analgesic drugs at any stage of disease;[64] however the aim of pain control with analgesics is to reduce pain quickly, not to prevent SREs. The WHO recommends a three-step analgesic ladder approach based on pain intensity including non-steroidal anti-inflammatory drugs (NSAIDs), paracetamol, and opioids, alone or in combination.[65–67] The drugs choice should be individualized and directed at relieving pain, improving QoL and increasing the patients functioning.

BTA are considered as a treatment option in patients with lung cancer and BM with a life expectancy over three months at least either to reduce the chances of SREs and to improve pain control especially in case of multiple skeletal metastases.

Several agents belong to this latter category including Bisphosphonates and Denosumab.[68] This latter interacts with RANK-L, thus interfering with its binding to RANK on osteoclasts; Bisphosphonates instead directly act on osteoclasts, compromising their survival and consequently their bone-resorbing activity.[69] Moreover, Bisphosphonates have been shown to exert also a direct anti-tumor activity (in vitro and in vivo), and to stimulate an anti-cancer immune response.[68] Zoledronate in particular is proven to be the most effective in reducing serum calcium levels in patients with hypercalcemia, which is a serious and potentially life-threatening complication of lytic BM.[70]

Denosumab is as effective as the most widely used bisphosphonate in reducing the frequency of SREs in patients with lung cancer.[71] Therefore, Denosumab may be more compatible than Zoledronate for combination with first-line chemotherapy for lung cancer because dose adjustment for impaired renal function is not required.[72]

6.2 Radiotherapy

Radiotherapy (RT) is performed primarily to relieve pain, to take a bone affected from metastases under control and to prevent SREs such as pathologic fractures as well as spinal cord compression. Radioisotopes are a valid option in

case of more diffuse bone pain that is not eligible for palliative RT.[73] Treatment decisions regarding palliative external beam radiotherapy (EBRT) for BM should be based on individualized considerations of symptom burden, extent of disease, life expectancy, comorbidities, toxicity, prior treatment and patient wishes.[74,75]

The benefits of RT on bone pain are mainly related to its capability to induce ossification.[76] Moreover ionizing radiations are capable of osteoclasts activation downregulation and killing tumor cells thus ensuring a reduction in tumor volume preserving the discomfort to nearby nerves.[77]

About half of all patients with final stages NSCLC receive at least one course of palliative EBRT within 15 months of diagnosis.[76]

During RT the ossification of lytic BM begins 3–6 weeks after completing treatment, reaching its zenith within 6 months [80] and pain relief generally is achieved approximately in half of cases.[73] Beneficial effects on pain may necessitate several days to a few weeks, so analgesic medication must be optimized during that interval.[78]

The optimal fractionation schedule is still an unresolved issue. From a common sense perspective, the shortest RT regimen which maximizes outcomes in an evidence-based manner seems preferable for the treatment of symptomatic and uncomplicated bone metastases.[78–80] Therefore re-irradiation of the same anatomical site may be considered in case of inadequate pain relief, or to manage pain relapse after initial clinical benefit.

Metastatic SCC, which is considered a medical emergency, needs a prompt and aggressive treatment approach to preserve neurologic function and to early improve the patient's QoL.

Nowadays, evidence suggests that direct decompressive surgery plus postoperative RT seems to be superior to RT alone for spinal cord compression.[81] In those patients unfit for surgery instead, RT alone is the recommended treatment. Considering the limited expected survival in most of these patients and the fragile clinical situation, a shorter treatment program is highly desirable as shown by George R et al.[82]

Although data are few, a multiple fractionated treatment should be considered in those patients with impending fractures, in order to guarantee a tumor down-staging prior to surgical approach.[73]

Due to short life expectancy of metastatic lung cancer patients, acute toxicity is much more clinically relevant than late complications.[83]

6.3 Surgery

Orthopedic surgery shall be assessed in case of pathological/impending fractures to stabilize high-risk lesions due to preserve patient independence and quality of life.[84,85] The orthopaedic surgeon challenge is indeed to detect those patients who will take advantage from surgery given the substantial risk of complications.[86–89] Mirels proposed a scoring system based on four cancer characteristics: site of lesion, nature of lesion, size of lesion and pain. The overall score gives a recommendation for or against prophylactic fixation.[90,91]

The surgical approach to a patient affected by limb metastasis depends on several factors, firstly the expected survival of the patient is taken into consideration when choosing the type of surgical treatment for bone metastases of the limbs. In addition, further biological and functional issues to consider are: the presence of a single-lesion, the anatomical position (metaphysis or diaphysis), the bone mechanical strength (presence of impending/pathological fracture) and the lesion susceptibility to non-surgical therapies.[92]

The anatomical site of the lesion remains among the most influential factors in the surgical choice

according to the international guidelines.[93] However, there is no evenness about treating even among musculoskeletal oncological surgeons as evidence of how often the treatment choice is the assurance of multiple factors.[94]

The surgical approaches to the long bones could involve:

- Prosthetic reconstruction that should be preferable for pathological fractures or lesions at risk of fracture in the metaphysis and epiphysis of a long bone, especially the proximal femur and humerus.[95,96] This technique consists in surgical wide resection and replacement with arthroplasty implants; it is considered appropriate when the patient's life expectation exceeds 6–12 months.[97–99] The implant stem should be cemented considering these are often irradiated bones.[93] In case of large bone defects, megaprosthesis allows to replace skeletal segments such as the long bones of the upper and lower limbs and the relative joint. These latter allow a prompt recovery with lower risk of reoperation due to the implant failure or the disease progression.
- Intramedullary nailing should be considered in case of diaphyseal lesions of the long bones, in patients with good prognosis and poor expected response to adjuvant therapies. A nail reinforced with cement (polymethylmethacrylate, PMMA) with intralesional curettage could be an option in selected cases. Filling the cavity with PMMA has been proven to improve the mechanical strength of the system so as to obtain an additional adjuvant effect on the tumor cells.[100] The nail must always be as long as possible and locked.[101] Although conventional metal nails remain the gold standard for most long bone fixations, in the last few years Carbon-fiber-reinforced Polyetheretherketone (CFR-PEEK) nails are gaining interest because of their superior mechanical toughness and compatibility with radiotherapy and postoperative advanced imaging at the expanse of high cost.[102]
- Plate fixation with PMMA after resection and/or curettage is recommended in forearm lesions and in case of metastases of the metaepyphisis at the knee and distal humerus and tibia with extension of less than 50%.

Surgical approach to pelvic bone metastases could commence with a minimally invasive palliative treatment until wide resection and reconstruction with allograft or mega prosthesis.[103] The surgical technique decision is made mainly upon the lesion spread, the tumor response to adjuvant treatment and the patient's life expectancy.

Special attention has to be directed to osteolytic lesions in the periacetabular region as they can provoke pathological fractures and subsequent functional impairment.[104]

It is possible to rehire as follow:

- Cementoplasty is a minimally invasive technique consisting in percutaneously methylmethacrylate injection into the osteolytic lesion; should be considered in patients with a short life expectancy.[105,106]
- Harrington's procedure is an open technique in patients with larger defects , longer life expectancy, clinically eligible for major surgery; it consists of an intralesional curettage and PMMA filling and finally K-wires reinforcing.[107]
- Wide resection of the lesion with prosthetic reconstruction a suitable option for patients in which the tumor has infiltrated both anterior and posterior columns.[108,109] The periacetabular region can be replaced by custom-made or modular megaprosthesis, saddle prosthesis, or massive allograft in

combination with a total hip replacement. Non weight-bearing zones do not require any reconstruction following the tumor resection because the ambulation capability is still preserved.

In spinal metastases, the leading treatment goals are the maintenance or either the improvement in neurologic function and ambulation, the spinal stability, a durable tumor control and pain relief.[110–112] Current indications for surgery are radioresistant tumors, evidence of neurological function deterioration or tumor progression despite radiotherapy, radiological images showing fragments of bone in the spinal canal, spine instability due to fracture causing pain and neurological deficit, neurological deficit for >24 hours, or significant metastatic SCC and finally life expectancy of at least 3 months.[113]

Percutaneous vertebroplasty and kyphoplasty are considered the leading treatment for painful pathological fractures caused by metastatic spinal disease.[114] Vertebroplasty is a less invasive surgical treatment consisting in polymethylmethacrylate (PMMA) injection into the lesion whereas in kyphoplasty an inflatable balloon is placed in the vertebral body and to follow PMMA is injected.[115,116] The performance of a lesion biopsy prior to PMMA injection remains a fundamental step in both procedures.[117] In Hirabayashi et al. experience, pain relief was attained by 77% of patients overall and 70% of patients were able to walk after surgery showing a favorable outcome after surgery.[118]

The role for surgical palliative posterior stabilization remains consistent, although aiming at less aggressive and minimally invasive techniques. Minimization of surgical stress has been obtained using minimally invasive spine stabilization with percutaneous pedicle screws.[119,120]

Furthermore recent studies pointed out that minimally invasive spine stabilization without decompression is advantageous in many cases because of the shorter operation time, the less blood loss, a higher rate of discharge to home, and lower in-hospital mortality, indicating a procedure with lower invasiveness.[121]

The recent introduction of stereotactic radiosurgery into this field has been particularly transformative, offering precise delivery of tumoricidal radiation doses with sparing of adjacent tissues, it offers durable local tumor control with low complication rates.[122]

In patients with BM unsuitable to surgery, the minimally invasive therapies such as thermoablation with radio frequency or microwaves, cryoablation, alcoholization, embolization and electrochemotherapy may be used to contribute to pain control for lesions nonresponding to nonsurgical therapies.[123] These methods were initially developed for the treatment of benign lesions, but they have also proven their effectiveness in controlling the painful symptoms of metastatic bone disease. All of these methods have similar contraindication: the proximity (<1 cm) of the lesion to be treated to nerves, vascular or visceral structures.[47,124,125]

6.3.1 Postoperative Complications

Postoperative complications are more frequent in oncological patients who are usually debilitated, malnourished, and who have metabolic and/o hematological disorders.[126–128] Surgery site complications and general complications occur respectively in 9.4% and 11% of cases according to Bonevialle P. et al. experience.[129] In particular, patients affected by metastatic lung cancer have a median survival after surgery of about 3 months (95% , 2-5 months).[129]

Concerning surgical complications, hemorrhage is the most common, probably due to the tumor hypervascularity and the systemic effects of chemotherapy and radiotherapy.[130,131] Implant failure and superficial and deep infections are

also rather frequent complicating approximately 20% of the procedures.[95,131–133] Silver-coated prostheses may represent a valid option in limb salvage surgery after pathological fractures being intrinsically a protective factor mainly against early infections.[134–136]

However, patients with severely impaired walking capacity greatly benefited from surgery thereby improving their QoL.[129]

7. Prognosis

Lung cancer patient's survival has been prolonged by advances in healthcare technology. However, this has meant that the risk of bone metastases increases.[137] Regrettably bone metastases in lung cancer are still a poor prognosis predictor.[138]

Recent studies have shown that the isotype, the number of bone metastases, the clinical stage and the patient's performance status can be considered prognostic factors in patients with metastatic lung cancer and are directly proportional to survival rate.[139–142] From the analysis of a population-based cohort study about the distribution of bone metastases by cancers, it was found that while for breast and prostate cancer the proportion developing bone metastasis is rather stable over time, for lung cancer instead there seems to be a slight increase in proportion over time.[143] Furthermore the 1-year survival rate after bone metastases was lowest in patients with lung cancer (10%) and highest in patients with breast cancer (51%).[143] Three-year survival ranged from 2% for lung cancer, 12% and 25% for prostate and breast cancer respectively.[143] At the 5-years follow-up, only patients with breast cancer among all solid tumors had over 10% survival.[143] In addition bone metastases occurrence from primary cancer diagnoses ranged from close to 1 year for lung cancer (279–295 days) to several years for other solid tumors.[143]

All these latter data strengthen the idea that patients affected by metastatic lung cancer have indeed a poor prognosis. Therefore, to predict the individual survival prognosis may be useful to plan and achieve the best possible personalized treatment for each patient with bone metastases in lung cancer.

8. Conclusions

Bone metastases in patients with NSCLC are not a rare affair. Thus, a multidisciplinary approach with the involvement of various professional figures in order to guarantee the patient a linear course of treatment is needed. The early detection of BM is crucial in view of the various therapeutic options including systemic therapy, radiotherapy and the surgical approach, often combined. The lesion feature and the general condition of the patients are crucial to determine the operability and the therapeutic approach to the patient with lung cancer and BM. Treatment goal should be to obtain SREs prevention and control to guarantee patients a better QoL. Regrettably bone metastases in lung cancer indicates poor prognosis.

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