Chapter

Bone Metastases in Lung Cancer

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Abstract

Lung cancer patients frequently present with to bone metastases. Such lesions are responsible for increased morbidity, low quality of life, and increased costs to patients and the health care system. Pain is the most common symptom; however, these lesions also present as skeletal related events (SRE) which include pathological fractures, hypercalcemia, spinal cord and nerve compressions and cause the need for surgery and/or radiotherapy. Even though bone metastases are associated with poor prognosis, current treatment multimodalities continue to improve survival. Awareness and effective treatment of these lesions is paramount to maintain a good quality of life and function in lung cancer patients.

Keywords: bone metastases, lung cancer, diagnosis, treatment

1. Introduction

Lung cancer is the second most common cancer, for both genders. More than 235.000 new cases are expected to occur this year in the United States only. Additionally, this disease is also expected to cause more than 130.000 deaths yearly, being responsible for a fourth of the cancer fatalities in this country as well [1]. Lung cancer has different subtypes, the most frequent being Non-small cell lung cancer (NSCLC) which includes adenocarcinoma, squamous cell carcinoma and large cell carcinoma; those comprise 80% of the lung cancer cases [2].

This disease tends to have an asymptomatic presentation, leading to many of these patients presenting at a later stage with disease already spread to other sites [3]. Bone metastases occur when the tumor has spread from its original site, the lung, to bones. This event occurs via blood stream or lymphatic pathways [4]. Bone seeding is more frequent in the trunk bones due to a richer bone marrow, vast in blood vessels [5]. Prostate, breast and lung are the most common cancers to cause bone secondary disease [6]. Within the subtypes of lung cancer, adenocarcinoma is the subtype with the highest incidence of bone lesions [7]. Additionally, bone is the third most common site of spread for most cancers after lung and liver [8]. Likewise, bone metastases can be the initial presentation of an occult lung cancer. Occult primary malignancies occur in 4% of the cancer patients [9].

Obvious bone lesions are found in about 36% of these patients, while micro-metastasis in up to 60% of the lung cancer population [4]. An increased number of bone lesions is a reflection of more aggressive disease and as such is associated with decreased survival and a poor prognosis [10].

2. Clinical presentation

The axial bones are the most frequent location of bone lesions, the vertebral bodies being the most common followed by ribs, pelvis and calvarium (**Figure 1**) [7]. Less than 1% of bone lesions are present below the elbow or distal to the knee, but when those, also known as acral metastases, are present 44% are originated in the lung (**Figure 2**). Acral metastases are associated with a poor prognosis [11]. Bone metastases are known to cause pain and several other complications such as pathologic fractures, hypercalcemia, spinal cord and nerve compressions and cause the requirement for surgery and/or radiotherapy, all of these are known as skeletal related events (SRE) [4, 12]. Bone pain is present in about 80% of lung cancer patients at some point during their disease [4]. Approximately 10–30% of lung cancer patients will suffer a pathological fracture, fact that worsens survival times compared to patients without a fracture (**Figure 3**) [13, 14]. SREs are more likely to occur after a prior SRE has taken place [15]. More than half of these patients will suffer at least one SRE which will cause morbidity, will impair function and quality of life along with increased costs to the patient and health care system [16, 17]. On average patients suffer a SRE every 3 to 6 months, usually in periods of progression of their disease [4].

Hypercalcemia is a frequent SRE, present in one in eight patients, and oftentimes can be potentially life-threatening if untreated [18]. Hypercalcemia can occur associated with bone lesions or not; in the latter scenario it is due to an imbalance of

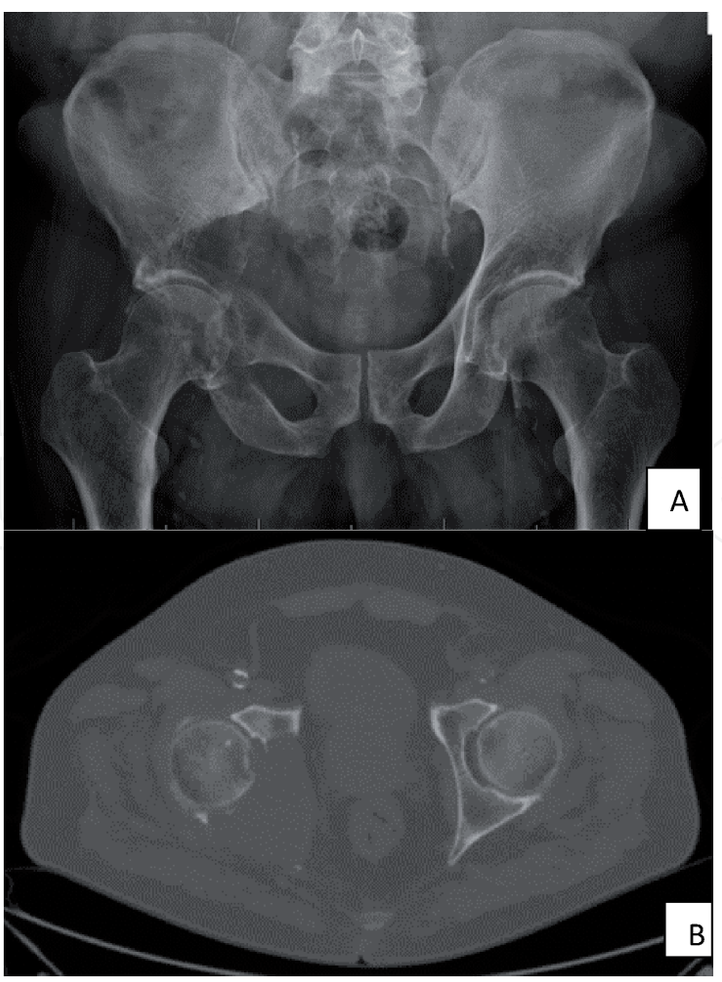

Figure 1.
Lung cancer metastatic bone lesion of the right acetabulum. Radiograph depicting a lytic lesion (A) and axial CT image demonstrating a lesion occupying all the posterior acetabulum (B).

Figure 2.
Distal bone metastasis on a lung cancer patient. Radiograph image demonstrating a lytic lesion in the proximal tibia, anterior–posterior and lateral view (A). MRI image, T1-sequence depicting a low signal lesion with interior necrosis (B). Sagittal view of CT scan image depicting the lytic lesion and soft tissue extension to the posterior compartment of the leg (C).

factors such as PTHrP and interleukin-1 among others that induce bone resorption [19]. Symptoms include nausea and vomiting, anorexia, fatigue, polyuria and polydipsia, and later on seizures, arrhythmia, ileus and even coma. Aggressive hydration and bisphosphonates are the treatment of choice [20].

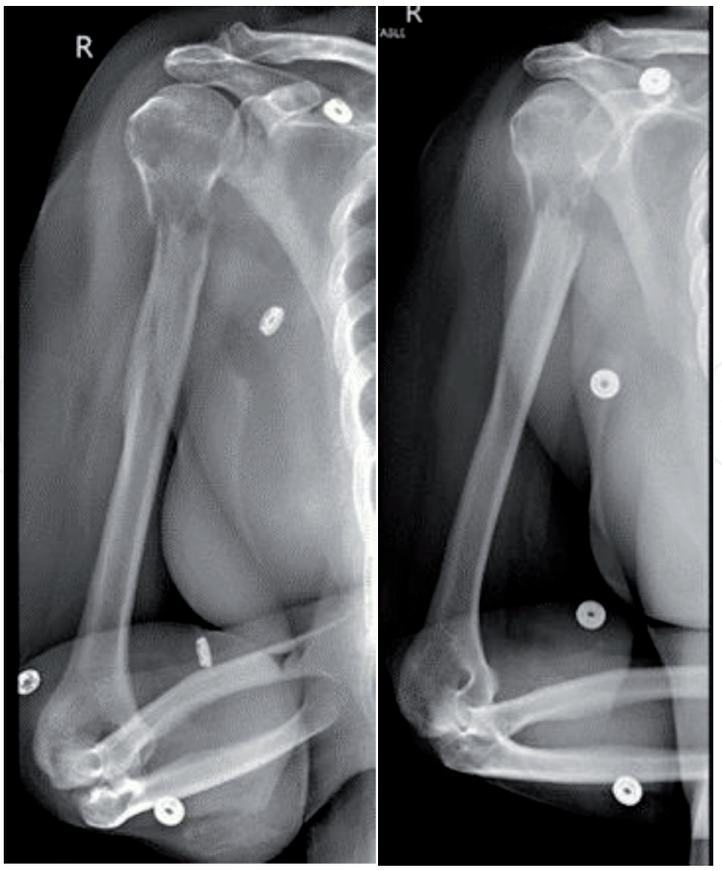

Figure 3.
Radiographic images, anterior–posterior and lateral of proximal right humerus lytic lesion and pathological fracture in a lung cancer patient.

3. Imaging studies

Obtaining dedicated imaging studies is indicated at initial staging or when a patient presents with symptoms such as bone pain. Radiographs are usually obtained as initial exam in the case of symptomatic patients to assess for bone lesions or a pathological fracture. Radiographs are considered of low sensitivity to detect bone lesions since more than 50% of the bone needs to be compromised to be clearly seen on plain films [21]. Lung cancer presents predominately with lytic lesions, although sclerotic and mixed have been described [21, 22]. Additionally, plain films are of low sensitivity to monitor response since it takes 3–6 months for a good response, new bone formation and sclerosis, to be visible [23]. CT scans are more sensitive and depict better resolution of bone trabeculae and cortical bone as well as better definition of sclerotic lesions and bone marrow lesions when present [24]. Usually not obtained as single bone study but rather as part of whole-body staging exams. MRI images in lung cancer patients are usually reserved for the study of the spine vertebral bodies and the potential involvement of the surrounding structures such as spinal cord and nerve roots due to tumor extension [25]. An alternative to assess bone lesions in the entire skeleton is bone scintigraphy, which is usually easily available (**Figure 4**). Bone scintigraphy has high sensitivity and can detect lesions earlier than observed in plan radiographs, however it is unspecific and has a high rate of false positives [26].

PET CT scans are widely used to stage patients and assess treatment response. This study produces high resolution images and detects increased metabolic activity for example in oncologic lesions (**Figure 5**). It has good sensitivity and specificity for metastatic spread diagnosis, allows for the assessment of visceral lesions at the same time and is able to detect bone lesions early [22, 27].

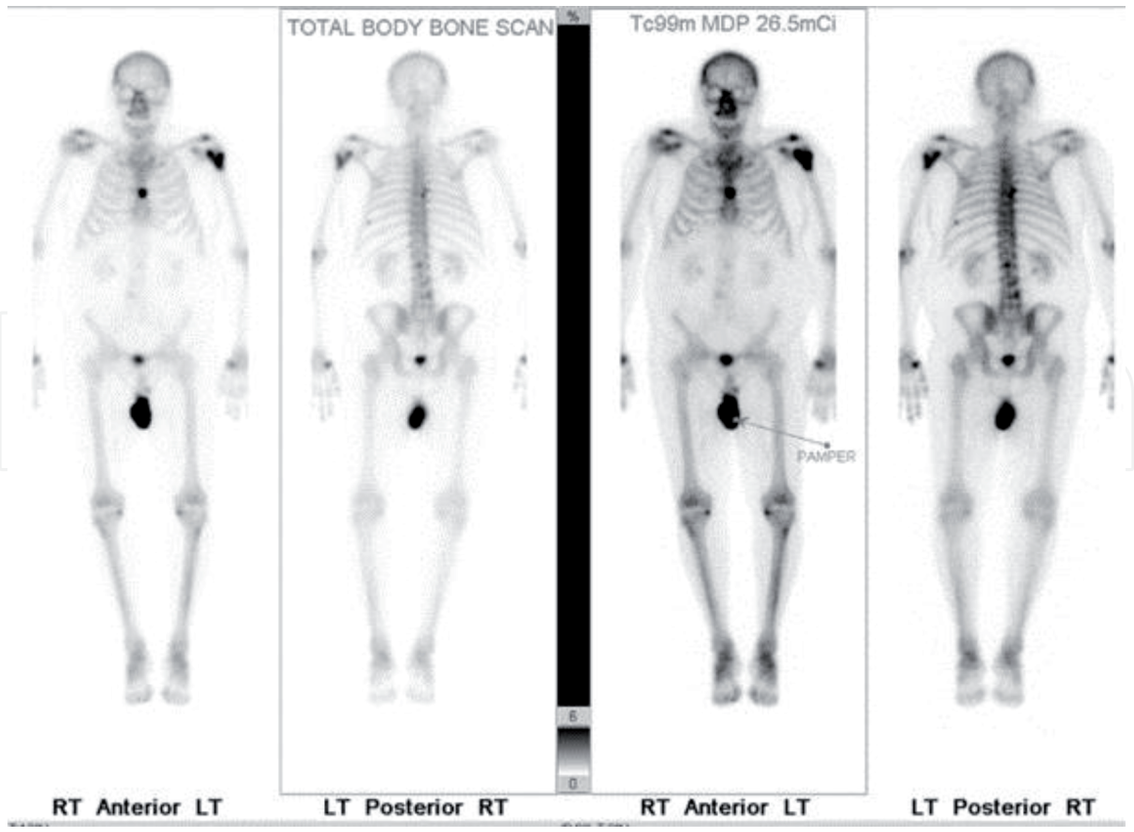

Figure 4.
Bone scintigraphy study with Tecnecium-99 depicting a lesion in the proximal left humerus and sternum.

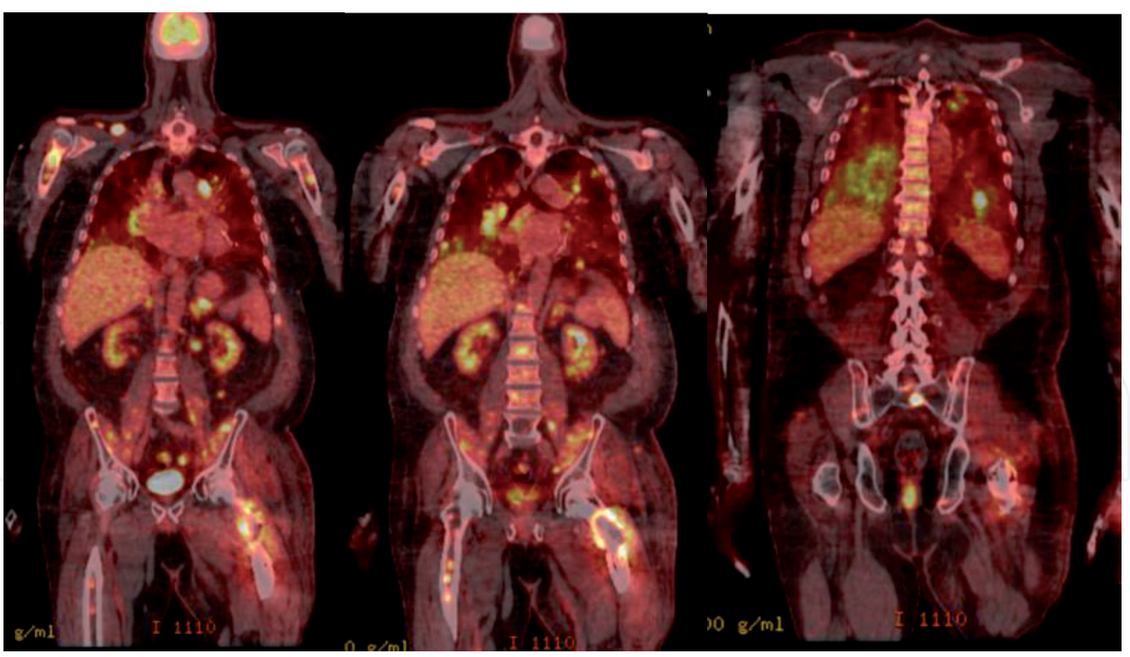

Figure 5.
PET CT images of a lung cancer patient demonstrating several metastatic lesions including the proximal left femur, right femur, proximal right humerus and spine among others.

4. Treatment

Treatment for bone lesions secondary to lung cancer can be divided in systemic and local therapies. The first line of treatment used to be Platinum-based chemotherapy, applied in 4 to 6 cycles followed by a period of observation [28]. Research

progress has led to the unveiling of potential new molecular abnormalities passible of targeting treatment, it is estimated that almost 70% of patients with advanced disease may present some of these targetable aberrations [29]. Systemic cancer-directed therapy is discussed in depth in other chapters of this book. In terms of systemic anti bone-resorption-treatments the current recommendations are for the administration of either bisphosphonates or Denosumab [30]. These drugs interfere with the vicious cycle where osteoclasts are stimulated due to an imbalance in local factors produced by the invading tumor cells, leading to a disbalance in the normal bone remodeling process, continuous bone resorption, lytic lesions, bone weakening and eventually a pathological fracture [31]. Inhibitors of bone resorption are known to relief pain, prevent and delay SREs, decrease the number of pathological fractures, have anti-tumor activity by inhibiting tumor cell growth and stimulation programmed cell death; and are the treatment for hypercalcemia as well [32, 33]. Common side effects associated to these drugs are nephrotoxicity, gastrointestinal discomfort and osteonecrosis of the jaw, physician and renal function monitoring are recommended [34].

Local treatments include radiation to the lesion and surgery. Radiotherapy it is used in the setting of bone metastatic spread as a palliative measure to control pain, prevent the progression of lesions into a pathological fracture of limbs, to control lesions locally, prophylactically and therapeutically for spinal cord compression [35]. Dose recommendations and delivery schedules vary and may range from a single fraction with a dose of 8 Gy to higher doses like 30 Gy in 8 to 10 fractions. Most patients achieve pain relief if not a complete response generally occurring in the first 2 weeks of treatment [36]. Bone response when present can be observed 3 to 6 weeks from the end of treatment and the maximum effect is detected after 6 months [37].

Surgery has a narrower indication spectrum in patients with metastatic lung cancer, usually being indicated for pathological or impending fractures, to maintain function and good quality of life and to prevent neurological damage. A bone lesion requiring surgery is an indication of a poorer prognosis on itself, thus the decision of proceeding with surgery and the type of surgery must be contrasted with the complications and the recovery time each procedure will entail. Prior studies have shown that 10% of the patients die within a month of the procedure and almost 80% do so within a year [13]. However, a more recent study has shown that if the patient has a good response to new biologic drug therapies, the one-year survival improves to over 60% making relevant the consideration for more durable orthopedic implants [38].

Surgical treatment of bone lesions of the limbs in general involve fixating the bone with either plates and screws or an intramedullary device. Additionally, in cases where the lesion is more advanced and near a joint, treatment involves resecting the bone and replacing it with an endoprosthetic implant. Each procedure has its own rates of complications and its own rates of hardware failure. Implants may fail for different reasons the most common being disease progression and mechanical fatigue, both are time and disease dependent factors that the surgeon must consider when choosing the most appropriate procedure. Ideally these patients are identified prior to fracture occurrence and a prophylactic fixation can be performed. A simple mechanism to identify impending fractures is through the Mirel's score which considers the characteristics of the patient's pain and the characteristics of the lesion on radiographic images (location, type of lesion, degree of extension) assigning each item a value and the ultimate sum will dictate the treatment between observation and an indication for prophylactic fixation [39]. Likewise, an alternative is the Harrington criteria that considers the size of the lesion, the percentage of cortical destruction, the presence of pain after radiation

and the pathologic avulsion of the lesser trochanter to suggest prophylactic fixation of the lesion [40]. Surgical intervention prior to the actual fracture, when indicated, has shown shorter hospital stay, decreased requirements for blood transfusion as well as improved functional outcomes [41, 42]. For femur diaphyseal lesions causing symptoms for an impending pathological fracture, the treatment of choice is a load-sharing intramedullary nail (**Figure 6**). For more extensive lesions where there is soft tissue extension of the bone lesion fixating the bone with plate and screws or a nail can be associated with curettage of the lesion and cement augmentation (**Figure 7**). Additionally, in case where the patient is identified late and there is extensive bone destruction located near a joint, bone resection and replacement may be indicated (**Figure 8**).

A very important aspect of the treatment of these patients, oftentimes forgotten or not given its rightful importance, is pain control. Most patients with metastatic bone cancer will experience moderate to severe pain at some point of their disease [4]. Moreover, pain originating in bones is the most common type of pain these patients experience at may at times seem exaggerated to the actual lesion

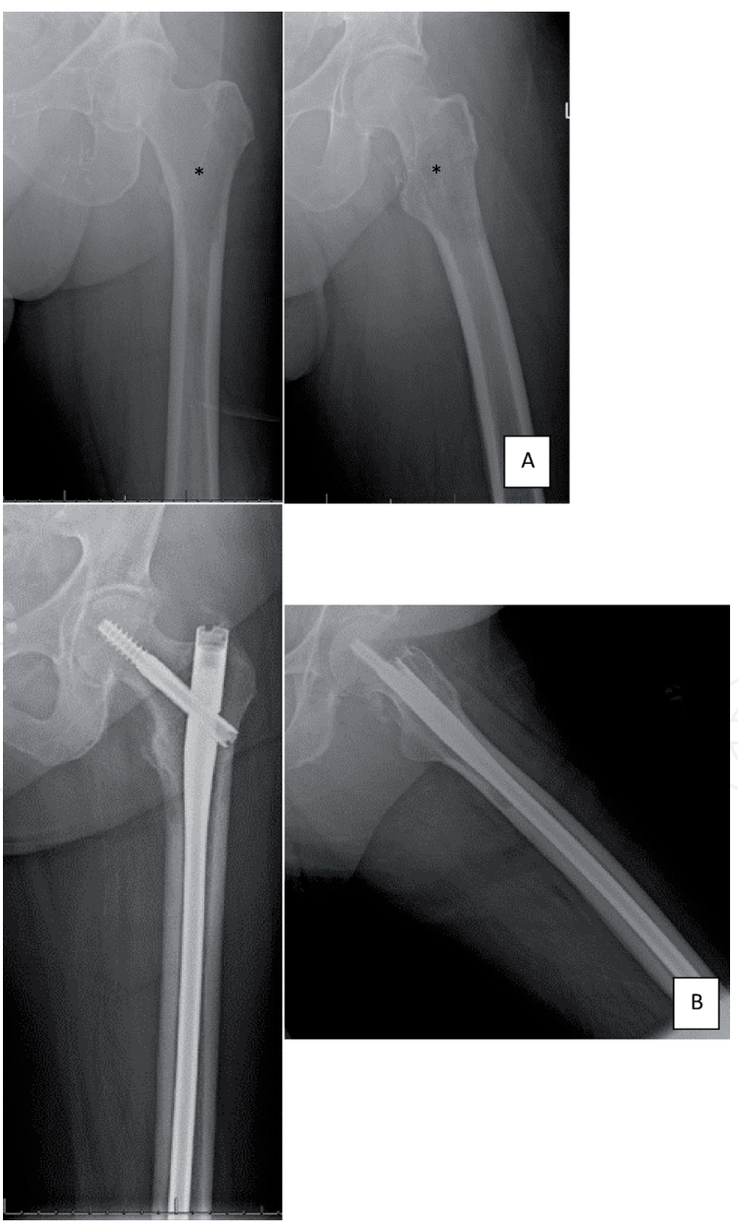

Figure 6.
Lung cancer patient with a lesion in the proximal femur (*) causing symptoms concerning for an impending fracture (A). The patient was treated with prophylactic fixation with an intramedullary long nail (B).

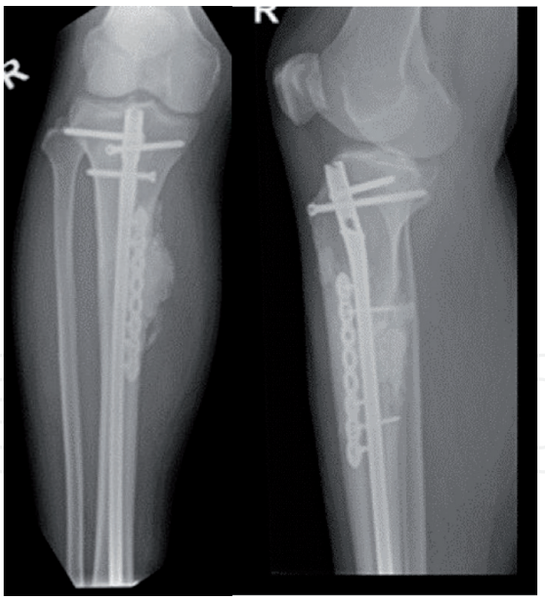

Figure 7.
Lung cancer patient had an extensive lesion in proximal tibia with soft tissue extension. The bone was fixated with a nail and plate and screws with curettage of lesion and cement augmentation. The patient had postoperative radiation of the leison as well.

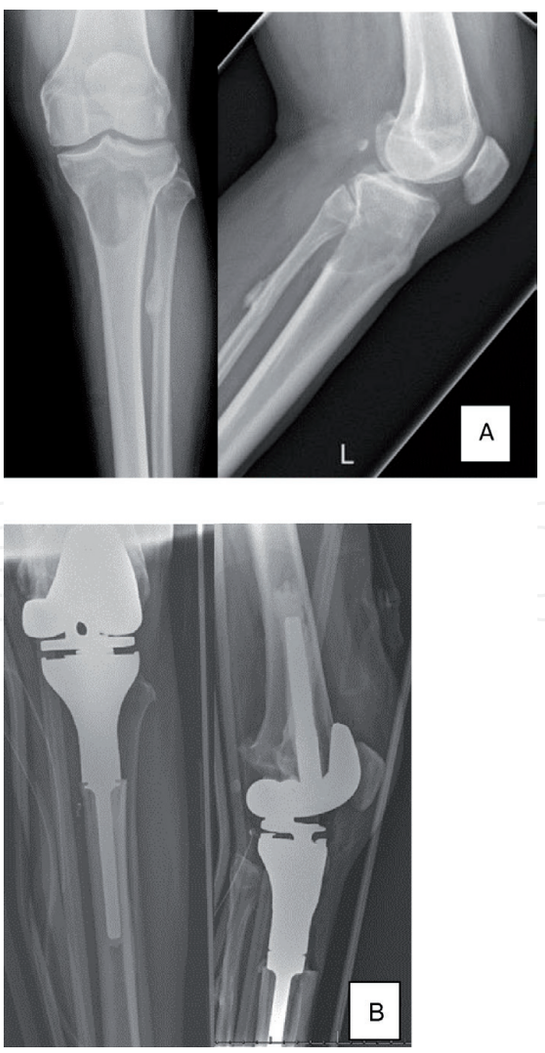

Figure 8.
Patient presented with an extensive proximal tibia lesion close to the knee joint (A). Bone resection and a proximal tibia replacement was performed (B).

proportion [43]. Pain derived from bone metastases is felt as dull, constant and increasing in intensity [43]. This more chronic type of pain is replaced by a more intense and severe pain, breakthrough pain, which is also more difficult to control. Breakthrough pain can occur spontaneously or associated with weight bearing of an affected extremity [44]. It is extremely high in intensity, last for only a few minutes but can repeat itself several times a day, thus can severely affect the function and life quality of the patient [45]. Since the pain mechanisms in bone metastases originated pain are multiple, so are the treatment modalities. Systemic and local therapy such as radiation to a specific lesion may help alleviate the pain by decreasing disease activity and lesion progression [46]. Analgesic treatment is according to the World Health Organization ladder and it can be use in conjunction with bone modifying agents like bisphosphonates or Denosumab, corticoids and anticonvulsant drugs [46].

5. Conclusion

Even though bone metastatic spread in lung cancer used to mean a poor prognosis for those patients, current multimodality therapies continue to improve survival. Awareness and effective treatment of these lesions is paramount to maintain a good quality of life and function. Skeletal events related to bone metastases can severely affect the patient, produce increased costs to the healthcare system and affect survival. Ideally, an oncology orthopedic specialist ought to be included in the multidisciplinary treating team from the moment of diagnosis of bone metastatic spread.

Conflict of interest

The authors state no conflict of interest related to the writing of this chapter.

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