Chapter 3

Recent Advances in the Diagnosis of Bone Metastasis from Lung Cancer

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Abstract

Lung cancer is the most common cause of death due to cancer, and the bones are one of the most common sites of metastasis. Bone metastases from lung cancer can result in skeletal-related events, reduced quality of life, and low survival rates. Therefore, its accurate and timely diagnosis will enable immediate treatment, which is essential for patients with lung carcinoma.

Introduction

Lung cancer is the main cause of death by malignancies worldwide [1]. Lung cancer is also one of the three most prevalent malignant neoplasms, second only to prostate cancer in men, and breast cancer in women [2]. Despite increased investment in research for novel treatments, mortality remains high, and the cure rate is approximately 15% [3].

Increased occurrence, difficulties in diagnosis, and the large potential for dissemination contribute to the dis-

ease's status as the main cause of death by neoplasms [4]. Patients are usually diagnosed at a stage when therapy is no longer possible, and the disease is locally advanced or widely disseminated. The bones are one of the predominant sites of metastasis, and contribute to the high morbidity, reducing patients' quality of life[3,5-7].

Epidemiology

Approximately 40% patients with non-small-cell carcinoma develop bone metastasis during the disease[6,8]. Studies comparing frequencies of non-small-cell carcinoma metastasis sites present an elevated frequency of bone dissemination (20-40%), which is comparable with liver (25-30%) and contralateral pulmonary metastases (40-50%)[9-12].

The histology of lung carcinoma is directly related to the risk of developing bone metastasis [3]. A recent study conducted by Oliveira et al. revealed a higher frequency of bone metastasis for adenocarcinoma (35.3%) and small-cell-carcinoma (31.2%), whilst squamous-cell and large-cell-carcinoma had lower occurrence rates (14.7% and 18,1%, respectively). These frequencies are related to a higher or lower risk of developing bone metastasis by adenocarcinoma and squamous-cell-carcinoma, respectively [3]. These results suggest that an adenocarcinoma diagnosis indicates a higher probability for patients with lung carcinoma developing bone metastasis, which justifies the recommendation of screening methods that enable early

detection and treatment, with direct benefits for patients' quality of life and possibility of increased survival.

Diagnosis

Time of Bone Metastasis Diagnosis

Bone metastasis may be diagnosed before, during, or subsequent to lung cancer diagnosis [3]. However, lung cancer is usually detected in the advanced stages, as symptoms during the early stages are uncommon [6]. Numerous studies have reported the manifestation of bone metastasis in initially unknown primary sites [13]. In general, it is considered that dissemination is indicative of an advanced stage as it occurs during the later stages of the disease, after the identification of the primary tumour. However, our clinical experience and scientific research have shown contradictory results.

Recent studies have indicated that the majority of patients with lung cancer presented with bone metastasis, during primary tumour diagnosis[3,8,10,14]. A large number of patients with bone metastasis identified at the same time of the primary tumour diagnosis (synchronous metastasis) were observed in studies by Sugiura et al., Tsuya site of et al.,Kosteva and Langer, and Oliveira et al.(46%, 65.7%, 66%, and 71.6%, respectively)[3,8,10,14].

Lung cancer is the most frequent cause of metastasis from a carcinoma of unknown primary, due to the high

frequency of advanced bone dissemination[15-17]. Shimada divided patients who developed bone metastasis into two groups: 1) existence of the primary tumour was apparent before bone metastasis was diagnosed (84 patients); 2) primary tumour had not been identified (61 patients).In the first group, the breast was the most frequent site of the primary tumour, followed by the lungs (13%), while the lungs were the most frequent site in the second group (38%)[17]. These results corroborate previous observations indicating that breast and prostate cancers are the most common cause of bone metastasis in patients with known cancer history. However, the lungs must be considered as the most probable primary site in whom a primary tumour has not previously been identified, and thus must be included in imaging investigations. Depth of lung cancer sites which hinders access during physical examinations and the lack of symptoms make patients to delay search for medical assistance. There is also a disseminating tendency of malignant lung cells even when the primary tumour is very small.

A large French prospective study revealed that 58% of lung cancer cases are initially diagnosed during stage IV[18]. The hypothesis that primary tumours simultaneously progress with metastasis has been widely reported[19]. Recent studies indicate that lung cancer bone dissemination is an advanced event that is not related to the size of the primary tumour[19-20]. Deberne et al. evaluated 55 patients diagnosed with bone metastasis at the time of lung cancer diagnosis. The majority of these patients (71%) presented withTx, T1, or T2 tumours, and N0 or N1 lymph node involvement, which reveals that bone metastasis represent an advanced dissemination, which is not related to tumour volume[20]. In the series reported by Sugiura et al., the majority of bone metastasis cases occurred up to 6 months after primary tumour diagnosis[8]. Sathiakumarreported a median of 5.4 months between malignant neoplasm and bone metastasis diagnoses among patients without bone metastasis during the initial stages of the disease[21].

Location

The spine has been identified as the most common site for bone metastasis in general carcinomas, including lung carcinoma[3,13,17,22-23]. Bone dissemination most frequently occurs through the axial skeleton (60% cases), pelvis, and proximal extremity of the femur.

A systematic review by Kuchuket al. revealed that the spine is the most frequent site for bone metastasis in patients with lung cancer (40-50%), followed by the ribs (20-27%) and pelvis (17-22%)[7-9,12]. The vertebral venous plexus, as described by Batson, is part of the axial dissemination mechanism involved in bone metastasis[24]. Batson hypothesized that bone metastasis arising from lung cancer is more frequent in the axial skeleton during more advanced stages than in the appendicular skeleton,

because of the presence of a non-valvular paravertebral venous system that links the lungs and the vertebrae[24].

The most frequently affected spinal site by metastasis is controversial. Deberne et al. observed that the thoracic spine (63%) was more frequently affected than the lumbar spine (33%)[20]. By contrast, Singh et al. and Oliveira et al. found that the thoracolumbar region was the most frequent site for skeletal metastasis arising from lung can

A peculiar characteristic associated with primary lung tumours is the possibility of distal dissemination to the elbows and knees, including the hands and feet. This probably occurs because of the capability of lung cancer cells also disseminating directly to the arterial circulation[19]. The metastasis of carcinomas located distal to the knees and elbows is rare[26]. However, its occurrence is most commonly reported in cases of tumours originating in thelungs[3].

Clinical Manifestations and Skeletal-Related Events

Pain is the most common symptom caused by bone metastasis, and frequently precedes the respiratory manifestations of lung cancer. Therefore, orthopaedists are often the first physicians sought by patients, and are occasionally accountable for investigating and diagnosing neoplasms.

In addition to pain, bone metastasis causes functional limitations and heightens the risk of pathological fracture, depending on the size and location. Neurological examination is relevant for patient evaluation, because of the risk of spinal cord compression by vertebrae lesions[7]. Perineum sensitivity and control of bladder and rectum sphincters must be evaluated in order to discard cauda quina syndrome, which requires immediate treatment. Spinal compression by vertebral collapse or tumour invasion is a common clinical presentation, and differential diagnosis between tumoural and infectious disease is the primary aim. Plain films of the spine as the first imaging study can demonstrate vertebral collapse with pedicles involvement, which may be indicative of a tumour. Disk destruction and perivertebral soft tissue involvement is suggestive of inflammatory disease. Magnetic resonance imaging (MRI) enhanced with gadolinium can be more specific to demonstrate tumoural invasion compared with CT.

Pain, pathological fracture, hypercalcemia, spinal cord compression, and the requirement of radiotherapy and surgery are frequent skeletal-related events in patients with bone metastasis due to lung cancer[5].

Terminally ill patients with bone metastasis due to lung cancer often present with skeletal-related events. Recent studies indicate that these events occur during the initial 5 months after the diagnosis of metastasis in the

majority of patients, and that the median survival rate after the first event is only 4 months[5,12]. In general, skeletal-related events are not a direct cause of mortality; however, they have a marked negative impact on the prognosis. Death may occur due to cancer and its related complications; however, bone metastasis less frequently result in acute hypercalcemia, which can be a direct cause of death[27].

Despite high mortality, poor prognosis, and the disabilities caused by bone metastasis, which also negatively affects patients' quality of life, orthopaedic surgeons should not adopt fatalistic postures. Proper diagnosis and treatment by orthopaedic oncologists is extremely important for easing pain, maintaining mobility and independence, and increasing the overall quality of life for these patients[7,28].

Imaging Evaluation

Bone metastasis diagnosis must be based on the correlation between clinical manifestations, imaging examinations, and anatomopathological studies.

X-ray examination is the first indicated method for evaluating osteoarticular pain. The lesion-detecting sensitivity of radiography is low when compared with those of bone scintigraphy and MRI, as 30% to 50% of cancellous bone destruction is needed to visualize a lytic lesion[23,29]. A patient with lung cancer and osteoarticular

pain may have a x-ray study of the site of pain in order to identify bone metastasis prior to the occurrence of pathological fractures. Aggressive bone destruction signs are suggestive of malignancy and an easy radiographic diagnosis.Subtle lesions may be missed and the absence of an identifiable lesion in x-ray in a symptomatic patient may indicate the need for proceeding investigation using a more sensitive method, such as computed tomography (CT), MRI, and bone scintigraphy. The radiographic aspect of bone metastasis from lung cancer is variable, but they are predominantly lytic lesions with ill-defined cortical destruction. The presence of a well-circumscribed erosion of the external surface of long tubular bone, predominantly the femur and humerus, known as "cookie-bite" sign is very suggestive of lung cancer metastasis. In general, metastasis to the long tubular bone will first reach the medullary cavity; however, bronchogenic carcinoma may metastasize to the surface of the bone[30]. The presence of rib erosion by carcinomas at the apex of the lung (Pancoast tumour) can be detected on chest film and are indicative of tumoral invasion.

Bone scintigraphy using ^{99}Tc-methylene diphosphonate is a useful and sensitive method for detecting modifications 3-18 months earlier compared with conventional radiography[31-32]. It is an effective method for screening the entire skeleton, which should be complemented with imaging examinations of the identified uptake areas

for improved lesion characterization, biopsy, and surgical treatment planning.

Bone scintigraphy was initially considered the most reliable method for the detection and monitoring of bone metastasis in patients with cancer[33-35]. Various studies have demonstrated the high sensitivity of this method for detecting bone metastasis, in addition to its relatively low cost[36-39]. It is still considered the best tool for diagnosis by certain authors, owing to an optimum cost/benefit ratio[40]. It is a highly sensitive examination; however, it has a low specificity[41-43]. The higher radioisotope yield occurs due to increases of osteoblastic activity and local blood flow, which also occur in other non-neoplasm conditions[44]. Therefore, we do not consider modifications only observed in bone scintigraphy to definitively confirm bone metastases diagnosis; thus, it must be complemented with simple radiography, and/or CT, and/or MRI, and often with a biopsy for histological confirmation.

CT and MRIhave a higher sensitivity and provides more detailed anatomic data compared with an x-ray study and bone scintigraphy. MRI has an important role in detecting bone metastasis in early stages[45] and it is considered a better technique for determining lesion extension and soft tissue penetration and for evaluating spine cord compression in spine lesions[44].

Although bone scintigraphy remains the most important and most cost-effective imaging modality for diagnosis, positron emission tomography (PET) is a more modern method for assessing the stage of *lung cancer* stage, and provides morphological and functional information of tissues (including bones)[40,47].

Biopsy

Histopathological examination of bone tissue samples, preferably obtained percutaneously guided by fluoroscopy or CT, is the gold standard for confirming a diagnosis of bone metastasis. Histological study during evaluation is mandatory for patients with single bone lesion without associated visceral metastases, in order to discard a second primary tumour [49].

The histological appearance of metastatic carcinoma is similar to that of the primary lesion. A compatible pulmonary lesion obtained with thoracicCT in association with histological identification of epithelium tissue in bone sample is substantially suggestive of metastatic lung cancer, and eliminates the need for primary site's histological biopsy. When needed, histopathological examinations of a bone biopsy product provide the diagnosis for well-differentiated cases. In other cases, additional immunohistochemical examinations is required to evaluate the presence of lung-cancer-specific epithelial markers[49].

Conclusion

Bone metastasis is a finding of advanced stage of cancer and leads to a high morbidity in lung cancer patients, affecting the survival prognosis. Lung can-

cer may have direct extension into the bone, lymphatic spread to the regional lymph nodes and haematogenous dissemination;however, distant bone metastasis can occur before regional spread, which may be misleading considering the size of the primary tumour. Accurate and timely diagnosis is essential for providing treatment, which leads to direct benefits to the quality of life of patients and survival rates.

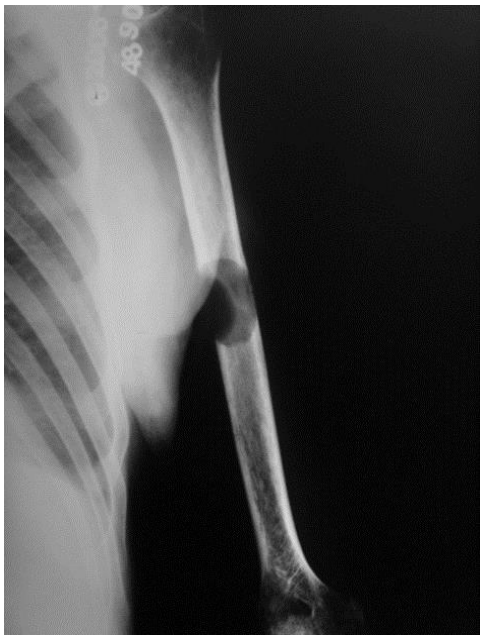

Figure 1: Lytic bone metastasis with well circumscribed erosion of the external surface of the humerus known by "cookie-bite" sign. In general, metastasis to long tubular bone reaches first the medullary cavity but bronchogenic carcinoma at the other hand, may metastasize to the surface of the bone.

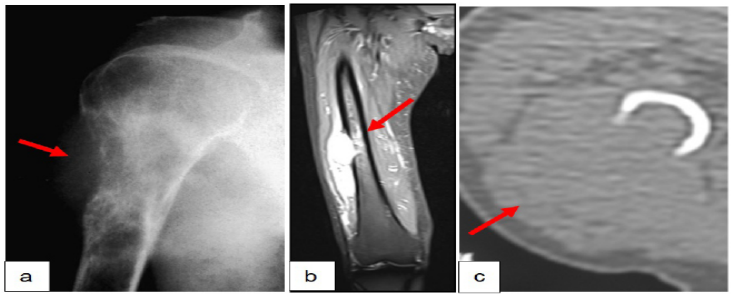

Figure 2: Plain film (a) shows a lytic lesion with aggressive radiological signs with ill defined margins and cortical destruction indicating soft tissue extension. MRI (b) depicts well the large soft tissue tumoral invasion and small medullary bone component. CT (c) shows the bone destruction but offers a limited view of the soft tissue component.

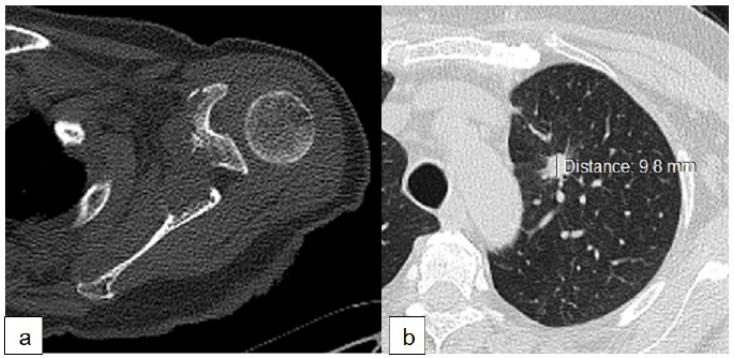

Figure 3: CT shows an ill-defined lytic lesion destroying the body of the scapula. The patient searched medical help because of shoulder pain. A characteristic tumoralspiculated nodule of less than 1,0 cm was found in the same exam. Courtesy from Dr. Tatiana MeloFernandes from Marcílio Dias Naval Hospital.

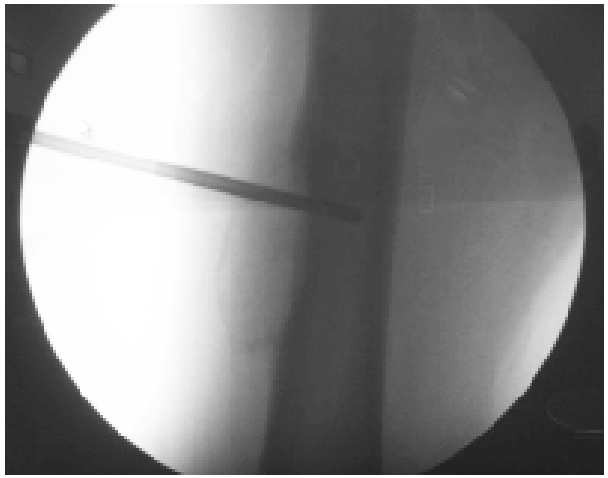

Figure 4: Fluorocopically-guided percutaneous bone biopsy.

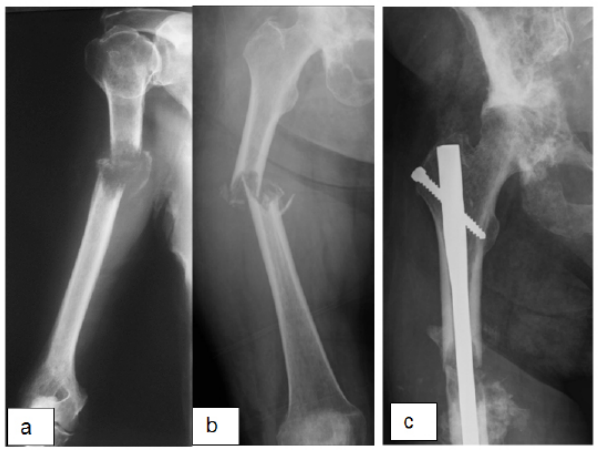

Figure 5: Pathologic fractures in proximal humerus (a) and proximal femur (b). Those lytic lesions are easily depicted but well defined contour of (b) induced to wrong diagnosis and inadequate approach (c).

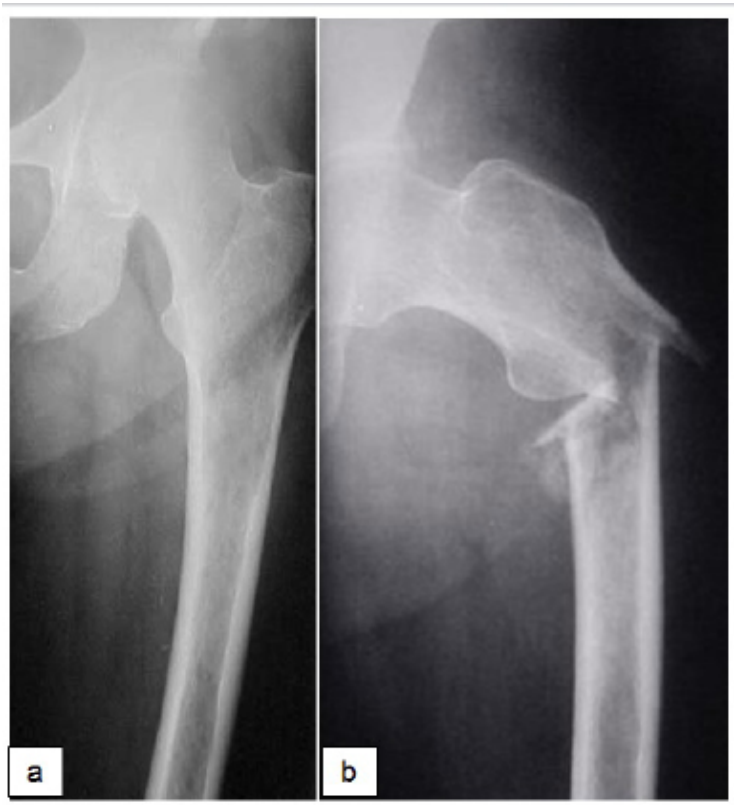

Figure 6: Lytic lesion can be missed in plain film until bone destruction leads to a pathologic fracture, as in this case of a moth-eaten pattern of bone destruction. Unrecognized pathologic fracture may delay diagnosis of the primary tumor. Courtesy from Dr. Walter Meohas from Trauma and Orthopaedics National Institute.

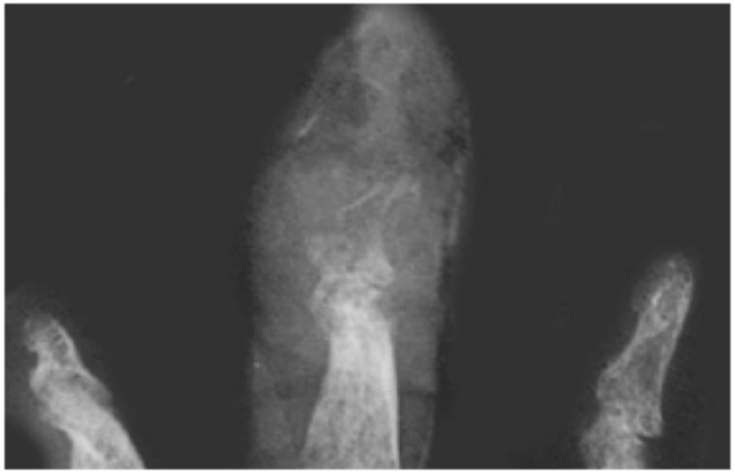

Figure 7: Distal phalanx destruction with soft tissue mass demonstrates an aggressive lesion. Although involvement of extremities is rare for bone metastasis, when it happens, lung cancer is the most common primary tumor.

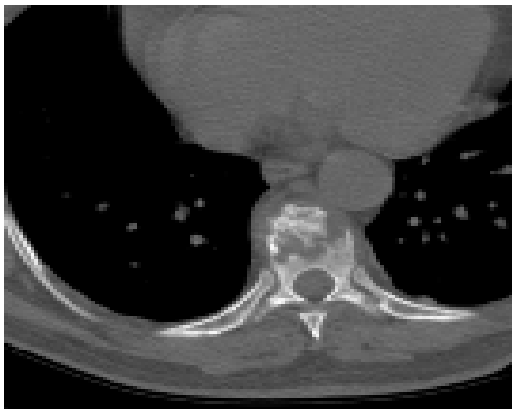

Figure 8: CT demonstrates lytic lesion of vertebral body with cortical destruction and soft tissue invasion.

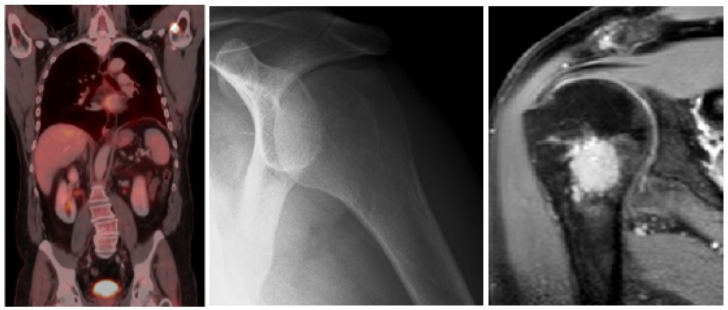

Figure 9: PET-CT made to stage lymph node involvement demonstrated an abnormal metabolic activity in the left proximal humerus. Plain film was normal but MR showed a focal lesion. The biopsy was guided by CT and the histopathologic study showed lung adenocarcinoma.

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