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# CT features of osteosarcoma lung metastasis: a retrospective study of 127 patients

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## ABSTRACT

**Objective:** Osteosarcoma lung metastases have a wide variety of CT presentations, representing a challenge for radiologists. Knowledge of atypical CT patterns of lung metastasis is important to differentiate it from benign lung disease and synchronous lung cancer, as well as to determine the extent of primary disease. The objective of this study was to analyze CT features of osteosarcoma lung metastasis before and during chemotherapy. **Methods:** Two radiologists independently reviewed chest CT images of 127 patients with histopathologically confirmed osteosarcoma treated between May 10, 2012 and November 13, 2020. The images were divided into two groups for analysis: images obtained before chemotherapy and images obtained during chemotherapy (initial CT examination). **Results:** Seventy-five patients were diagnosed with synchronous or metachronous lung metastases. The most common CT findings were nodules (in 95% of the patients), distributed bilaterally (in 86%), with no predominance regarding craniocaudal distribution (in 71%). Calcification was observed in 47%. Less common findings included intravascular lesions (in 16%), cavitation (in 7%), and the halo sign (in 5%). The primary tumor size was significantly greater (i.e., > 10 cm) in patients with lung metastasis. **Conclusions:** On CT scans, osteosarcoma lung metastases typically appear as bilateral solid nodules. However, they can have atypical presentations, with calcification being the most common. Knowledge of the typical and atypical CT features of osteosarcoma lung metastasis could play a key role in improving image interpretation in these cases.

**Keywords:** Neoplasm metastasis/lung; Osteosarcoma; Tomography, X-ray computed.

## INTRODUCTION

Osteosarcoma is the most common primary malignant bone tumor in children and young adults, with an estimated global incidence of 2-4 million cases per year.[1-5] Despite the development of multimodal therapies, such as those involving surgery, systemic therapy, and immunotherapy, the prognosis of osteosarcoma remains poor, and patient survival correlates strongly with treatment response and metastatic status.[4] The prognosis is also related to other variables, such as primary tumor location and size; patient sex and age; and histological subtype.[6-8] The lungs are the most common site of osteosarcoma metastasis, with osteosarcoma lung metastases being observed in approximately 80% of patients.[9] The 5-year survival rates in patients without and with osteosarcoma lung metastases are approximately 70% and 20%, respectively.[4,10,11]

Primary osteosarcoma involves the distal femur, proximal tibia, and proximal humerus in more than 75% of cases, other long and flat bones being affected in the remaining cases.[12] Osteosarcoma can metastasize to virtually any site or organ, mostly to the lungs, but occasionally to bone and lymph nodes. At the time of diagnosis, 18-30% of patients with osteosarcoma have metastatic disease, the lungs being the most commonly affected site.[13]

Reported risk factors for pulmonary lesions in patients with osteosarcoma include male sex, primary malignant bone tumor of the femur or tibia, and primary tumor size.[9] In addition, the number, distribution (unilateral or bilateral), and location of lung metastases may have prognostic value.[2] Thus, the correct diagnosis and characterization of these lesions has an impact on patient management.

Chest CT is the gold standard for the detection of lung metastases and may aid in distinguishing lung metastasis from benign lung disease. Radiologically, lung metastases typically appear as multiple peripheral round nodules of varying sizes in the lower lobes. However, osteosarcoma lung metastases may have atypical radiological features, which make their diagnosis challenging. On CT scans, lung metastases can have an extremely heterogeneous appearance, including calcification, hemorrhage halos around nodules, cavitation, pneumothorax, tumor embolism, an endobronchial location, solitary masses, dilated vessels within masses, and sterilized metastasis.[14,15]

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The purpose of this retrospective study was to determine the most common distribution, morphological characteristics, and chest CT features of osteosarcoma lung metastases. Epidemiological aspects and prognostic factors were also explored.

## METHODS

### *Patients*

This study was approved by the local research ethics committee, which waived the requirement for informed consent because of the retrospective nature of the study. All of the patients with osteosarcoma treated at the Brazilian National Cancer Institute between May 10, 2012 and November 13, 2020 (n = 156) were assessed for eligibility for inclusion in the study. Those who were included had an osteosarcoma diagnosis confirmed by primary tumor biopsy and had undergone chest CT examination. Those who did not undergo chest CT before chemotherapy (n = 29) were excluded. The study sample comprised 127 patients, 75 of whom had been diagnosed with synchronous or metachronous lung metastases.

Demographic data (including patient age and sex), mortality data, and clinical data (including the histological type, location, and size of the primary tumor) were collected. The lung metastases that were identified at the time of diagnosis were classified as synchronous, whereas those representing relapse despite chemotherapy for the primary tumor were classified as metachronous.[16]

### *CT protocol and image analysis*

Although all of the patients included in the study were recruited from the same institution, some CT examinations were performed at other institutions, with different scanners. Nevertheless, the technical parameters were the same for all chest CT examinations: 1–2.5-mm slice thickness with up to 10-mm increments. Images were acquired from the lung apices to the diaphragm at the end of a deep inhalation, with the patients in the supine position. Two radiologists (one with 4 years of experience and the other with 13 years of experience) retrospectively and independently reviewed the chest CT images, with any disagreement being resolved by discussion until consensus was reached.

Images were interpreted with the aid of a digital database system (CARESTREAM Vue PACS, version 12.1.0.0365; Carestream Health, Rochester, NY, USA), lung parenchymal window settings (width, 1,200-1600 HU; level, −500 to −700 HU) and mediastinal window settings (width, 350-450 HU; level, 20-50 HU) being used. The observers performed maximum intensity projection reconstruction for accurate identification of pulmonary nodules.

CT images of primary osteosarcoma were analyzed in order to determine tumor size and location. Primary tumor sizes were classified as ≤ 5 cm, 6-10 cm, or > 10 cm.

Two groups of images were evaluated: the group of images obtained before chemotherapy and that of those obtained during chemotherapy (i.e., 3-12 months after initiation of chemotherapy).

Lung metastases were defined as lung lesions suspicious for malignancy, the number and/or dimensions of which increased progressively on serial CT examinations, as well as those found in patients undergoing metastasectomy. In accordance with the Fleischner Society glossary of terms for thoracic imaging,[17] lung metastases were classified on the basis of the following: pattern (nodule or mass); shape (smooth, lobulated, or spiculated); density (solid, nonsolid, or partially solid); presence of calcification, the halo sign, or cavitation; number of lesions (≤ 3, 4-10, or > 10); and size (as well as changes in size). The distribution of metastases in the lung parenchyma was classified on the basis of the following: laterality (unilateral or bilateral metastases); symmetry and the most affected lung (right or left lung); axial distribution (central, peripheral, or random distribution); and craniocaudal distribution (upper, middle, or lower lung).

The presence of pleural effusion and lymph node enlargement was recorded. Lung metastasis complications such as pneumothorax, vascular thrombosis, and pericardial effusion were also recorded.

## RESULTS

### *Demographic and clinical characteristics*

The study sample comprised 127 patients with osteosarcoma in the 5- to 72-year age bracket (mean age, 20 ± 12.7 years). Seventy-five (59%) of the patients (61% of whom were male; mean age, 18 ± 11.3 years) had lung metastases, and 53 (41%) of the patients (54% of whom male; mean age, 25 ± 14 years) did not.

The most common primary tumor location was the femur (in 53% of the study sample), and this location was more common in patients with lung metastasis than in those without (57% vs. 45%). Other primary tumor sites were the tibia (in 21%), humerus (in 7%), jaw (in 5%), and fibula (in 4%). Primary tumors of the foot, sacrum, scapula, clavicle, radius, ulna, sphenoid sinus, frontal bone, and retroauricular space occurred at a frequency of 1%.

The most common histological type was classic osteosarcoma (in 81%). Other histological types included high-grade osteosarcoma (in 6%), telangiectatic osteosarcoma (in 6%), small cell osteosarcoma (in 2%), parosteal osteosarcoma (in 2%), epithelioid osteosarcoma (in 1%), and giant cell osteosarcoma (in 1%). One case of osteosarcoma secondary to fibrous dysplasia was observed in a patient without lung metastasis (1%).

At admission, 10% of the primary tumors were < 6 cm in size, 27% were 6-10 cm in size, and 63% were > 10 cm in size. Primary tumor size was greater in patients with lung metastasis (> 10 cm in 81% of the cases) than in those without (< 10 cm in 36% of the cases). During the study period, death occurred more frequently in the group of patients with lung metastasis than in that of those without (77% vs. 21%).

### *CT findings before and during chemotherapy*

#### *Before chemotherapy*

Seventy-five patients underwent CT examination before chemotherapy. Lung metastasis was observed in 72 (96%). Lesion size ranged from 0.3 cm to 7.8 cm in diameter (mean, 1.3 ± 1.5 cm), and nodules predominated, being observed in 69 patients (96%). Margins were smooth in 55 (76%) and lobulated in 17 (24%). Solid lesions predominated, being observed in 70 patients (97%; Figure 1). Semisolid nodules were observed in 2 (3%). Calcification was observed in 23 (32%; Figure 2), and cavitation was observed in 3 (4%).

Pulmonary involvement was bilateral in 58 patients (80%), with no predominance regarding the affected lung (n = 49; 68%) or craniocaudal distribution (n = 48; 66%) in most of the cases. Peripheral lesions predominated in 40 patients (55%), and no specific axial distribution was observed in 32 (45%). Fewer than 3 lesions were observed in 17 patients (23%), 4-10 lesions were observed in 25 (35%), and > 10 lesions were observed in 30 (42%).

The halo sign, which is an area of ground-glass opacity surrounding a nodule or mass, was observed in 4 patients (5%; Figure 3). Eleven patients (15%) showed intravascular lesions (Figure 4). Pleural effusion and lymph node enlargement were observed in 4 patients (5%; Figure 5). In 2 patients (3%), pneumothorax was identified as a complication of lung metastasis (Figure 3).

Of the 72 patients presenting with lung metastasis before chemotherapy, 2 were lost to follow-up. Of the remaining 70 patients, 58 died during the study period (mean survival, 18.5 ± 16 months). Pulmonary masses > 3 cm were observed only in patients who died (n = 3; 5%), and cases of patients with more than 3 lesions predominated in the nonsurviving group (n = 44; 79%). Bilateral involvement was more common among the patients who died (n = 47; 84%).

#### *During chemotherapy*

Of the 75 patients who underwent CT before treatment, 14 did not undergo follow-up CT examination. On follow-up CT scans, lung metastases ranged from 0.3 cm to 14 cm in diameter (mean, 2.6 ± 2.9 cm), and nodules predominated, being observed in 57 patients (93%). Smooth margins were observed in 36 patients (59%). Most of the lesions were solid (n = 58; 95%). Semisolid nodules were observed in 3 patients (5%). Calcifications were observed in 22 (36%), and cavitations were observed in 4 (6%).

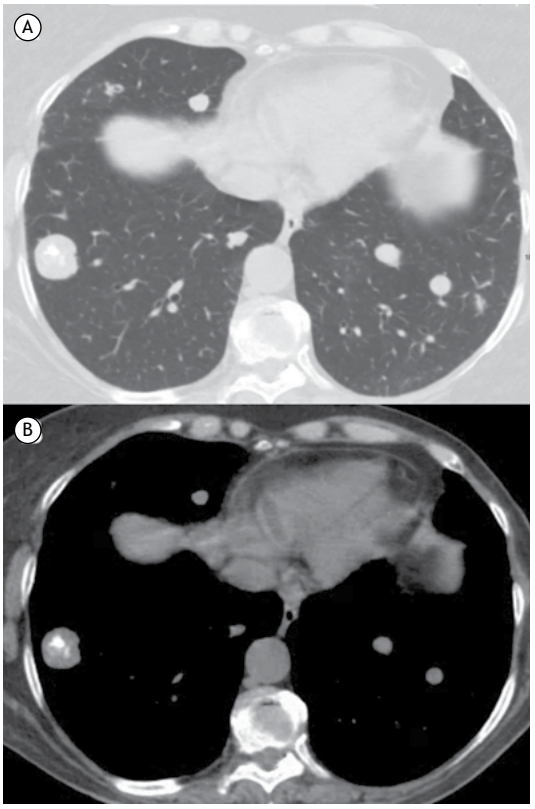


**Figure 1.** A 72-year-old woman with primary osteosarcoma of the femur. In A and B, CT scans showing multiple nodules of various sizes in both lungs, with the largest nodule being on the right side and showing inner calcification. The patient died 9 months after treatment initiation.

Pulmonary involvement was bilateral in 57 patients (93%), with no predominance regarding the affected lung (n = 42; 69%) or craniocaudal distribution (n = 46; 75%) in most of the cases. Peripheral lesions predominated in 28 patients (46%), and no specific axial distribution was observed in 32 (52%). Fewer than 3 lesions were observed in 5 patients (8%), 4-10 lesions were observed in 20 (33%), and > 10 lesions were observed in 36 (59%).

The halo sign was observed in 1 patient (2%). Eleven patients (8%) had intravascular lesions, and 1 (2%) had an endobronchial lesion (Figure 5). Complications occurred in 2 patients: pneumothorax, in 1 (2%); and central line–associated thrombosis, in 1 (2%). Table 1 summarizes the main CT features of metastatic lung lesions.

The lesions were stable from baseline in 6 patients (10%), and decreased in size or disappeared in 11 (18%). In 44 patients (72%), the lesions progressed over time, with lesion growth or new lesion appearance (Figure 4), the mean size having increased from 1.3 cm at baseline to 2.6 cm. Changes in morphological patterns occurred in 17 patients (71%); in 14 of those patients, smooth lesions became lobulated.

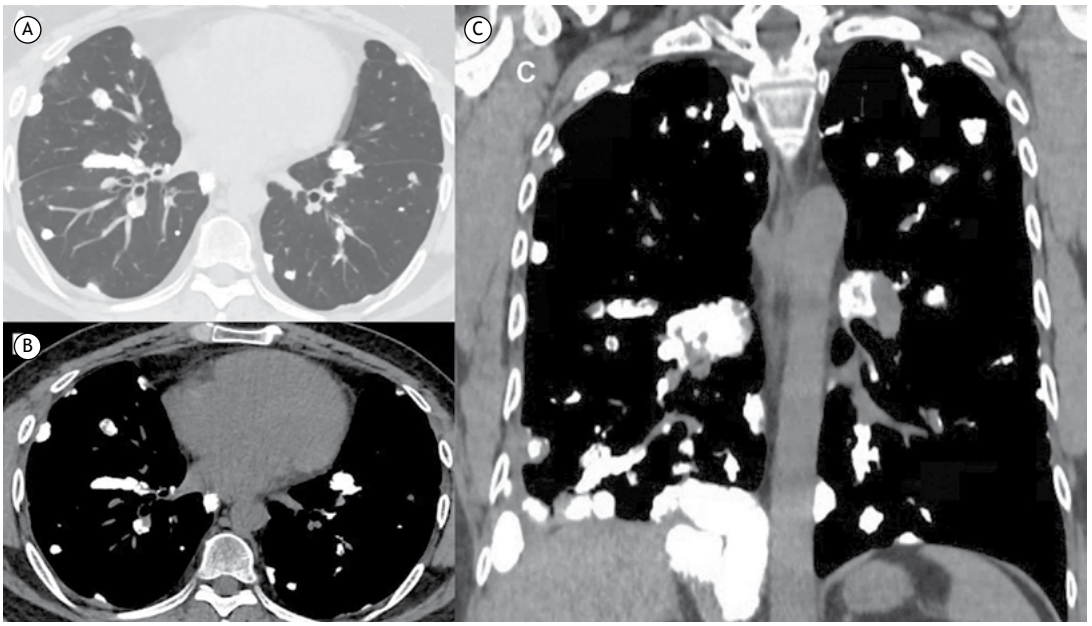


**Figure 2.** A 44-year-old man with primary osteosarcoma of the femur. In A, B, and C, CT scans showing multiple calcified nodules and masses in both lungs.

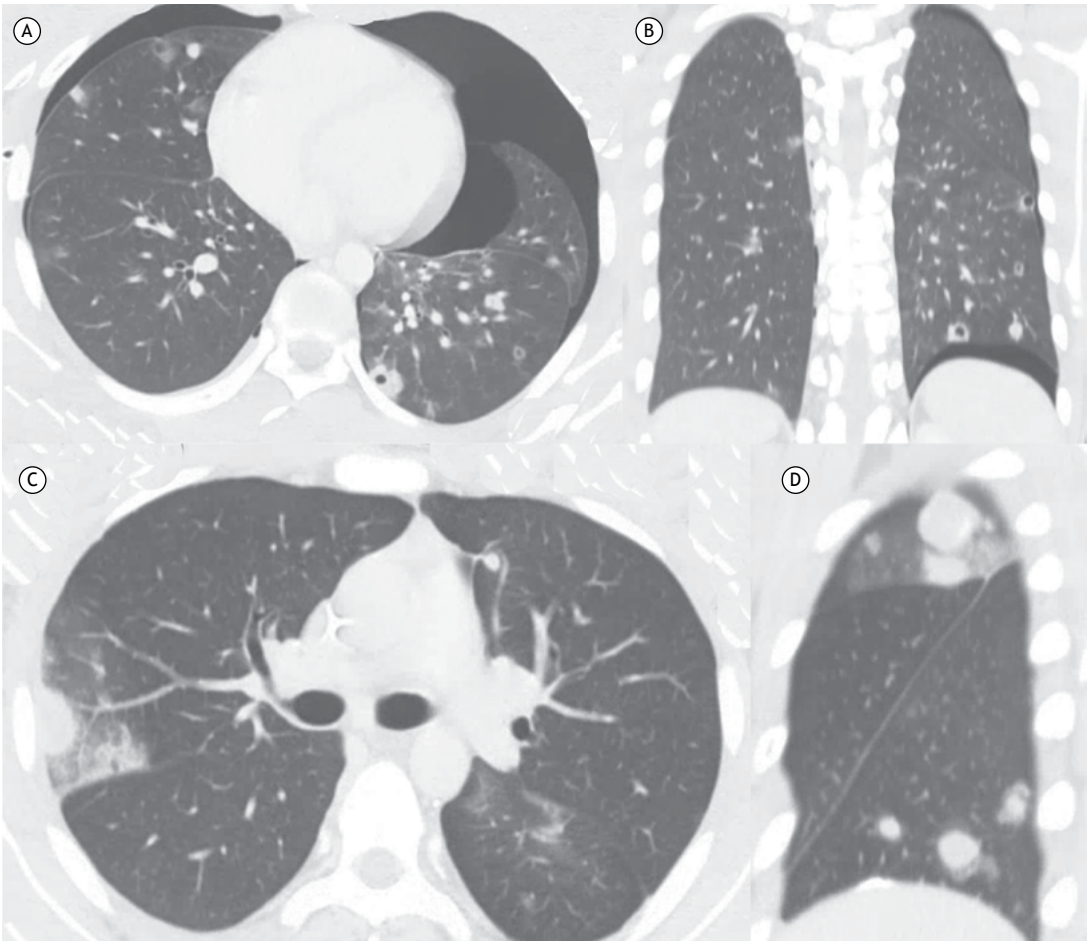


**Figure 3.** A 16-year-old boy with primary osteosarcoma of the femur. In A and B, CT scans performed at the time of diagnosis, showing multiple cavitary lung lesions with bilateral pneumothorax. In C and D, CT scans performed 5 months after initiation of chemotherapy, showing growth of the nodules, which are surrounded by ground-glass halos (indicating hemorrhagic pulmonary metastases).

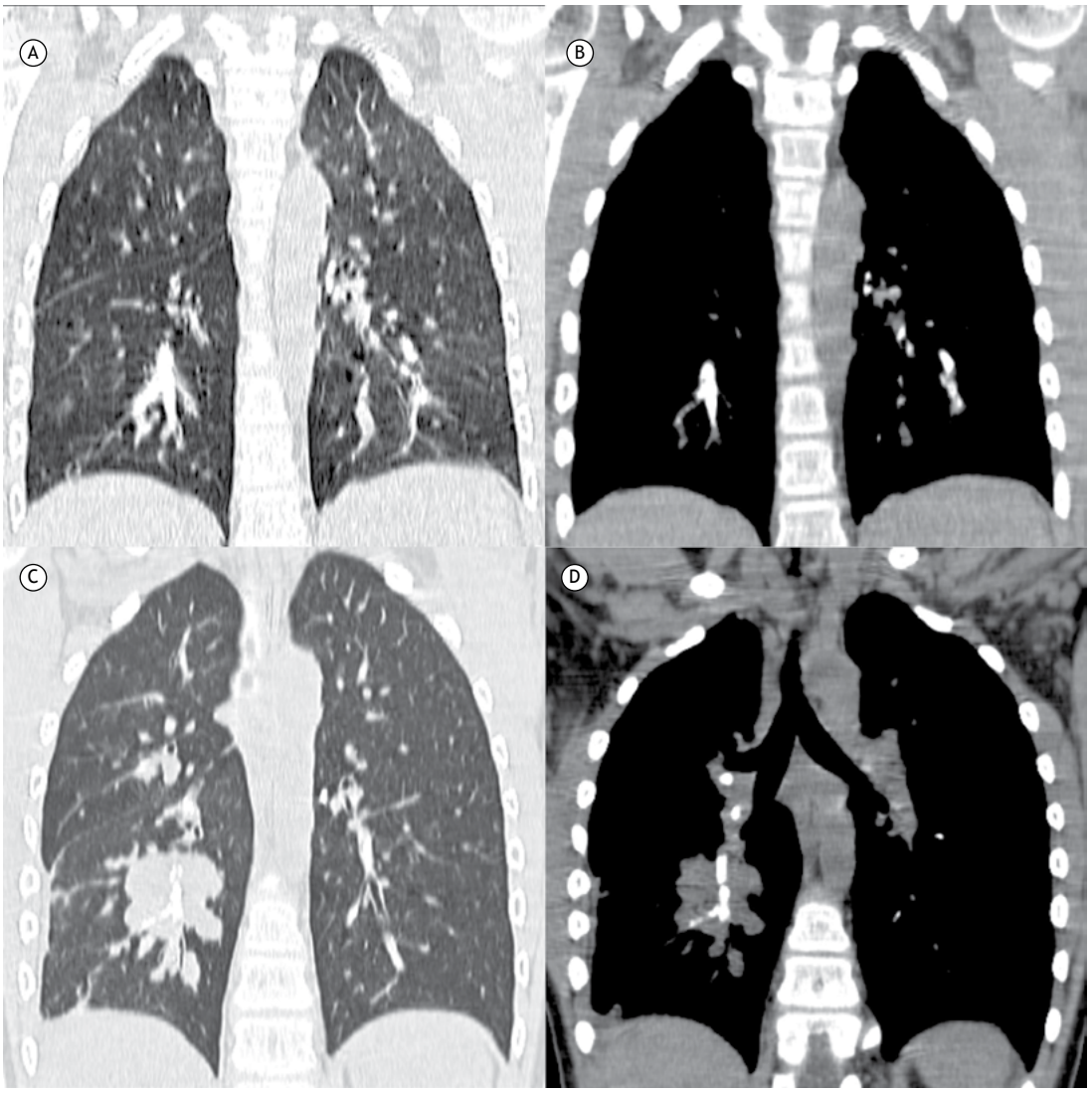


**Figure 4.** A 7-year-old boy with primary osteosarcoma of the femur. In A and B, CT scans showing calcified intravascular lung metastasis, which was confirmed by biopsy. In C and D, CT scans acquired 6 months later, showing progression of the lung lesions, with mass formation on the right.

## DISCUSSION

In our study, patient age ranged from 5 years to 72 years. The incidence of osteosarcoma was highest in males in the second decade of life, and the most common primary tumor sites were the femur and the tibia, findings that are consistent with the literature.[1,3,4,18,19]

The lung is the most common site of osteosarcoma metastasis.[20] Risk factors for osteosarcoma lung metastasis include male sex, primary malignant bone tumor of the femur or tibia, and primary tumor size.[9] In our study, 59% of the patients had lung metastases. Of those, 61% were male. The most common primary tumor sites were the femur and the tibia (in 52% and 22%, respectively). The primary tumor size was > 10 cm in 81% of the cases.

Patients with osteosarcoma lung metastases have a dismal prognosis, with an estimated 5-year survival rate of 20%.[4,10] Our findings of worse prognosis and lower mean survival in patients with lung metastasis than in those without (26 ± 25 months vs. 64 ± 33 months) are consistent with the literature.[4,10]

Chest CT is a recommended component of the initial evaluation of patients with osteosarcoma, because of the high prevalence of lung metastasis and its significant impact on prognosis.[3,4,9,21] Recognition of the most common morphological CT characteristics of osteosarcoma lung metastasis is of fundamental importance, especially for small lesions, which are difficult to characterize and biopsy.[22] In the present study, there was a predominance of solid nodules (in 96% of the patients) with smooth margins (in 68%), distributed peripherally (in 55%) and bilaterally (in

80%). These findings are consistent with the typical radiological appearance of lung metastases.[14,22,23]

Cicarese et al.[2] found that 61.6% of their patients had calcification and the lesions increased in size and progressively calcified over time. Brader et al.[24] described that, in their population, the osteoid matrix produced by the osteosarcoma cell may form bone and lead to calcification in pulmonary nodules. In our study, calcification was observed in less than 50% of our patients. The fact that this imaging pattern was less common in our study may be attributable to the fact that we evaluated CT images obtained within 12 months of chemotherapy initiation. The literature contains little information regarding atypical presentations of lung metastases. In a retrospective analysis of CT and pathological findings for resected osteosarcoma lung metastases, the masses were not nodular in 14.1% of cases, and the presence of striae, consolidation, pleural/cavitary lesions, ground-glass opacity, irregular shapes, and the halo sign varied widely.[2] Cavitation was present in only a few of our patients (7%) and was associated with pneumothorax in 2. Hemorrhagic metastases, which are characterized by nodular opacities with ground-glass halos and which reflect fragile new blood vessels and, consequently, vessel rupture,[25] were observed in 4% of our patients.

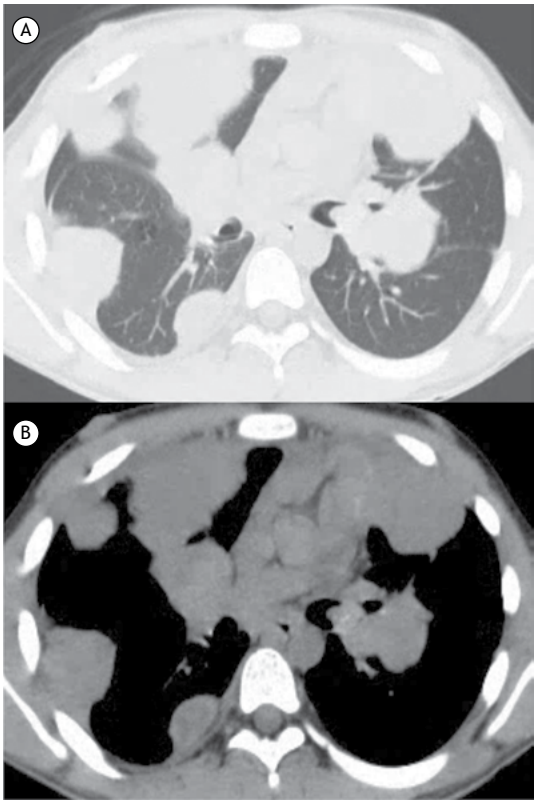


**Figure 5.** A 15-year-old boy with primary osteosarcoma of the femur. In A and B, CT scans showing multiple irregularly shaped masses in both lungs, with invasion of the left main bronchus.

Another atypical presentation of osteosarcoma lung metastasis was intravascular lesion (in 16%), which has rarely been reported in the literature. Intravascular metastasis usually affects small or medium-sized pulmonary arteries, a radiological diagnosis therefore being difficult.[26] Intravascular tumor embolism should be differentiated from pulmonary thromboembolism because they are managed differently.

Endobronchial metastasis is also a rare form of pulmonary involvement in osteosarcoma, being found in only 1 patient in our study. It can occur as secondary metastasis or as direct metastasis to the tracheobronchial tree from an extrapulmonary lesion.[25,27,28] Pleural effusion and lymph node involvement were also uncommon in our study. We found no reports on the incidence of pleural effusion in patients with osteosarcoma and one report on the incidence of lymph node involvement in such patients, the reported incidence being < 3%.[15]

In a follow-up study of osteosarcoma lung metastases, disease progression was observed in 59.4% of cases.[2] We observed disease progression in a larger proportion of patients (72%) and changes in morphological patterns in 17 patients (71%); in 14 of those patients, smooth lesions became lobulated.

Smaller numbers of metastatic lung lesions have been related to better survival and may reflect a low disease burden or favorable tumor biology.[11]

**Table 1.** CT features of osteosarcoma lung metastasis before and during chemotherapy.[a]

| CT feature | Before chemotherapy (n = 72) | During chemotherapy (n = 61) |
|---|---|---|
| Nodule | 69 (96%) | 57 (93%) |
| with calcification | 23 (32%) | 22 (36%) |
| with cavitation | 3 (4%) | 4 (6%) |
| with the halo sign | 4 (5%) | 1 (2%) |
| Intravascular lesion | 11 (15%) | 11 (8%) |
| Endobronchial lesion | 0 (0%) | 1 (2%) |
| Pleural effusion | 4 (5%) | 6 (10%) |
| Lymph node enlargement | 4 (5%) | 5 (8%) |
| Pneumothorax | 2 (3%) | 1 (2%) |
| Vascular thrombosis | 0 (0%) | 1 (2%) |

[a]Data expressed as n (%).

Furthermore, the number of pulmonary nodules detected on baseline CT scans is believed to have greater prognostic significance than does lesion size.[2,21] In our study, many of the patients who died during the study period had > 10 lesions on CT scans obtained before chemotherapy. All 3 patients with pulmonary masses on initial CT scans died. However, because this is a small number of patients, we were unable to assess the impact of this parameter on patient survival.

The present study has some limitations. It was a retrospective study, and the CT techniques varied widely because the examinations were performed on different scanners. Moreover, because we did not have full clinical and disease progression data for all patients, it was difficult to establish clinical and radiological correlations.

In conclusion, the most common CT findings in our patients were solid nodules with smooth margins, predominantly distributed peripherally and bilaterally. Nevertheless, lung metastases can have atypical presentations, with calcification being the most common. Given that the detection of lung metastases and their number and size at the time of diagnosis have a strong impact on the prognosis of patients with osteosarcoma, clinicians must be able to recognize the common and uncommon imaging presentations of lung lesions in these patients.

## AUTHOR CONTRIBUTIONS

JAMS: data collection; editing and review of the manuscript. EM: data analysis; supervision; editing and review of the manuscript. VBA: data analysis; editing and review of the manuscript. MMB: conception and design of the study; editing and review of the manuscript. All authors read and approved the final version of the manuscript.

## CONFLICTS OF INTEREST

None declared.

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