

Review Article: The Diagnosis of Pulmonary Metastases on Chest Computed Tomography in Primary Bone Sarcoma and Musculoskeletal Soft Tissue Sarcoma.

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Shortened title: Diagnosis of Pulmonary Mets on Chest CT in Bone & Soft Tissue Sarcoma

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Abstract

The lungs are the commonest site of metastasis for primary high-grade bone and soft tissue sarcoma, but current guidelines on the management of pulmonary nodules do not specifically cater for this group of patients. The current article reviews the literature from the past 20 years that has reported the CT features of pulmonary metastases in the setting of known primary bone and soft tissue sarcoma, with emphasis on osteosarcoma, chondrosarcoma, and trunk and extremity soft tissue sarcoma, the aim being to aid radiologists who report chest CT of musculoskeletal sarcoma patients in deciding which lesions should be considered metastatic, which lesions are indeterminate and require follow-up, and which lesions are of no concern.

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Introduction

The lungs are the commonest site of metastatic disease at presentation and relapse in patients with high-grade bone and soft tissue sarcoma, and therefore high-resolution chest computed tomography (CT) is required for both staging and surveillance in both conditions[1,2]. However, there are currently no guidelines as to which CT features allow a confident non-invasive diagnosis of pulmonary metastases based on nodule size, characteristics, or number, which creates challenges for radiologists reporting chest CT studies in this patient group. Most clinical studies related to pulmonary metastases in bone and soft tissue sarcoma simply state that metastases were present, without describing the CT features which led to the diagnosis. Also, it is well-recognised that not all pulmonary nodules identified on chest CT in patients with sarcoma represent metastases[3,4], and that chest CT is relatively insensitive compared to lung palpation/thoracotomy in the identification of pulmonary metastases[5–7].

The aim of the current article is to review the published literature from 2000 onwards relating to pulmonary metastases in bone and soft-tissue sarcoma, with an emphasis on studies which provide details of nodule characteristics on CT which were diagnostic of pulmonary metastatic disease.

Primary Bone Sarcoma

Primary bone sarcomas are rare, accounting for <0.2% of all cancers[8]. Osteosarcoma (OS) and Ewing sarcoma (ES) are the commonest bone sarcomas in children and adolescents, while chondrosarcoma (CS) is the commonest bone sarcoma in adults[9]. With regards to the investigation of pulmonary metastases in bone sarcoma, most studies have focused on high-grade intra-medullary OS.

Osteosarcoma

Of 1,765 patients with newly diagnosed OS registered in the neoadjuvant Cooperative Osteosarcoma Study Group studies before 1999, 202 patients (11.4%) had metastases at diagnosis[10]. The incidence of pulmonary metastases in less common sub-types of OS such as parosteal OS is much lower, and almost confined to dedifferentiated parosteal OS particularly when associated with local recurrence[11].

Several studies have examined the relevance of pulmonary nodules identified on staging chest CT in OS, the most informative being those which compared nodule characteristics on CT with histology from biopsy or metastasectomy. The earliest is by Picci et al[12] who studied 51 patients considered to have pulmonary metastases based on chest CT who underwent surgical resection. All nodules were considered to represent metastases irrespective of size. They evaluated nodule number, location (unilateral vs. bilateral), size and presence of calcifications. Histological analysis confirmed metastases in 29 (57%) patients and no metastases in the remainder, with 109 of 204 (53%) excised nodules representing metastases. Regarding nodule number, only 4 of 13 (31%) patients with a single nodule at surgery had metastases, while all 7 patients (100%) with >7 nodules had metastases. With regards to nodule size, 68% of non-metastatic nodules were <5mm in size compared to 35% of metastases (p=0.035). Non-metastatic nodules were more likely to show no change in size (63% vs 22%; p=0.01), and were also more likely to show no change in their number or size following chemotherapy. Conversely, either an increase or decrease in the number or size of nodules was more likely to indicate metastases. Nodule density did not differentiate between benign lesions and metastases. The commonest histological diagnoses of non-metastatic lesions included atelectasis, lymphoid inflammation/infiltration and interstitial fibrosis. Therefore, if all pulmonary nodules in OS patients were considered to be metastatic, the positive predictive value of CT was only 53%. Brader et al[13] reviewed the CT features of 30 children with OS who underwent thoracotomy due to apparent increase in nodule size. In total, 117 nodules were resected, 80 (68%) of which were malignant in 25 (83.3%) patients indicating that 5 (16.7%) patients had only benign nodules. Between 68-74% of nodules were correctly classified by the CT reporting radiologists. The only features significantly associated with malignant histology were nodule size >/= 5mm **(Figs. 1 and 2)** and nodule calcification **(Figs. 2 and 3)**, which had odds ratios (OR) of 6.09-6.77 and 8.47-17.44 for metastases. The commonest causes of benign nodules were fibrosis and lymph nodes. Ciccarese et al[14] reviewed chest CTs in 70 patients with OS referred for thoracotomy with 283 nodules seen on CT having been resected. Of these, 234 (82.7%) were metastases. The mean maximal diameter of metastases was 9.6mm (+/-8.9mm) compared to 3.7mm (+/-2.2mm) for benign lesions ($p<0.0001$), with an optimal cut-off of 6mm for distinguishing benign from malignant nodules. Lesions >6mm in size had a specificity of 89.8% for metastases while the specificity was 100% for nodules >13mm. Calcification was noted in 61.6% of malignant nodules compared to 12% of benign nodules ($p<0.0001$), the pattern of calcifications varying from complete (28.7%) **(Fig. 2)** to partial (71.3%) **(Fig. 3)**. Both benign and malignant lesions had a nodular shape in >85% of cases, but atypical morphology of metastases was seen in 14.1%, the commonest being the presence of striae, consolidation, and cavitation. In 3 cases, pneumothorax was the presenting feature of metastasis. When comparing multiple CT studies, benign lesions remained stable or resolved in 87.7% of patients on follow-up while almost 60% of metastases progressed. The presence of bilateral nodules was not a differentiating feature, but benign nodules were more frequently sub-pleural in location ($p=0.002$).

Several studies have been published which investigated chest CT findings in a mixed group of patients, but with a significant proportion having OS. McCarville et al[15] assessed differentiating features between benign and malignant pulmonary nodules in 50 children/young adults with solid tumours, 30 of which were OS. After exclusions, 41 patients remained with a total of 81

nodules that had histological correlation. Twenty-four of 41 patients (58%) had at least 1 biopsy proven malignant nodule while 17 (42%) had only benign nodules. In 15 cases, multiple nodules were sampled and 4 had both benign and malignant nodules. Of the 81 nodules, 45 (55.6%) were benign with the commonest 3 diagnoses being fibrosis (n=12), granuloma (n=9) and lymphatic tissue (n=8). Features predictive of malignant nodules included distinct nodule margins, development of new nodules, bilaterality and a larger number of nodules (specific number not stated). However, larger nodule size was not predictive of malignancy. Absalon et al[16] reviewed chest CT studies in 210 children and young adults with sarcoma, 61 (29.1%) of whom had OS. They looked at the relevance of lung lesions at presentation, defining round opacities </= 3cm as nodules and lesions >3cm as masses. Lesions were seen in 72 (34.3%) of patients overall and 36.1% of OS patients. Of the total group, 6 lesions were >3cm and presumed to be malignant so not further assessed. Of the remaining 66, the median size of the largest nodule was 5mm (range 1-20mm). Histological analysis was available in 24 cases (18 cases of OS), 10 of which were metastases, 5 granulomata, while the remainder showed normal lung, fibrosis or lymphatic tissue. For the 24 cases with histological confirmation, the significant predictive factors for metastases were nodule number >3 and bilateral distribution. Although there was a tendency to nodule size >5mm being associated with metastases, this did not reach statistical significance. Cho et al[17] performed computerized texture analysis of 42 nodules resected from 16 children with OS, 24 (57.1%) of which proved to be metastases. Logistic regression analysis showed that higher mean attenuation (OR 1.014; p=003) and larger effective diameter (OR 1.745; p=0.012) were significant differentiators for pulmonary metastases. A sub-group analysis was undertaken of small (<5mm) non-calcified nodules, which showed that small metastases could be differentiated from non-malignant nodules based on higher mean attenuation (OR 1.007; p=0.008).

The relevance of so-called ‘indeterminate’ nodules has also been reviewed, these generally being nodules </=5mm in size. Cipriano et al[18] reviewed 126 young patients with sarcoma (66 OS) to determine the relevance of what they termed pulmonary ‘micronodules’. Based on chest CT appearances, patients were classified as having no nodules (Group 1), a single <5mm nodule (Group 2), >1 nodule <5mm (Group 3) or any nodule >5mm (Group 4). Significantly decreased survival was seen in Group 3 patients compared to Group 1, but there was no statistically significant difference between Groups 1 and 2 or 4. Ghosh et al[19] investigated the relevance of indeterminate pulmonary nodules (IPN) in 104 patients with OS, these being defined as non-calcified nodules <10mm in size. Follow-up CT studies were reviewed in patients whose initial studies were classified as non-metastatic (n=55) or indeterminate (n=30). Of the latter sub-group, 21 (70%) remained static, 6 (20%) progressed to metastases at the same site as the IPN while 3 (10%) progressed to metastases separate from the IPN. Of the 21 cases that remained stable only 2 (9.5%) were >5mm in size, while of the 6 IPNs which progressed to metastases 3 (50%) were >5mm in size (p=0.014). No other features in terms of nodule number or location were predictive of IPNs progressing to metastases.

The relevance of CT detected pulmonary nodules at follow-up has also been investigated. Fernandez-Pineda et al[20] identified 16 patients with OS between 1982-2007 who had a solitary pulmonary nodule (SPN) on CT following treatment, and in all cases only a single metastasis was identified at thoracotomy. They suggested that in this small group of patients a minimally invasive approach to nodule removal could be considered. Similarly, Daw et al[21] reported on young (<21 yrs) OS patients who had no metastases at presentation but relapsed with a SPN >1 year after diagnosis. Over 50% of these were long term survivors. McCarville et al[22] identified recurrent pulmonary nodules in 32 of 35 OS patients following thoracotomy, 19 of whom underwent resection of the recurrent lesions and 1 who died underwent an autopsy, with 18 of 20 confirmed to have metastatic disease. The only CT finding predictive of metastases

was progressive pleural thickening, while the occurrence of a SPN in the contralateral lung was almost always associated with a benign process. CT could not distinguish reliably between benign and metastatic recurrent pulmonary disease.

A summary of the CT features suggestive of pulmonary metastases in OS is presented in Table 1.

Ewing Sarcoma

There were no studies which reported on the CT characteristics of pulmonary metastases in Ewing sarcoma specifically. Therefore, the same features reported for osteosarcoma are used when assessing patients with Ewing sarcoma, apart from nodule calcification.

Chondrosarcoma

The incidence of lung metastases in chondrosarcoma (CS) overall is extremely low, metastases being seen on chest CT in 4.3% of patients with high-grade CS and 30% with dedifferentiated CS[23]. The diagnostic significance of pulmonary nodules on chest CT in patients with CS of bone was reported in detail by McLoughlan et al[24]. They reviewed chest CT studies in 444 patients with either newly diagnosed or recurrent CS, of whom 92 (20%) were found to have at least 1 pulmonary nodule. Fourteen patients were excluded from the review leaving a total of 78 cases with at least a single pulmonary nodule, 49 (63%) on initial chest CT and 29 (37%) at follow-up. Of these, 26 nodules were >10mm in dimension of which 24 (92.3%) were metastatic, all but 1 occurring in high-grade CS (n=17) or differentiated CS (n=6). The single metastasis associated with Grade 1 CS occurred at the time of local recurrence. The 2 non-metastatic nodules (1 in Grade 1 and 1 in Grade 3 CS) were single, unilateral, peripheral in location and irregular in contour. Of the 24 metastases, 19 (79.2%) were solid, 4 (16.7%) were calcified, 18 (75%) were multiple, 11 (45.8%) were located peripherally, 16 (66.75) were bilateral and 19 (79.2%) had a lobular contour **(Fig. 4)**. Nodules measuring <10mm were

classified as indeterminate pulmonary nodules (IPNs), which accounted for 52 of 78 (66.7%) identified lesions. Of these, 40 (76.9%) were considered non-metastatic based on a stable appearance or resolution on subsequent imaging, while 12 (23.1%) were considered metastatic based on growth and/or increase in nodule number **(Fig. 5)**. Of the 40 IPNs, 20 (50%) were associated with Grade 1 CS and 18 (45%) with Grade 2 CS, 20 (50%) appeared solid, 11 (27.5%) ground-glass and 9 (22.5%) were calcified. Twenty-one (52.5%) were single and 19 (47.5%) multiple, 38 (95%) peripheral and 31 (77.5%) unilateral, while 29 (72.5%) had smooth margins and 11 (27.5%) were irregular in outline. Conversely, of the 12 IPNs which progressed to metastases, 10 (83.3%) were associated with high-grade or dedifferentiated CS, all (100%) were solid in configuration, 9 (75%) were multiple, all (100%) were either peripherally and peripherally/centrally located, 8 (66.7%) were unilateral and 5 (41.7%) were smooth in contour while the remainder were lobular. Therefore, when combining the characteristics of all 36 metastases, 75% were multiple, 66.7% were >10mm in size, 86.1% were solid in density, 72.2% had a lobular contour, only 1 was purely centrally located, and 55.6% were bilateral.

A summary of the CT features suggestive of pulmonary metastases in CS is presented in Table 2.

Bone and Extremity or Trunk Soft Tissue Sarcoma

Several studies combined the results of bone and soft tissue sarcomas (STS), 2 of which had a large proportion of OS as discussed above[16,18]. Mayo et al[25] reviewed the relevance of incidental findings on chest/abdomen/pelvis CT studies in 149 patients presenting with a variety of bone and STSs, 135 (91%) of whom had at least a single abnormality. Of these, 49 (33%) had indeterminate lung nodules (lesions <1 cm which were not obviously granulomata or lymph nodes). Of these, 15 (31%) proved to be metastatic disease manifest by increase in size and/or number of nodules within 6 months of diagnosis. Factors suggestive of indeterminate nodules being metastatic were primary tumour size >14 cm (p<0.001), and indeterminate nodules measuring 7-10mm in size were more likely metastatic than those measuring <7mm although this did not reach statistical significance (p=0.427). Indeterminate nodules were also more likely to be metastatic for high-grade primary sarcomas (p=0.042), while no indeterminate nodules for low-grade primary tumours progressed to metastases.

Extremity and Trunk Soft Tissue Sarcoma

The incidence of pulmonary metastases in STS was the subject of a report by Billingsley et al[26]. Of 3,149 adult patients with STS at all sites treated at Memorial Sloan-Kettering Cancer Centre between 1982-1997, 719 (22.8%) were diagnosed with pulmonary metastases at either presentation or follow-up based on chest radiography and/or CT. Of 403 patients presenting to the centre with STS, 129 (32%) had synchronous pulmonary metastases, while the remainder developed metastases at follow-up. Christie-Large et al[27] determined the incidence of pulmonary metastases on chest radiography/CT in 1,170 patients with a newly diagnoses STS including all age groups, 96 (8.2%) patients being diagnosed with a metastasis. Most recently, Saifuddin et al[28] reported on the incidence of pulmonary metastases in patients with trunk and extremity STS based on 2 nodule size criteria, >5mm and >10mm. Based on a >5mm nodule size 36.5% of patients had no metastases, 21% had metastases and 42.5% of studies were considered indeterminate (size <5mm), while based on a >10mm nodule size 36.5% of patients had no metastases, 14% had metastases and 49.5% of studies were considered indeterminate (size <10mm). There was no histological correlation.

The value of chest radiography and CT at presentation for different surgical stages of STS has been investigated. Fleming et al[29] reviewed 125 patients with American Joint Committee on Cancer (AJCC) Stage T1 (<5cm) STS, 51 of whom underwent chest CT. Forty-nine (96.1%) had grade 2 or grade 3 lesions. Only a single patient with suspicion of a metastasis on CXR had metastatic disease confirmed on CT, although the CT criteria for diagnosis of metastases were not given. Porter et al[30] performed a similar analysis for 600 patients with AJCC Stage T2 (> 5cm) STS. Of patients who underwent routine chest CT, 19.2% demonstrated pulmonary metastases. Indeterminate nodules were defined as non-calcified nodules <5mm in diameter, and therefore it is assumed that the definition of pulmonary metastases was based on the presence of non-calcified nodules >5mm in size.

Nakamura et al[31] provided a detailed analysis of pulmonary nodules identified on chest CT in 124 patients (mean age 61 years; range 8-94 years) with high-grade STS, 49 (39.5%) having pulmonary nodules at presentation. Of these, 34 (69.4%) had benign lesions, 13 (26.5%) had metastases, 1 (0.8%) had a lung carcinoma while 1 (0.8%) remained indeterminate. During follow-up, pulmonary nodules developed in 30 of the 124 patients, of which 7 (23.3%) were benign, 21 (70%) were metastases while 2 (6.7%) were lung cancers. Nodules were diagnosed as being metastatic if there was histological confirmation from CT-guided biopsy or if there was an increase in number and/or size at follow-up. Nodules were considered benign if proven histologically or if there was no increase in size and/or number over a minimum of 1-year follow-up. Features which significantly differentiated malignant from benign nodules were nodule size (malignant median 6.1mm; benign median 3.5mm: p<0.0001), nodule number (malignant median 2 (range 1-5); benign 1 (range 1-2): p=0.0008) **(Fig. 6)**, and timing of nodule detection (13 of 34 at presentation were metastases compared to 21 of 30 at follow-up: p<0.0001). Twenty percent of patients with nodules </= 3mm had metastases, while 32.7% of patients with nodules </= 5mm had metastases. Conversely, 92.3% of patients with nodules > 5mm had metastases. Therefore, the timing of nodule detection in patients with STS is also of relevance to the likelihood of metastases, in addition to nodule size.

The relevance to outcome of indeterminate pulmonary nodules (IPN) has been reported by Rissing et al[32], who prospectively studied 331 consecutive sarcoma patients. Indeterminate nodules were defined as non-calcified sub-centimetre nodules within the lung parenchyma, and all such cases were followed-up with repeat chest CT at a 2-3-month interval. Seventy-one (21%) had an indeterminate nodule on initial chest CT, 26 with a single nodule, 14 with 2 nodules and 31 with 3 or more nodules. Of these 71, 20 (28%) progressed to metastatic disease at a mean of 12.4 months, 18 (90%) at the site of initial IPN while 2 developed a metastasis at another site while the IPN remained stable. When comparing outcome, patients with IPNs >/= 5mm in size had a worse prognosis than those with a normal chest CT, but a better prognosis than those with definite metastases. IPNs <5mm in size had no effect on outcome.

Regarding specific STS sub-types, the relevance of IPNs at presentation in children with non-metastatic rhabdomyosarcoma has been investigated[33]. IPN were defined as </= 4 pulmonary nodules <5 mm or 1 nodule measuring >5mm but <10 mm, and were identified in 21.2% of 316 children. The remaining children had no lung nodules identified on CT, and no significant difference was demonstrated in 5-year event free survival or overall survival between the two groups. Therefore, IPNs as defined were considered of no clinical relevance.

With regards to follow-up, Baig et al[34] reviewed the value of repeat chest CT at first local recurrence of trunk and extremity STS, identifying a prevalence of 23.9% pulmonary metastases, which supports the need for chest CT at the time of local recurrence in line with the UK guidelines for the management of soft tissue sarcoma[2].

CT Features of Benign Intra-pulmonary Lymph Nodes

Sykes et al[35] compared the CT appearances of benign intrapulmonary lymph nodes (IP-LN) with sarcoma metastases. Chest CT studies of 41 patients with benign IP-LN and 33 patients with sarcoma metastases were retrospectively reviewed and compared with pathology. Of 57 benign IP-LN, 26 (46%) were sub-pleural in location, 38 (67%) were oval in shape **(Fig. 7)**, and 46 (81%) were located in the lower lungs, while 43 (75%) had a lymphatic distribution on

CT and 54 (95%) at pathological review. Of 98 sarcoma metastases 13 (13%) were sub-pleural in location, 15 (15%) were oval, and 56 (57%) were in the lower lungs, while 29 (30%) had a lymphatic distribution on CT and 45 (46%) at pathological review. Therefore, benign IP-LNs are more likely to be oval, to occur in a lymphatic distribution and to be located sub-pleurally than sarcoma metastases.

Discussion

The current article has aimed to determine features on chest CT which are likely to be indicative of pulmonary metastases in high-grade primary bone and musculoskeletal STS. This was primarily achieved by reviewing those studies where nodules identified on chest CT had been excised and there was therefore definitive histological confirmation as to whether they represented metastases or non-metastatic lesions. Therefore, the question has to be raised as to whether this introduced selection bias, since for most of the studies it was not absolutely clear as to why patients had undergone thoracotomy. Nevertheless, the overall findings for both bone and STS were that non-calcified nodules >10mm in diameter should be considered metastatic, non-calcified nodules >6mm are very likely to be metastatic, while non-calcified nodules <5mm in diameter were unlikely to be metastatic. The latter was true even for children with osteosarcoma. In the setting of osteosarcoma, calcified nodules were also more likely to be metastases, while a small proportion of lung metastases in chondrosarcoma were calcified. Another potential limitation of some of the reported studies was the criterion of increasing nodule number or size being indicative of metastases. Brader et al[13] found that 32% of nodules that had apparently increased in size in children with osteosarcoma were in fact benign **(Fig. 8)**.

Regarding nodule size, the findings for bone and STS are similar to those reported in patients with extra-pulmonary cancers of other types. Hanamiya et al[36] reported on the frequency and relevance of pulmonary nodules demonstrated on thin-section chest CT in 308 patients with extra-pulmonary cancers, less than 10 of whom had STS. One or more non-calcified pulmonary nodules were identified in 75% of patients, and nodules <10 mm in size were more likely to be benign while those >10 mm were more likely to be malignant. Ninety-one percent of nodules within 10 mm of the pleura were benign whereas 47% of nodules >10 mm from the pleura were malignant. Caparica et al[4] reviewed needle biopsy findings of pulmonary nodules in 228 patients with non-pulmonary cancers over a 36-month period, less than 14 cases being sarcomas. Sixty-four percent had metastatic disease, 26.3% were diagnosed with a new lung cancer and 9.6% of cases had a benign diagnosis. On multivariate analysis, findings which were significantly predictive of metastases were multiple nodules >5mm in size and the presence of cavitation.

The 2017 Fleischner Society Guidelines for the assessment of incidental pulmonary nodules do not cater for patients with known primary malignancies[37]. In this clinical scenario, Bueno et al[38] suggested that the clinical and imaging management should be aimed at ruling out or confirming the presence of pulmonary metastases, with shorter interval for imaging follow-up and biopsy being placed higher in the management algorithm. Conversely, the British Thoracic Society (BTS) Guidelines for assessment of pulmonary nodules includes those identified in staging patients with known malignancy[39,40]. Several of their reviewed series revealed conflicting associations of extra-pulmonary cancers with their likelihood of pulmonary metastases. Overall, it was suggested that nodules <5mm in size require no follow-up, and that nodules measuring 5-6mm in size should have follow-up imaging in 1 year. However, the latter timescale is unacceptable to patients with known sarcoma or to the oncologists treating them.

Also, as detailed in the above review, it is clear that a small percentage of nodules <5mm in size are metastatic based on growth at follow-up.

In conclusion, the current article has reviewed the available literature form the past 20 years which has assessed the features of pulmonary metastases on chest CT in patients with bone and STS. These would suggest that non-calcified nodules >10mm in size should be considered metastatic, but there is lack of consensus regarding nodules measuring between 5-10mm. Nodules <5mm are likely to be benign, but calcified nodules in a setting of osteosarcoma or chondrosarcoma are likely to be malignant. At present, there are no clear guidelines for the management of pulmonary nodules identified on chest CT in patients with sarcoma.

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Tables

Table 1. Summary of features of pulmonary metastases on chest CT for osteosarcoma.

Features of pulmonary metastases in osteosarcoma
Features likely indicative of metastases: • Multiple nodules (especially >7) • Nodule size >5mm (>6mm specificity ~90%; >13mm specificity 100%) • Nodule calcification (~60% vs 12% in benign nodules) • Change in number or size of nodules after chemotherapy Features likely indicative of benign nodules: • Single nodule (~70% non-metastatic) • Nodule size <5mm (~70% non-metastatic) • Sub-pleural location • No change in size or number after chemotherapy

Table 2. Summary of features of pulmonary metastases on chest CT for chondrosarcoma.

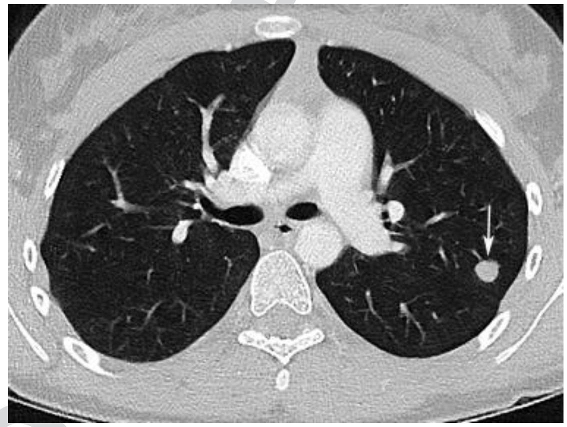
Features of pulmonary metastases in chondrosarcoma
Nodule size >10mm: • ~92% metastatic • Particularly in HG-CD and DD-CS Nodule size <10mm: • ~77% non-metastatic • Low-grade CS • But more likely metastatic in HG-VS or DD-CS

Table 3. Summary of features of pulmonary metastases on chest CT for soft tissue sarcoma.

Features of pulmonary metastases in soft tissue sarcoma
Features likely indicative of metastases: • Nodule size >5mm (~92% metastatic; median size of metastases 6.1mm)) • New nodules at follow-up (~70% metastatic) Features likely indicative of benign nodules: • Nodule size <5mm (~67% non-metastatic; median size of benign nodules 3.5mm) • Nodule size <3mm (~80% non-metastatic) • No increase in size or number after 1-year follow-up

Figures

a



b

Fig. 1 A 14-year-old girl with femoral osteosarcoma. Chest CT demonstrates multiple nodules (arrows) measuring >5mm in size consistent with pulmonary metastases.

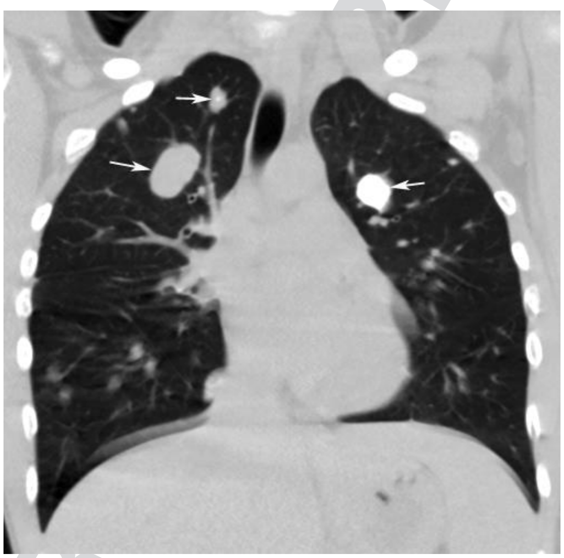
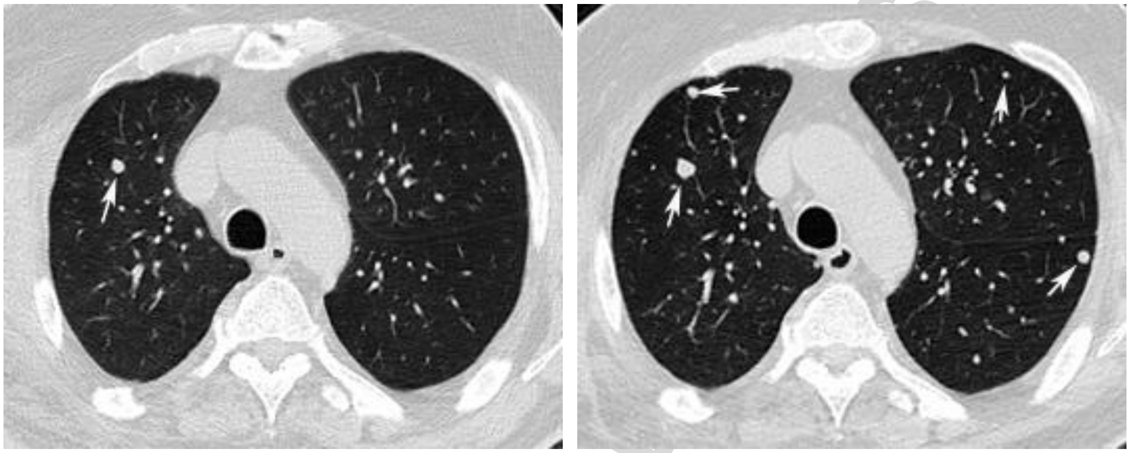


Fig. 2 A 12-year-old girl with tibial osteosarcoma. Chest CT demonstrates multiple large nodules (arrows) measuring >5mm in size consistent with pulmonary metastases. The lesion on the left is completely calcified.

Fig. 3 A 32-year-old female with scapular osteosarcoma. Chest CT demonstrates a partially calcified peripheral nodule (arrow) measuring >5mm in size. Histologically confirmed pulmonary metastasis.

Fig. 4 A 36-year-old female with recurrent scapular high-grade chondrosarcoma. Chest CT demonstrates a large lobular calcified pulmonary nodule (arrow) measuring >10mm in size. Histologically confirmed pulmonary metastasis.



a b

Fig. 5 A 61-year-old male with previously resected right scapular grade 2 chondrosarcoma. (a) Chest CT 13-months after diagnosis demonstrates a single <10mm pulmonary nodule (arrow) which is indeterminate in nature. (b) Chest CT 23 months after diagnosis shows growth of the indeterminate nodule and at least 3 new nodules (arrows) consistent with pulmonary metastases.

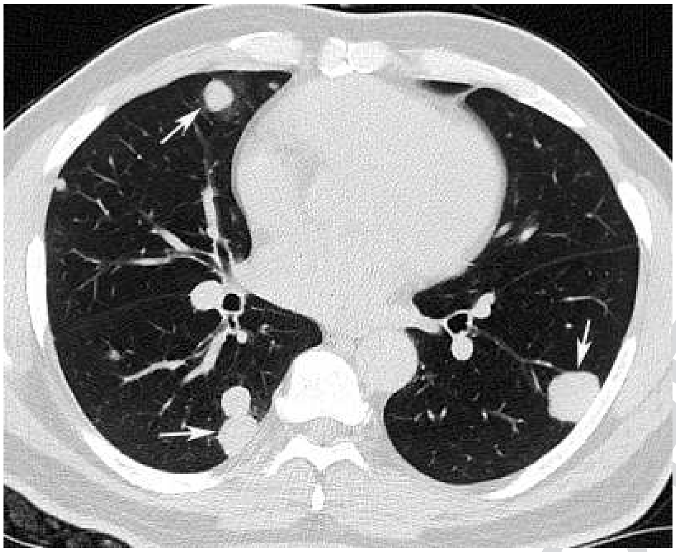
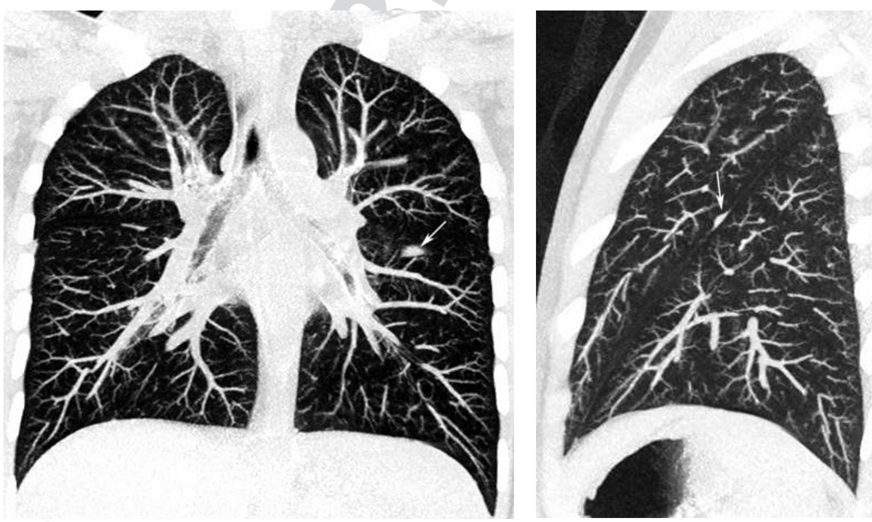
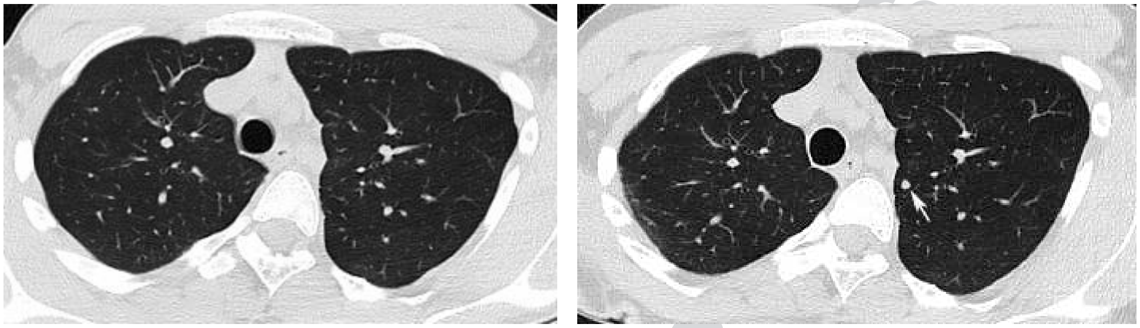


Fig. 6 A 63-year-old male with undifferentiated pleomorphic sarcoma of the thigh. Chest CT demonstrates multiple peripheral pulmonary nodules (arrows) measuring >10mm in size consistent with pulmonary metastases.



a b

Fig. 7 A 10-year-old boy with fibular Ewing sarcoma. (a) Coronal and (b) sagittal chest CT images demonstrate a single oval pulmonary nodule (arrows) related to the left oblique fissure consistent with and intra-pulmonary lymph node.



a b

Fig. 8 A 16-year-old boy with right scapular Ewing sarcoma. (a) Chest CT at presentation shows no evidence of metastases. (b) Chest CT 22-months later demonstrates a single left para-mediastinal pulmonary nodule (arrow) thought to be consistent with development of a pulmonary metastasis as there was an increase in size 5 months later from 3 to 5mm. However, histology revealed a benign inflammatory lesion.

Review Article: The Diagnosis of Pulmonary Metastases on Chest Computed Tomography in Primary Bone Sarcoma and Musculoskeletal Soft Tissue Sarcoma.

Shortened title: Diagnosis of Pulmonary Mets on Chest CT in Bone & Soft Tissue Sarcoma

Abstract

The lungs are the commonest site of metastasis for primary high-grade bone and soft tissue sarcoma, but current guidelines on the management of pulmonary nodules do not specifically cater for this group of patients. The current article reviews the literature from the past 20 years that has reported the CT features of pulmonary metastases in the setting of known primary bone and soft tissue sarcoma, with emphasis on osteosarcoma, chondrosarcoma, and trunk and extremity soft tissue sarcoma, the aim being to aid radiologists who report chest CT of musculoskeletal sarcoma patients in deciding which lesions should be considered metastatic, which lesions are indeterminate and require follow-up, and which lesions are of no concern.

Introduction

The lungs are the commonest site of metastatic disease at presentation and relapse in patients with high-grade bone and soft tissue sarcoma, and therefore thin section chest computed tomography (CT) is required for both staging and surveillance in both conditions[1,2]. However, there are currently no guidelines as to which CT features allow a confident non-invasive diagnosis of pulmonary metastases based on nodule size, characteristics, or number, which creates challenges for radiologists reporting chest CT studies in this patient group. Most clinical studies related to pulmonary metastases in bone and soft tissue sarcoma simply state that metastases were present, without describing the CT features which led to the diagnosis. Also, it is well-recognised that not all pulmonary nodules identified on chest CT in patients with sarcoma represent metastases[3,4], and that chest CT is relatively insensitive compared to lung palpation/thoracotomy in the identification of pulmonary metastases[5–7].

The aim of the current article is to review the published literature from 2000 onwards relating to pulmonary metastases in bone and soft-tissue sarcoma, with an emphasis on studies which provide details of nodule characteristics on CT which were diagnostic of pulmonary metastatic disease.

Primary Bone Sarcoma

Primary bone sarcomas are rare, accounting for <0.2% of all cancers[8]. Osteosarcoma (OS) and Ewing sarcoma (ES) are the commonest bone sarcomas in children and adolescents, while chondrosarcoma (CS) is the commonest bone sarcoma in adults[9]. With regards to the investigation of pulmonary metastases in bone sarcoma, most studies have focused on high-grade intra-medullary OS.

Osteosarcoma

Of 1,765 patients with newly diagnosed OS registered in the neoadjuvant Cooperative Osteosarcoma Study Group studies before 1999, 202 patients (11.4%) had metastases at diagnosis[10]. The incidence of pulmonary metastases in less common sub-types of OS such as parosteal OS is much lower, and almost confined to dedifferentiated parosteal OS particularly when associated with local recurrence[11].

Several studies have examined the relevance of pulmonary nodules identified on staging chest CT in OS, the most informative being those which compared nodule characteristics on CT with histology from biopsy or metastasectomy. The earliest is by Picci et al[12] who studied 51 patients considered to have pulmonary metastases based on chest CT who underwent surgical resection. All nodules were considered to represent metastases irrespective of size. They evaluated nodule number, location (unilateral vs. bilateral), size and presence of calcifications. Histological analysis confirmed metastases in 29 (57%) patients and no metastases in the remainder, with 109 of 204 (53%) excised nodules representing metastases. Regarding nodule number, only 4 of 13 (31%) patients with a single nodule at surgery had metastases, while all 7 patients (100%) with >7 nodules had metastases. With regards to nodule size, 68% of non-metastatic nodules were <5mm in size compared to 35% of metastases ($p=0.035$). Non-metastatic nodules were more likely to show no change in size (63% vs 22%; $p=0.01$) and were also more likely to show no change in their number or size following chemotherapy. Conversely, either an increase or decrease in the number or size of nodules was more likely to indicate metastases. Nodule density did not differentiate between benign lesions and metastases. The commonest histological diagnoses of non-metastatic lesions included atelectasis, lymphoid inflammation/infiltration and interstitial fibrosis. Therefore, if all pulmonary nodules in OS patients were considered metastatic, the positive predictive value of CT was only 53%. Brader et al[13] reviewed the CT features of 30 children with OS who underwent thoracotomy due to apparent increase in nodule size. In total, 117 nodules were resected, 80 (68%) of which were malignant in 25 (83.3%) patients indicating that 5 (16.7%) patients had only benign nodules. Between 68-74% of nodules were correctly classified by the CT reporting radiologists. The only features significantly associated with malignant histology were nodule size >/= 5mm **(Figs. 1 and 2)** and nodule calcification **(Figs. 2 and 3)**, which had odds ratios (OR) of 6.09-6.77 and 8.47-17.44 for metastases. The commonest causes of benign nodules were fibrosis and lymph nodes. Ciccarese et al[14] reviewed chest CTs in 70 patients with OS referred for thoracotomy, with 283 nodules seen on CT having been resected. Of these, 234 (82.7%) were metastases. The mean maximal diameter of metastases was 9.6mm (+/-8.9mm) compared to 3.7mm (+/-2.2mm) for benign lesions (p<0.0001), with an optimal cut-off of 6mm for distinguishing benign from malignant nodules. Lesions >6mm in size had a specificity of 89.8% for metastases while the specificity was 100% for nodules >13mm. Calcification was noted in 61.6% of malignant nodules compared to 12% of benign nodules (p<0.0001), the pattern of calcification varying from complete (28.7%) **(Fig. 2)** to partial (71.3%) **(Fig. 3)**. Both benign and malignant lesions had a nodular shape in >85% of cases, but atypical morphology of metastases was seen in 14.1%, the commonest being the presence of striae, consolidation, and cavitation. In 3 cases, pneumothorax was the presenting feature of metastasis. When comparing multiple CT studies, benign lesions remained stable or resolved in 87.7% of patients on follow-up while almost 60% of metastases progressed. The presence of bilateral nodules was not a differentiating feature, but benign nodules were more frequently sub-pleural in location (p=0.002).

Several studies have been published which investigated chest CT findings in a mixed group of patients, but with a significant proportion having OS. McCarville et al[15] assessed differentiating features between benign and malignant pulmonary nodules in 50 children/young adults with solid tumours, 30 of which were OS. After exclusions, 41 patients remained with a total of 81

nodules that had histological correlation. Twenty-four of 41 patients (58%) had at least 1 biopsy proven malignant nodule while 17 (42%) had only benign nodules. In 15 cases, multiple nodules were sampled and 4 had both benign and malignant nodules. Of the 81 nodules, 45 (55.6%) were benign with the commonest 3 diagnoses being fibrosis (n=12), granuloma (n=9) and lymphatic tissue (n=8). Features predictive of malignant nodules included distinct nodule margins, development of new nodules, bilaterality and a larger number of nodules (specific number not stated). However, larger nodule size was not predictive of malignancy. Absalon et al[16] reviewed chest CT studies in 210 children and young adults with sarcoma, 61 (29.1%) of whom had OS. They looked at the relevance of lung lesions at presentation, defining round opacities </= 3cm as nodules and lesions >3cm as masses. Lesions were seen in 72 (34.3%) patients overall and 36.1% of OS patients. Of the total group, 6 lesions were >3cm and presumed to be malignant, so not further assessed. Of the remaining 66, the median size of the largest nodule was 5mm (range 1-20mm). Histological analysis was available in 24 cases (18 cases of OS), 10 of which were metastases, 5 granulomata, while the remainder showed normal lung, fibrosis or lymphatic tissue. For the 24 cases with histological confirmation, the significant predictive factors for metastases were nodule number >3 and bilateral distribution. Although there was a tendency to nodule size >5mm being associated with metastases, this did not reach statistical significance. Cho et al[17] performed computerized texture analysis of 42 nodules resected from 16 children with OS, 24 (57.1%) of which proved to be metastases. Logistic regression analysis showed that higher mean attenuation (OR 1.014; p=003) and larger effective diameter (OR 1.745; p=0.012) were significant differentiators for pulmonary metastases. A sub-group analysis was undertaken of small (<5mm) non-calcified nodules, which showed that small metastases could be differentiated from non-malignant nodules based on higher mean attenuation (OR 1.007; p=0.008).

The relevance of so-called 'indeterminate' nodules has also been reviewed, these generally being nodules </=5mm in size. Cipriano et al[18] reviewed 126 young patients with sarcoma (66 OS) to determine the relevance of what they termed pulmonary 'micronodules'. Based on chest CT appearances, patients were classified as having no nodules (Group 1), a single <5mm nodule (Group 2), >1 nodule <5mm (Group 3) or any nodule >5mm (Group 4). Significantly decreased survival was seen in Group 3 patients compared to Group 1, but there was no statistically significant difference between Groups 1 and 2 or 4. Ghosh et al[19] investigated the relevance of indeterminate pulmonary nodules (IPN) in 104 patients with OS, these being defined as non-calcified nodules <10mm in size. Follow-up CT studies were reviewed in patients whose initial studies were classified as non-metastatic (n=55) or indeterminate (n=30). Of the latter sub-group, 21 (70%) remained static, 6 (20%) progressed to metastases at the same site as the IPN, while 3 (10%) progressed to metastases separate from the IPN. Of the 21 cases that remained stable only 2 (9.5%) were >5mm in size, while of the 6 IPNs which progressed to metastases 3 (50%) were >5mm in size (p=0.014). No other features in terms of nodule number or location were predictive of IPNs progressing to metastases.

The relevance of CT detected pulmonary nodules at follow-up has also been investigated. Fernandez-Pineda et al[20] identified 16 patients with OS between 1982-2007 who had a solitary pulmonary nodule (SPN) on CT following treatment, and in all cases only a single metastasis was identified at thoracotomy. They suggested that in this small group of patients a minimally invasive approach to nodule removal could be considered. Similarly, Daw et al[21] reported on young (<21 yrs) OS patients who had no metastases at presentation but relapsed with a SPN >1 year after diagnosis. Over 50% of these were long term survivors. McCarville et al[22] identified recurrent pulmonary nodules in 32 of 35 OS patients following thoracotomy, 19 of whom underwent resection of the recurrent lesions and 1 who died underwent an autopsy, with 18 of 20 confirmed to have metastatic disease. The only CT finding predictive of metastases

was progressive pleural thickening, while the occurrence of a SPN in the contralateral lung was almost always associated with a benign process. CT could not distinguish reliably between benign and metastatic recurrent pulmonary disease.

A summary of the CT features suggestive of pulmonary metastases in OS is presented in Table 1.

Ewing Sarcoma

There were no studies which reported on the CT characteristics of pulmonary metastases in Ewing sarcoma specifically. Therefore, the same features reported for osteosarcoma are used when assessing patients with Ewing sarcoma, apart from nodule calcification.

Chondrosarcoma

The incidence of lung metastases in chondrosarcoma (CS) overall is extremely low, metastases being seen on chest CT in 4.3% of patients with high-grade CS and 30% with dedifferentiated CS[23]. The diagnostic significance of pulmonary nodules on chest CT in patients with CS of bone was reported in detail by McLoughlan et al[24]. They reviewed chest CT studies in 444 patients with either newly diagnosed or recurrent CS, of whom 92 (20%) were found to have at least 1 pulmonary nodule. Fourteen patients were excluded from the review leaving a total of 78 cases with at least a single pulmonary nodule, 49 (63%) on initial chest CT and 29 (37%) at follow-up. Of these, 26 nodules were >10mm in dimension of which 24 (92.3%) were metastatic, all but 1 occurring in high-grade CS (n=17) or differentiated CS (n=6). The single metastasis associated with Grade 1 CS occurred at the time of local recurrence. The 2 non-metastatic nodules (1 in Grade 1 and 1 in Grade 3 CS) were single, unilateral, peripheral in location and irregular in contour. Of the 24 metastases, 19 (79.2%) were solid, 4 (16.7%) were calcified, 18 (75%) were multiple, 11 (45.8%) were located peripherally, 16 (66.75) were bilateral and 19 (79.2%) had a lobular contour **(Fig. 4)**. Nodules measuring <10mm were

classified as indeterminate pulmonary nodules (IPNs), which accounted for 52 of 78 (66.7%) identified lesions. Of these, 40 (76.9%) were considered non-metastatic based on a stable appearance or resolution on subsequent imaging, while 12 (23.1%) were considered metastatic based on growth and/or increase in nodule number **(Fig. 5)**. Of the 40 IPNs, 20 (50%) were associated with Grade 1 CS and 18 (45%) with Grade 2 CS, 20 (50%) appeared solid, 11 (27.5%) ground-glass and 9 (22.5%) were calcified. Twenty-one (52.5%) were single and 19 (47.5%) multiple, 38 (95%) peripheral and 31 (77.5%) unilateral, while 29 (72.5%) had smooth margins and 11 (27.5%) were irregular in outline. Conversely, of the 12 IPNs which progressed to presumed metastases, 10 (83.3%) were associated with high-grade or dedifferentiated CS, all (100%) were solid in configuration, 9 (75%) were multiple, all (100%) were either peripherally and peripherally/centrally located, 8 (66.7%) were unilateral and 5 (41.7%) were smooth in contour while the remainder were lobular. Therefore, when combining the characteristics of all 36 metastases, 75% were multiple, 66.7% were >10mm in size, 86.1% were solid in density, 72.2% had a lobular contour, only 1 was purely centrally located, and 55.6% were bilateral.

A summary of the CT features suggestive of pulmonary metastases in CS is presented in Table 2.

Bone and Extremity or Trunk Soft Tissue Sarcoma

Several studies combined the results of bone and soft tissue sarcomas (STS), 2 of which had a large proportion of OS as discussed above[16,18]. Mayo et al[25] reviewed the relevance of incidental findings on chest/abdomen/pelvis CT studies in 149 patients presenting with a variety of bone and STSs, 135 (91%) of whom had at least a single abnormality. Of these, 49 (33%) had indeterminate lung nodules (lesions <1 cm which were not obviously granulomata or lymph nodes). Of these, 15 (31%) were assumed to be metastatic disease manifest by increase in size and/or number of nodules within 6 months of diagnosis. Factors suggestive of indeterminate nodules being metastatic were primary tumour size >14 cm (p<0.001), and indeterminate nodules measuring 7-10mm in size were more likely metastatic than those measuring <7mm although this did not reach statistical significance (p=0.427). Indeterminate nodules were also more likely to be metastatic for high-grade primary sarcomas (p=0.042), while no indeterminate nodules for low-grade primary tumours progressed to metastases.

Extremity and Trunk Soft Tissue Sarcoma

The incidence of pulmonary metastases in STS was the subject of a report by Billingsley et al[26]. Of 3,149 adult patients with STS at all sites treated at Memorial Sloan-Kettering Cancer Centre between 1982-1997, 719 (22.8%) were diagnosed with pulmonary metastases at either presentation or follow-up based on chest radiography and/or CT. Of 403 patients presenting to the centre with STS, 129 (32%) had synchronous pulmonary metastases, while the remainder developed metastases at follow-up. Christie-Large et al[27] determined the incidence of pulmonary metastases on chest radiography/CT in 1,170 patients with a newly diagnoses STS including all age groups, 96 (8.2%) patients being diagnosed with a metastasis. Most recently, Saifuddin et al[28] reported on the incidence of pulmonary metastases in patients with trunk and extremity STS based on 2 nodule size criteria, >5mm and >10mm. Based on a >5mm nodule size 36.5% of patients had no metastases, 21% had metastases and 42.5% of studies were considered indeterminate (size <5mm), while based on a >10mm nodule size 36.5% of patients had no metastases, 14% had metastases and 49.5% of studies were considered indeterminate (size <10mm). There was no histological correlation.

The value of chest radiography and CT at presentation for different surgical stages of STS has been investigated. Fleming et al[29] reviewed 125 patients with American Joint Committee on Cancer (AJCC) Stage T1 (<5cm) STS, 51 of whom underwent chest CT. Forty-nine (96.1%)

had grade 2 or grade 3 lesions. Only a single patient with suspicion of a metastasis on CXR had metastatic disease confirmed on CT, although the CT criteria for diagnosis of metastases were not given. Porter et al[30] performed a similar analysis for 600 patients with AJCC Stage T2 (> 5cm) STS. Of patients who underwent routine chest CT, 19.2% demonstrated pulmonary metastases. Indeterminate nodules were defined as non-calcified nodules <5mm in diameter, and therefore it is assumed that the definition of pulmonary metastases was based on the presence of non-calcified nodules >5mm in size.

Nakamura et al[31] provided a detailed analysis of pulmonary nodules identified on chest CT in 124 patients (mean age 61 years; range 8-94 years) with high-grade STS, 49 (39.5%) having pulmonary nodules at presentation. Of these, 34 (69.4%) had benign lesions, 13 (26.5%) had metastases, 1 (0.8%) had a lung carcinoma while 1 (0.8%) remained indeterminate. During follow-up, pulmonary nodules developed in 30 of the 124 patients, of which 7 (23.3%) were benign, 21 (70%) were considered metastases while 2 (6.7%) were lung cancers. Nodules were diagnosed as being metastatic if there was histological confirmation from CT-guided biopsy or if there was an increase in number and/or size at follow-up. Nodules were considered benign if proven histologically or if there was no increase in size and/or number over a minimum of 1-year follow-up. Features which significantly differentiated malignant from benign nodules were nodule size (malignant median 6.1mm; benign median 3.5mm: p<0.0001), nodule number (malignant median 2 (range 1-5); benign 1 (range 1-2): p=0.0008) **(Fig. 6)**, and timing of nodule detection (13 of 34 at presentation were metastases compared to 21 of 30 at follow-up: p<0.0001). Twenty percent of patients with nodules </= 3mm had metastases, while 32.7% of patients with nodules </= 5mm had metastases. Conversely, 92.3% of patients with nodules > 5mm had metastases. Therefore, the timing of nodule detection in patients with STS is also of relevance to the likelihood of metastases, in addition to nodule size.

The relevance to outcome of indeterminate pulmonary nodules (IPN) has been reported by Rissing et al[32], who prospectively studied 331 consecutive sarcoma patients. Indeterminate nodules were defined as non-calcified sub-centimetre nodules within the lung parenchyma, and all such cases were followed-up with repeat chest CT at a 2-3-month interval. Seventy-one (21%) had an indeterminate nodule on initial chest CT, 26 with a single nodule, 14 with 2 nodules and 31 with 3 or more nodules. Of these 71, 20 (28%) progressed to presumed metastatic disease at a mean of 12.4 months, 18 (90%) at the site of initial IPN while 2 developed a metastasis at another site while the IPN remained stable. When comparing outcome, patients with IPNs >/= 5mm in size had a worse prognosis than those with a normal chest CT, but a better prognosis than those with definite metastases. IPNs <5mm in size had no effect on outcome.

Regarding specific STS sub-types, the relevance of IPNs at presentation in children with non-metastatic rhabdomyosarcoma has been investigated[33]. IPN were defined as </= 4 pulmonary nodules <5 mm or 1 nodule measuring >5mm but <10 mm, being identified in 21.2% of 316 children. The remaining children had no lung nodules identified on CT, and no significant difference was demonstrated in 5-year event free survival or overall survival between the two groups. Therefore, IPNs as defined were considered of no clinical relevance.

With regards to follow-up, Baig et al[34] reviewed the value of repeat chest CT at first local recurrence of trunk and extremity STS, identifying a prevalence of 23.9% pulmonary metastases. This supports the need for chest CT at the time of local recurrence, in line with the UK guidelines for the management of soft tissue sarcoma[2].

CT Features of Benign Intra-pulmonary Lymph Nodes

Sykes et al[35] compared the CT appearances of benign intrapulmonary lymph nodes (IP-LN) with sarcoma metastases. Chest CT studies of 41 patients with benign IP-LN and 33 patients with sarcoma metastases were retrospectively reviewed and compared with pathology. Of 57 benign IP-LN, 26 (46%) were sub-pleural in location, 38 (67%) were oval in shape **(Fig. 7)**, and 46 (81%) were located in the lower lungs, while 43 (75%) had a lymphatic distribution on CT and 54 (95%) at pathological review. Of 98 sarcoma metastases 13 (13%) were sub-pleural in location, 15 (15%) were oval, and 56 (57%) were in the lower lungs, while 29 (30%) had a lymphatic distribution on CT and 45 (46%) at pathological review. Therefore, benign IP-LNs are more likely to be oval, to occur in a lymphatic distribution and to be located sub-pleurally than sarcoma metastases.

Discussion

The current article has aimed to determine features on chest CT which are likely to be indicative of pulmonary metastases in high-grade primary bone and musculoskeletal STS. This was primarily achieved by reviewing those studies where nodules identified on chest CT had been excised, and there was therefore definitive histological confirmation as to whether they represented metastases or non-metastatic lesions. Therefore, the question has to be raised as to whether this introduced selection bias, since for most of the studies it was not absolutely clear as to why patients had undergone thoracotomy. Nevertheless, the overall findings for both bone and STS were that non-calcified nodules >10mm in diameter should be considered metastatic, non-calcified nodules >6mm are highly likely to be metastatic, while non-calcified nodules <5mm in diameter were unlikely to be metastatic. The latter was true even for children with osteosarcoma. In the setting of osteosarcoma, calcified nodules were also more likely to be metastases, while a small proportion of lung metastases in chondrosarcoma were calcified. Another potential limitation of some of the reported studies was the criterion of increasing nodule number or size being indicative of metastases. Brader et al[13] found that 32% of nodules that had apparently increased in size in children with osteosarcoma were in fact benign **(Fig. 8)**.

Regarding nodule size, the findings for bone and STS are similar to those reported in patients with extra-pulmonary cancers of other types. Hanamiya et al[36] reported on the frequency and relevance of pulmonary nodules demonstrated on thin-section chest CT in 308 patients with extra-pulmonary cancers, less than 10 of whom had STS. One or more non-calcified pulmonary nodules were identified in 75% of patients, and nodules <10 mm in size were more likely to be benign while those >10 mm were more likely to be malignant. Ninety-one percent of nodules within 10 mm of the pleura were benign whereas 47% of nodules >10 mm from the pleura were malignant. Caparica et al[4] reviewed needle biopsy findings of pulmonary nodules in 228 patients with non-pulmonary cancers over a 36-month period, less than 14 cases being sarcomas. Sixty-four percent had metastatic disease, 26.3% were diagnosed with a new lung cancer and 9.6% of cases had a benign diagnosis. On multivariate analysis, findings which were significantly predictive of metastases were multiple nodules >5mm in size and the presence of cavitation.

The 2017 Fleischner Society Guidelines for the assessment of incidental pulmonary nodules do not cater for patients with known primary malignancies[37]. In this clinical scenario, Bueno et al[38] suggested that the clinical and imaging management should be aimed at ruling out or confirming the presence of pulmonary metastases, with shorter interval for imaging follow-up and biopsy being placed higher in the management algorithm. Conversely, the British Thoracic Society (BTS) Guidelines for assessment of pulmonary nodules includes those identified in staging patients with known malignancy[39,40]. Several of their reviewed series revealed conflicting associations of extra-pulmonary cancers with their likelihood of pulmonary metastases. Overall, it was suggested that nodules <5mm in size required no follow-up, and that nodules measuring 5-6mm in size should have follow-up imaging in 1 year. However, the latter timescale is unacceptable to patients with known sarcoma or to the oncologists treating them. Also, as detailed in the above review, it is clear that a small percentage of nodules <5mm in size may be metastatic based on growth at follow-up.

In conclusion, the current article has reviewed the available literature form the past 20 years which has assessed the features of pulmonary metastases on thin section chest CT in patients with bone and STS. These would suggest that non-calcified nodules >10mm in size should be considered metastatic, but there is lack of consensus regarding nodules measuring between 5-10mm. Nodules <5mm are likely to be benign, but calcified nodules in a setting of osteosarcoma or chondrosarcoma are likely to be malignant. At present, there are no clear guidelines for the management of pulmonary nodules identified on chest CT in patients with musculoskeletal sarcoma.

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Tables

Table 1. Summary of features of pulmonary metastases on chest CT for osteosarcoma.

Features of pulmonary metastases in osteosarcoma (OS)
Features likely indicative of metastases: • Multiple nodules (especially >7) • Nodule size >5mm (>6mm specificity ~90%; >13mm specificity 100%) • Nodule calcification (~60% vs 12% in benign nodules) • Change in number or size of nodules after chemotherapy Features likely indicative of benign nodules: • Single nodule (~70% non-metastatic) • Nodule size <5mm (~70% non-metastatic) • Sub-pleural location • No change in size or number after chemotherapy

Table 2. Summary of features of pulmonary metastases on chest CT for chondrosarcoma.

Features of pulmonary metastases in chondrosarcoma (CS)
Nodule size >10mm: • ~92% metastatic • Particularly in high-grade chondrosarcoma (HG-CS) and dedifferentiated chondrosarcoma (DD-CS) Nodule size <10mm: • ~77% non-metastatic • Low-grade chondrosarcoma (CS) • But more likely metastatic in high-grade chondrosarcoma (HG-CS) and dedifferentiated chondrosarcoma (DD-CS)

Table 3. Summary of features of pulmonary metastases on chest CT for soft tissue sarcoma.

Features of pulmonary metastases in soft tissue sarcoma (STS)
Features likely indicative of metastases: • Nodule size >5mm (~92% metastatic; median size of metastases 6.1mm)) • New nodules at follow-up (~70% metastatic) Features likely indicative of benign nodules: • Nodule size <5mm (~67% non-metastatic; median size of benign nodules 3.5mm) • Nodule size <3mm (~80% non-metastatic) • No increase in size or number after 1-year follow-up

Table 4. Summary of CT features of benign intra-pulmonary lymph nodes.

Features of benign intra-pulmonary lymph nodes
• Sub-pleural in location (46%) • Oval in shape (67%) • Located in the lower lungs (81%) • Lymphatic distribution (75%)

Figures

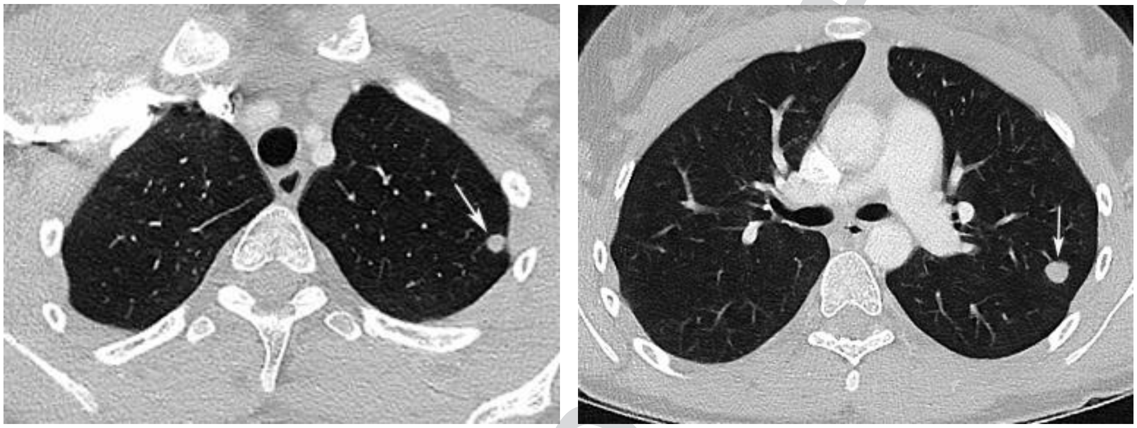

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Fig. 1 A 14-year-old girl with femoral osteosarcoma. Chest CT demonstrates multiple nodules (arrows) measuring >5mm in size consistent with pulmonary metastases.

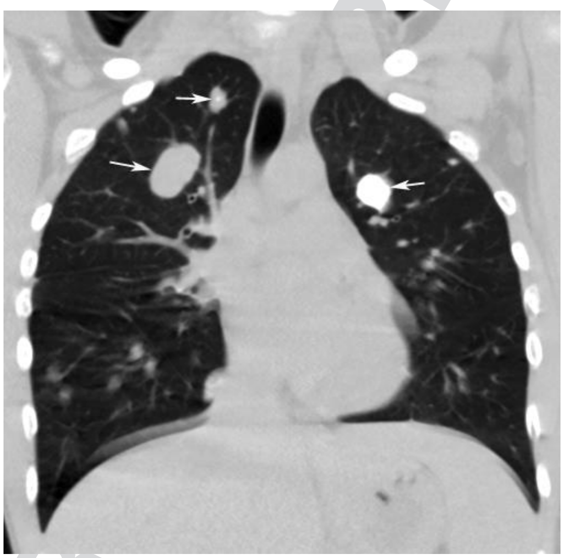

Fig. 2 A 12-year-old girl with tibial osteosarcoma. Chest CT demonstrates multiple large nodules (arrows) measuring >5mm in size consistent with pulmonary metastases. The lesion on the left is completely calcified.

Fig. 3 A 32-year-old female with scapular osteosarcoma. Chest CT demonstrates a partially calcified peripheral nodule (arrow) measuring >5mm in size. Histologically confirmed pulmonary metastasis.

Fig. 4 A 36-year-old female with recurrent scapular high-grade chondrosarcoma. Chest CT demonstrates a large lobular calcified pulmonary nodule (arrow) measuring >10mm in size. Histologically confirmed pulmonary metastasis.

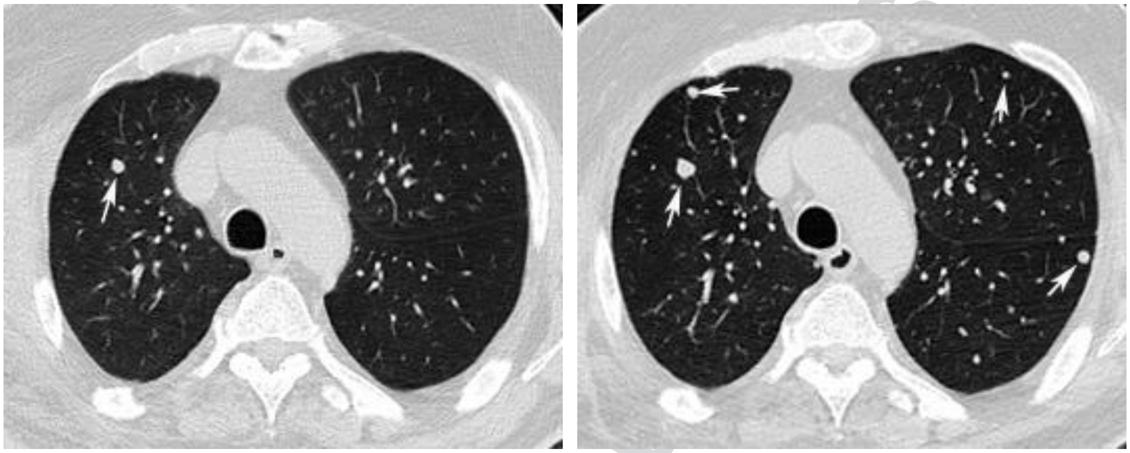

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Fig. 5 A 61-year-old male with previously resected right scapular grade 2 chondrosarcoma. (a) Chest CT 13-months after diagnosis demonstrates a single <10mm pulmonary nodule (arrow) which is indeterminate in nature. (b) Chest CT 23 months after diagnosis shows growth of the indeterminate nodule and at least 3 new nodules (arrows) consistent with pulmonary metastases.

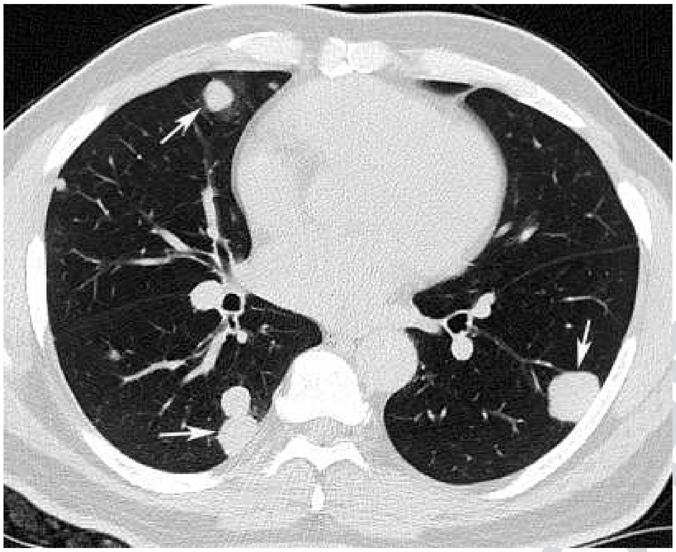

Fig. 6 A 63-year-old male with undifferentiated pleomorphic sarcoma of the thigh. Chest CT demonstrates multiple peripheral pulmonary nodules (arrows) measuring >10mm in size consistent with pulmonary metastases.

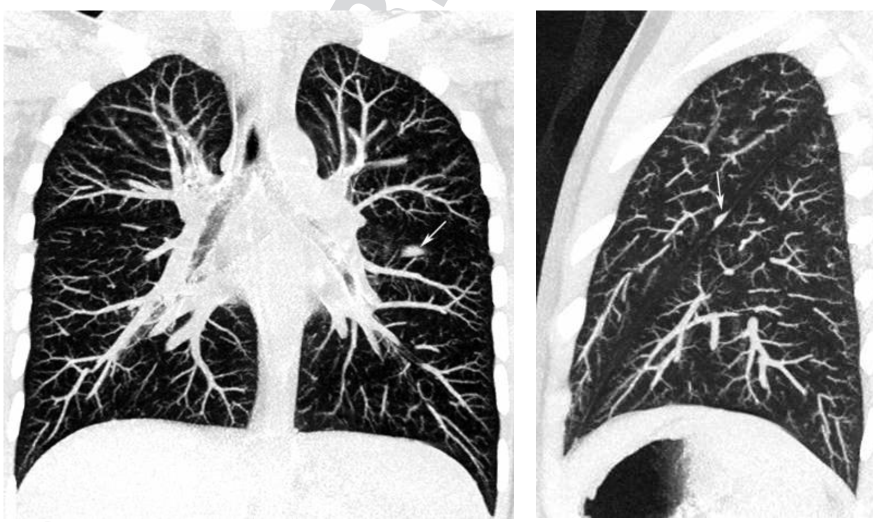

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Fig. 7 A 10-year-old boy with fibular Ewing sarcoma. (a) Coronal and (b) sagittal chest CT images demonstrate a single oval pulmonary nodule (arrows) related to the left oblique fissure consistent with an intra-pulmonary lymph node.

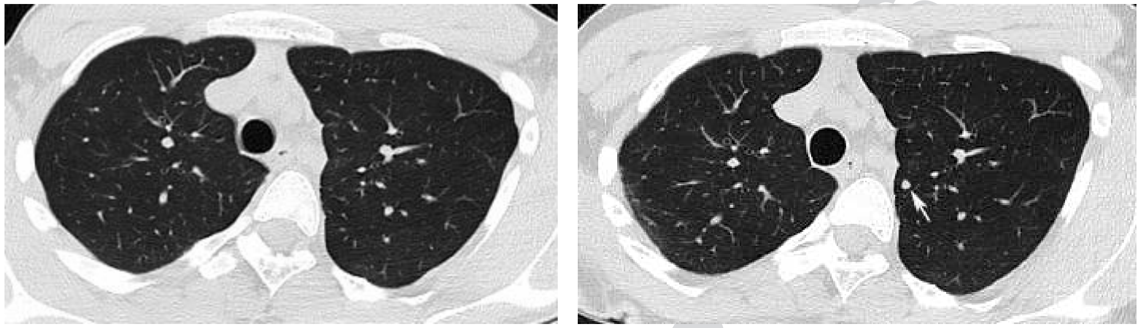

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Fig. 8 A 16-year-old boy with right scapular Ewing sarcoma. (a) Chest CT at presentation shows no evidence of metastases. (b) Chest CT 22-months later demonstrates a single left para-mediastinal pulmonary nodule (arrow) thought to be consistent with development of a pulmonary metastasis as there was an increase in size 5 months later from 3 to 5mm. However, histology revealed a benign inflammatory lesion.

Review Article: The Diagnosis of Pulmonary Metastases on Chest Computed Tomography in Primary Bone Sarcoma and Musculoskeletal Soft Tissue Sarcoma.

Shortened title: Diagnosis of Pulmonary Mets on Chest CT in Bone & Soft Tissue Sarcoma

Abstract

The lungs are the commonest site of metastasis for primary high-grade bone and soft tissue sarcoma, but current guidelines on the management of pulmonary nodules do not specifically cater for this group of patients. The current article reviews the literature from the past 20 years that has reported the CT features of pulmonary metastases in the setting of known primary bone and soft tissue sarcoma, with emphasis on osteosarcoma, chondrosarcoma, and trunk and extremity soft tissue sarcoma, the aim being to aid radiologists who report chest CT of musculoskeletal sarcoma patients in deciding which lesions should be considered metastatic, which lesions are indeterminate and require follow-up, and which lesions are of no concern.

Introduction

The lungs are the commonest site of metastatic disease at presentation and relapse in patients with high-grade bone and soft tissue sarcoma, and therefore thin section chest computed tomography (CT) is required for both staging and surveillance in both conditions[1,2]. However, there are currently no guidelines as to which CT features allow a confident non-invasive diagnosis of pulmonary metastases based on nodule size, characteristics, or number, which creates challenges for radiologists reporting chest CT studies in this patient group. Most clinical studies related to pulmonary metastases in bone and soft tissue sarcoma simply state that metastases were present, without describing the CT features which led to the diagnosis. Also, it is well-recognised that not all pulmonary nodules identified on chest CT in patients with sarcoma represent metastases[3,4], and that chest CT is relatively insensitive compared to lung palpation/thoracotomy in the identification of pulmonary metastases[5–7].

The aim of the current article is to review the published literature from 2000 onwards relating to pulmonary metastases in bone and soft-tissue sarcoma, with an emphasis on studies which provide details of nodule characteristics on CT which were diagnostic of pulmonary metastatic disease.

Primary Bone Sarcoma

Primary bone sarcomas are rare, accounting for <0.2% of all cancers[8]. Osteosarcoma (OS) and Ewing sarcoma (ES) are the commonest bone sarcomas in children and adolescents, while chondrosarcoma (CS) is the commonest bone sarcoma in adults[9]. With regards to the investigation of pulmonary metastases in bone sarcoma, most studies have focused on high-grade intra-medullary OS.

Osteosarcoma

Of 1,765 patients with newly diagnosed OS registered in the neoadjuvant Cooperative Osteosarcoma Study Group studies before 1999, 202 patients (11.4%) had metastases at diagnosis[10]. The incidence of pulmonary metastases in less common sub-types of OS such as parosteal OS is much lower, and almost confined to dedifferentiated parosteal OS particularly when associated with local recurrence[11].

Several studies have examined the relevance of pulmonary nodules identified on staging chest CT in OS, the most informative being those which compared nodule characteristics on CT with histology from biopsy or metastasectomy. The earliest is by Picci et al[12] who studied 51 patients considered to have pulmonary metastases based on chest CT who underwent surgical resection. All nodules were considered to represent metastases irrespective of size. They evaluated nodule number, location (unilateral vs. bilateral), size and presence of calcifications. Histological analysis confirmed metastases in 29 (57%) patients and no metastases in the remainder, with 109 of 204 (53%) excised nodules representing metastases. Regarding nodule number, only 4 of 13 (31%) patients with a single nodule at surgery had metastases, while all 7 patients (100%) with >7 nodules had metastases. With regards to nodule size, 68% of non-metastatic nodules were <5mm in size compared to 35% of metastases (p=0.035). Non-metastatic nodules were more likely to show no change in size (63% vs 22%; p=0.01) and were also more likely to show no change in their number or size following chemotherapy. Conversely, either an increase or decrease in the number or size of nodules was more likely to indicate metastases. Nodule density did not differentiate between benign lesions and metastases. The commonest histological diagnoses of non-metastatic lesions included atelectasis, lymphoid inflammation/infiltration and interstitial fibrosis. Therefore, if all pulmonary nodules in OS patients were considered metastatic, the positive predictive value of CT was only 53%. Brader et al[13] reviewed the CT features of 30 children with OS who underwent thoracotomy due to apparent increase in nodule size. In total, 117 nodules were resected, 80 (68%) of which were malignant in 25 (83.3%) patients indicating that 5 (16.7%) patients had only benign nodules. Between 68-74% of nodules were correctly classified by the CT reporting radiologists. The only features significantly associated with malignant histology were nodule size >/= 5mm **(Figs. 1 and 2)** and nodule calcification **(Figs. 2 and 3)**, which had odds ratios (OR) of 6.09-6.77 and 8.47-17.44 for metastases. The commonest causes of benign nodules were fibrosis and lymph nodes. Ciccarese et al[14] reviewed chest CTs in 70 patients with OS referred for thoracotomy, with 283 nodules seen on CT having been resected. Of these, 234 (82.7%) were metastases. The mean maximal diameter of metastases was 9.6mm (+/-8.9mm) compared to 3.7mm (+/-2.2mm) for benign lesions ($p<0.0001$), with an optimal cut-off of 6mm for distinguishing benign from malignant nodules. Lesions >6mm in size had a specificity of 89.8% for metastases while the specificity was 100% for nodules >13mm. Calcification was noted in 61.6% of malignant nodules compared to 12% of benign nodules ($p<0.0001$), the pattern of calcification varying from complete (28.7%) **(Fig. 2)** to partial (71.3%) **(Fig. 3)**. Both benign and malignant lesions had a nodular shape in >85% of cases, but atypical morphology of metastases was seen in 14.1%, the commonest being the presence of striae, consolidation, and cavitation. In 3 cases, pneumothorax was the presenting feature of metastasis. When comparing multiple CT studies, benign lesions remained stable or resolved in 87.7% of patients on follow-up while almost 60% of metastases progressed. The presence of bilateral nodules was not a differentiating feature, but benign nodules were more frequently sub-pleural in location ($p=0.002$).

Several studies have been published which investigated chest CT findings in a mixed group of patients, but with a significant proportion having OS. McCarville et al[15] assessed differentiating features between benign and malignant pulmonary nodules in 50 children/young adults with solid tumours, 30 of which were OS. After exclusions, 41 patients remained with a total of 81

nodules that had histological correlation. Twenty-four of 41 patients (58%) had at least 1 biopsy proven malignant nodule while 17 (42%) had only benign nodules. In 15 cases, multiple nodules were sampled and 4 had both benign and malignant nodules. Of the 81 nodules, 45 (55.6%) were benign with the commonest 3 diagnoses being fibrosis (n=12), granuloma (n=9) and lymphatic tissue (n=8). Features predictive of malignant nodules included distinct nodule margins, development of new nodules, bilaterality and a larger number of nodules (specific number not stated). However, larger nodule size was not predictive of malignancy. Absalon et al[16] reviewed chest CT studies in 210 children and young adults with sarcoma, 61 (29.1%) of whom had OS. They looked at the relevance of lung lesions at presentation, defining round opacities </= 3cm as nodules and lesions >3cm as masses. Lesions were seen in 72 (34.3%) patients overall and 36.1% of OS patients. Of the total group, 6 lesions were >3cm and presumed to be malignant, so not further assessed. Of the remaining 66, the median size of the largest nodule was 5mm (range 1-20mm). Histological analysis was available in 24 cases (18 cases of OS), 10 of which were metastases, 5 granulomata, while the remainder showed normal lung, fibrosis or lymphatic tissue. For the 24 cases with histological confirmation, the significant predictive factors for metastases were nodule number >3 and bilateral distribution. Although there was a tendency to nodule size >5mm being associated with metastases, this did not reach statistical significance. Cho et al[17] performed computerized texture analysis of 42 nodules resected from 16 children with OS, 24 (57.1%) of which proved to be metastases. Logistic regression analysis showed that higher mean attenuation (OR 1.014; p=003) and larger effective diameter (OR 1.745; p=0.012) were significant differentiators for pulmonary metastases. A sub-group analysis was undertaken of small (<5mm) non-calcified nodules, which showed that small metastases could be differentiated from non-malignant nodules based on higher mean attenuation (OR 1.007; p=0.008).

The relevance of so-called 'indeterminate' nodules has also been reviewed, these generally being nodules </=5mm in size. Cipriano et al[18] reviewed 126 young patients with sarcoma (66 OS) to determine the relevance of what they termed pulmonary 'micronodules'. Based on chest CT appearances, patients were classified as having no nodules (Group 1), a single <5mm nodule (Group 2), >1 nodule <5mm (Group 3) or any nodule >5mm (Group 4). Significantly decreased survival was seen in Group 3 patients compared to Group 1, but there was no statistically significant difference between Groups 1 and 2 or 4. Ghosh et al[19] investigated the relevance of indeterminate pulmonary nodules (IPN) in 104 patients with OS, these being defined as non-calcified nodules <10mm in size. Follow-up CT studies were reviewed in patients whose initial studies were classified as non-metastatic (n=55) or indeterminate (n=30). Of the latter sub-group, 21 (70%) remained static, 6 (20%) progressed to metastases at the same site as the IPN, while 3 (10%) progressed to metastases separate from the IPN. Of the 21 cases that remained stable only 2 (9.5%) were >5mm in size, while of the 6 IPNs which progressed to metastases 3 (50%) were >5mm in size (p=0.014). No other features in terms of nodule number or location were predictive of IPNs progressing to metastases.

The relevance of CT detected pulmonary nodules at follow-up has also been investigated. Fernandez-Pineda et al[20] identified 16 patients with OS between 1982-2007 who had a solitary pulmonary nodule (SPN) on CT following treatment, and in all cases only a single metastasis was identified at thoracotomy. They suggested that in this small group of patients a minimally invasive approach to nodule removal could be considered. Similarly, Daw et al[21] reported on young (<21 yrs) OS patients who had no metastases at presentation but relapsed with a SPN >1 year after diagnosis. Over 50% of these were long term survivors. McCarville et al[22] identified recurrent pulmonary nodules in 32 of 35 OS patients following thoracotomy, 19 of whom underwent resection of the recurrent lesions and 1 who died underwent an autopsy, with 18 of 20 confirmed to have metastatic disease. The only CT finding predictive of metastases

was progressive pleural thickening, while the occurrence of a SPN in the contralateral lung was almost always associated with a benign process. CT could not distinguish reliably between benign and metastatic recurrent pulmonary disease.

A summary of the CT features suggestive of pulmonary metastases in OS is presented in Table 1.

Ewing Sarcoma

There were no studies which reported on the CT characteristics of pulmonary metastases in Ewing sarcoma specifically. Therefore, the same features reported for osteosarcoma are used when assessing patients with Ewing sarcoma, apart from nodule calcification.

Chondrosarcoma

The incidence of lung metastases in chondrosarcoma (CS) overall is extremely low, metastases being seen on chest CT in 4.3% of patients with high-grade CS and 30% with dedifferentiated CS[23]. The diagnostic significance of pulmonary nodules on chest CT in patients with CS of bone was reported in detail by McLoughlan et al[24]. They reviewed chest CT studies in 444 patients with either newly diagnosed or recurrent CS, of whom 92 (20%) were found to have at least 1 pulmonary nodule. Fourteen patients were excluded from the review leaving a total of 78 cases with at least a single pulmonary nodule, 49 (63%) on initial chest CT and 29 (37%) at follow-up. Of these, 26 nodules were >10mm in dimension of which 24 (92.3%) were metastatic, all but 1 occurring in high-grade CS (n=17) or differentiated CS (n=6). The single metastasis associated with Grade 1 CS occurred at the time of local recurrence. The 2 non-metastatic nodules (1 in Grade 1 and 1 in Grade 3 CS) were single, unilateral, peripheral in location and irregular in contour. Of the 24 metastases, 19 (79.2%) were solid, 4 (16.7%) were calcified, 18 (75%) were multiple, 11 (45.8%) were located peripherally, 16 (66.75) were bilateral and 19 (79.2%) had a lobular contour **(Fig. 4)**. Nodules measuring <10mm were

classified as indeterminate pulmonary nodules (IPNs), which accounted for 52 of 78 (66.7%) identified lesions. Of these, 40 (76.9%) were considered non-metastatic based on a stable appearance or resolution on subsequent imaging, while 12 (23.1%) were considered metastatic based on growth and/or increase in nodule number **(Fig. 5)**. Of the 40 IPNs, 20 (50%) were associated with Grade 1 CS and 18 (45%) with Grade 2 CS, 20 (50%) appeared solid, 11 (27.5%) ground-glass and 9 (22.5%) were calcified. Twenty-one (52.5%) were single and 19 (47.5%) multiple, 38 (95%) peripheral and 31 (77.5%) unilateral, while 29 (72.5%) had smooth margins and 11 (27.5%) were irregular in outline. Conversely, of the 12 IPNs which progressed to presumed metastases, 10 (83.3%) were associated with high-grade or dedifferentiated CS, all (100%) were solid in configuration, 9 (75%) were multiple, all (100%) were either peripherally and peripherally/centrally located, 8 (66.7%) were unilateral and 5 (41.7%) were smooth in contour while the remainder were lobular. Therefore, when combining the characteristics of all 36 metastases, 75% were multiple, 66.7% were >10mm in size, 86.1% were solid in density, 72.2% had a lobular contour, only 1 was purely centrally located, and 55.6% were bilateral.

A summary of the CT features suggestive of pulmonary metastases in CS is presented in Table 2.

Bone and Extremity or Trunk Soft Tissue Sarcoma

Several studies combined the results of bone and soft tissue sarcomas (STS), 2 of which had a large proportion of OS as discussed above[16,18]. Mayo et al[25] reviewed the relevance of incidental findings on chest/abdomen/pelvis CT studies in 149 patients presenting with a variety of bone and STSs, 135 (91%) of whom had at least a single abnormality. Of these, 49 (33%) had indeterminate lung nodules (lesions <1 cm which were not obviously granulomata or lymph nodes). Of these, 15 (31%) were assumed to be metastatic disease manifest by increase in size and/or number of nodules within 6 months of diagnosis. Factors suggestive of indeterminate nodules being metastatic were primary tumour size >14 cm ($p<0.001$), and indeterminate nodules measuring 7-10mm in size were more likely metastatic than those measuring <7mm although this did not reach statistical significance ($p=0.427$). Indeterminate nodules were also more likely to be metastatic for high-grade primary sarcomas ($p=0.042$), while no indeterminate nodules for low-grade primary tumours progressed to metastases.

Extremity and Trunk Soft Tissue Sarcoma

The incidence of pulmonary metastases in STS was the subject of a report by Billingsley et al[26]. Of 3,149 adult patients with STS at all sites treated at Memorial Sloan-Kettering Cancer Centre between 1982-1997, 719 (22.8%) were diagnosed with pulmonary metastases at either presentation or follow-up based on chest radiography and/or CT. Of 403 patients presenting to the centre with STS, 129 (32%) had synchronous pulmonary metastases, while the remainder developed metastases at follow-up. Christie-Large et al[27] determined the incidence of pulmonary metastases on chest radiography/CT in 1,170 patients with a newly diagnoses STS including all age groups, 96 (8.2%) patients being diagnosed with a metastasis. Most recently, Saifuddin et al[28] reported on the incidence of pulmonary metastases in patients with trunk and extremity STS based on 2 nodule size criteria, >5mm and >10mm. Based on a >5mm nodule size 36.5% of patients had no metastases, 21% had metastases and 42.5% of studies were considered indeterminate (size <5mm), while based on a >10mm nodule size 36.5% of patients had no metastases, 14% had metastases and 49.5% of studies were considered indeterminate (size <10mm). There was no histological correlation.

The value of chest radiography and CT at presentation for different surgical stages of STS has been investigated. Fleming et al[29] reviewed 125 patients with American Joint Committee on Cancer (AJCC) Stage T1 (<5cm) STS, 51 of whom underwent chest CT. Forty-nine (96.1%)

had grade 2 or grade 3 lesions. Only a single patient with suspicion of a metastasis on CXR had metastatic disease confirmed on CT, although the CT criteria for diagnosis of metastases were not given. Porter et al[30] performed a similar analysis for 600 patients with AJCC Stage T2 (> 5cm) STS. Of patients who underwent routine chest CT, 19.2% demonstrated pulmonary metastases. Indeterminate nodules were defined as non-calcified nodules <5mm in diameter, and therefore it is assumed that the definition of pulmonary metastases was based on the presence of non-calcified nodules >5mm in size.

Nakamura et al[31] provided a detailed analysis of pulmonary nodules identified on chest CT in 124 patients (mean age 61 years; range 8-94 years) with high-grade STS, 49 (39.5%) having pulmonary nodules at presentation. Of these, 34 (69.4%) had benign lesions, 13 (26.5%) had metastases, 1 (0.8%) had a lung carcinoma while 1 (0.8%) remained indeterminate. During follow-up, pulmonary nodules developed in 30 of the 124 patients, of which 7 (23.3%) were benign, 21 (70%) were considered metastases while 2 (6.7%) were lung cancers. Nodules were diagnosed as being metastatic if there was histological confirmation from CT-guided biopsy or if there was an increase in number and/or size at follow-up. Nodules were considered benign if proven histologically or if there was no increase in size and/or number over a minimum of 1-year follow-up. Features which significantly differentiated malignant from benign nodules were nodule size (malignant median 6.1mm; benign median 3.5mm: p<0.0001), nodule number (malignant median 2 (range 1-5); benign 1 (range 1-2): p=0.0008) **(Fig. 6)**, and timing of nodule detection (13 of 34 at presentation were metastases compared to 21 of 30 at follow-up: p<0.0001). Twenty percent of patients with nodules </= 3mm had metastases, while 32.7% of patients with nodules </= 5mm had metastases. Conversely, 92.3% of patients with nodules > 5mm had metastases. Therefore, the timing of nodule detection in patients with STS is also of relevance to the likelihood of metastases, in addition to nodule size.

The relevance to outcome of indeterminate pulmonary nodules (IPN) has been reported by Rissing et al[32], who prospectively studied 331 consecutive sarcoma patients. Indeterminate nodules were defined as non-calcified sub-centimetre nodules within the lung parenchyma, and all such cases were followed-up with repeat chest CT at a 2-3-month interval. Seventy-one (21%) had an indeterminate nodule on initial chest CT, 26 with a single nodule, 14 with 2 nodules and 31 with 3 or more nodules. Of these 71, 20 (28%) progressed to presumed metastatic disease at a mean of 12.4 months, 18 (90%) at the site of initial IPN while 2 developed a metastasis at another site while the IPN remained stable. When comparing outcome, patients with IPNs >/= 5mm in size had a worse prognosis than those with a normal chest CT, but a better prognosis than those with definite metastases. IPNs <5mm in size had no effect on outcome.

Regarding specific STS sub-types, the relevance of IPNs at presentation in children with non-metastatic rhabdomyosarcoma has been investigated[33]. IPN were defined as </= 4 pulmonary nodules <5 mm or 1 nodule measuring >5mm but <10 mm, being identified in 21.2% of 316 children. The remaining children had no lung nodules identified on CT, and no significant difference was demonstrated in 5-year event free survival or overall survival between the two groups. Therefore, IPNs as defined were considered of no clinical relevance.

With regards to follow-up, Baig et al[34] reviewed the value of repeat chest CT at first local recurrence of trunk and extremity STS, identifying a prevalence of 23.9% pulmonary metastases. This supports the need for chest CT at the time of local recurrence, in line with the UK guidelines for the management of soft tissue sarcoma[2].

CT Features of Benign Intra-pulmonary Lymph Nodes

Sykes et al[35] compared the CT appearances of benign intrapulmonary lymph nodes (IP-LN) with sarcoma metastases. Chest CT studies of 41 patients with benign IP-LN and 33 patients with sarcoma metastases were retrospectively reviewed and compared with pathology. Of 57 benign IP-LN, 26 (46%) were sub-pleural in location, 38 (67%) were oval in shape **(Fig. 7)**, and 46 (81%) were located in the lower lungs, while 43 (75%) had a lymphatic distribution on CT and 54 (95%) at pathological review. Of 98 sarcoma metastases 13 (13%) were sub-pleural in location, 15 (15%) were oval, and 56 (57%) were in the lower lungs, while 29 (30%) had a lymphatic distribution on CT and 45 (46%) at pathological review. Therefore, benign IP-LNs are more likely to be oval, to occur in a lymphatic distribution and to be located sub-pleurally than sarcoma metastases.

Discussion

The current article has aimed to determine features on chest CT which are likely to be indicative of pulmonary metastases in high-grade primary bone and musculoskeletal STS. This was primarily achieved by reviewing those studies where nodules identified on chest CT had been excised, and there was therefore definitive histological confirmation as to whether they represented metastases or non-metastatic lesions. Therefore, the question has to be raised as to whether this introduced selection bias, since for most of the studies it was not absolutely clear as to why patients had undergone thoracotomy. Nevertheless, the overall findings for both bone and STS were that non-calcified nodules >10mm in diameter should be considered metastatic, non-calcified nodules >6mm are highly likely to be metastatic, while non-calcified nodules <5mm in diameter were unlikely to be metastatic. The latter was true even for children with osteosarcoma. In the setting of osteosarcoma, calcified nodules were also more likely to be metastases, while a small proportion of lung metastases in chondrosarcoma were calcified. Another potential limitation of some of the reported studies was the criterion of increasing nodule number or size being indicative of metastases. Brader et al[13] found that 32% of nodules that had apparently increased in size in children with osteosarcoma were in fact benign **(Fig. 8)**.

Regarding nodule size, the findings for bone and STS are similar to those reported in patients with extra-pulmonary cancers of other types. Hanamiya et al[36] reported on the frequency and relevance of pulmonary nodules demonstrated on thin-section chest CT in 308 patients with extra-pulmonary cancers, less than 10 of whom had STS. One or more non-calcified pulmonary nodules were identified in 75% of patients, and nodules <10 mm in size were more likely to be benign while those >10 mm were more likely to be malignant. Ninety-one percent of nodules within 10 mm of the pleura were benign whereas 47% of nodules >10 mm from the pleura were malignant. Caparica et al[4] reviewed needle biopsy findings of pulmonary nodules in 228 patients with non-pulmonary cancers over a 36-month period, less than 14 cases being sarcomas. Sixty-four percent had metastatic disease, 26.3% were diagnosed with a new lung cancer and 9.6% of cases had a benign diagnosis. On multivariate analysis, findings which were significantly predictive of metastases were multiple nodules >5mm in size and the presence of cavitation.

The 2017 Fleischner Society Guidelines for the assessment of incidental pulmonary nodules do not cater for patients with known primary malignancies[37]. In this clinical scenario, Bueno et al[38] suggested that the clinical and imaging management should be aimed at ruling out or confirming the presence of pulmonary metastases, with shorter interval for imaging follow-up and biopsy being placed higher in the management algorithm. Conversely, the British Thoracic Society (BTS) Guidelines for assessment of pulmonary nodules includes those identified in staging patients with known malignancy[39,40]. Several of their reviewed series revealed conflicting associations of extra-pulmonary cancers with their likelihood of pulmonary metastases. Overall, it was suggested that nodules <5mm in size required no follow-up, and that nodules measuring 5-6mm in size should have follow-up imaging in 1 year. However, the latter timescale is unacceptable to patients with known sarcoma or to the oncologists treating them. Also, as detailed in the above review, it is clear that a small percentage of nodules <5mm in size may be metastatic based on growth at follow-up.

In conclusion, the current article has reviewed the available literature form the past 20 years which has assessed the features of pulmonary metastases on thin section chest CT in patients with bone and STS. These would suggest that non-calcified nodules >10mm in size should be considered metastatic, but there is lack of consensus regarding nodules measuring between 5-10mm. Nodules <5mm are likely to be benign, but calcified nodules in a setting of osteosarcoma or chondrosarcoma are likely to be malignant. At present, there are no clear guidelines for the management of pulmonary nodules identified on chest CT in patients with musculoskeletal sarcoma.

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Tables

Table 1. Summary of features of pulmonary metastases on chest CT for osteosarcoma.

Features of pulmonary metastases in osteosarcoma (OS)
Features likely indicative of metastases: • Multiple nodules (especially >7) • Nodule size >5mm (>6mm specificity ~90%; >13mm specificity 100%) • Nodule calcification (~60% vs 12% in benign nodules) • Change in number or size of nodules after chemotherapy Features likely indicative of benign nodules: • Single nodule (~70% non-metastatic) • Nodule size <5mm (~70% non-metastatic) • Sub-pleural location • No change in size or number after chemotherapy

Table 2. Summary of features of pulmonary metastases on chest CT for chondrosarcoma.

Features of pulmonary metastases in chondrosarcoma (CS)
Nodule size >10mm: • ~92% metastatic • Particularly in high-grade chondrosarcoma (HG-CS) and dedifferentiated chondrosarcoma (DD-CS) Nodule size <10mm: • ~77% non-metastatic • Low-grade chondrosarcoma (CS) • But more likely metastatic in high-grade chondrosarcoma (HG-CS) and dedifferentiated chondrosarcoma (DD-CS)

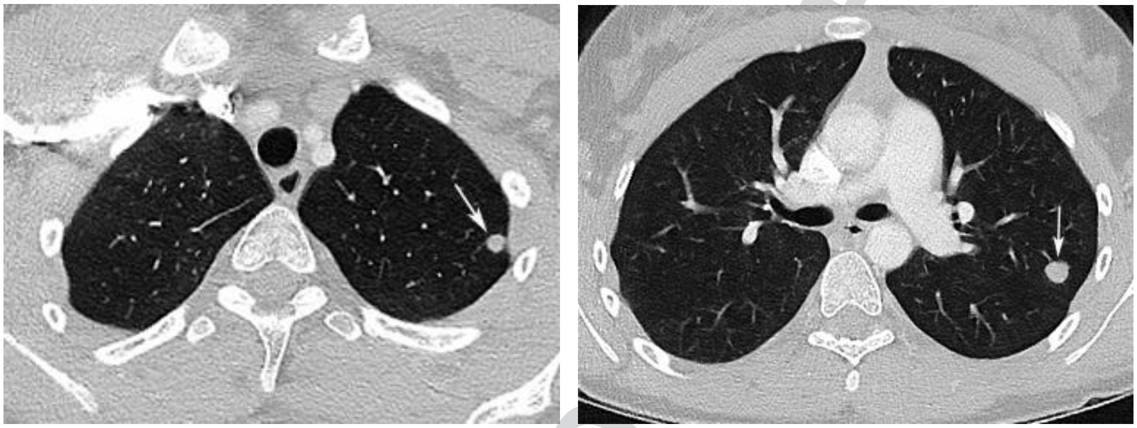
Table 3. Summary of features of pulmonary metastases on chest CT for soft tissue sarcoma.

Features of pulmonary metastases in soft tissue sarcoma (STS)
Features likely indicative of metastases: • Nodule size >5mm (~92% metastatic; median size of metastases 6.1mm)) • New nodules at follow-up (~70% metastatic) Features likely indicative of benign nodules: • Nodule size <5mm (~67% non-metastatic; median size of benign nodules 3.5mm) • Nodule size <3mm (~80% non-metastatic) • No increase in size or number after 1-year follow-up

Table 4. Summary of CT features of benign intra-pulmonary lymph nodes.

Features of benign intra-pulmonary lymph nodes
• Sub-pleural in location (46%) • Oval in shape (67%) • Located in the lower lungs (81%) • Lymphatic distribution (75%)

Figures



a b

Fig. 1 A 14-year-old girl with femoral osteosarcoma. Chest CT demonstrates multiple nodules (arrows) measuring >5mm in size consistent with pulmonary metastases.

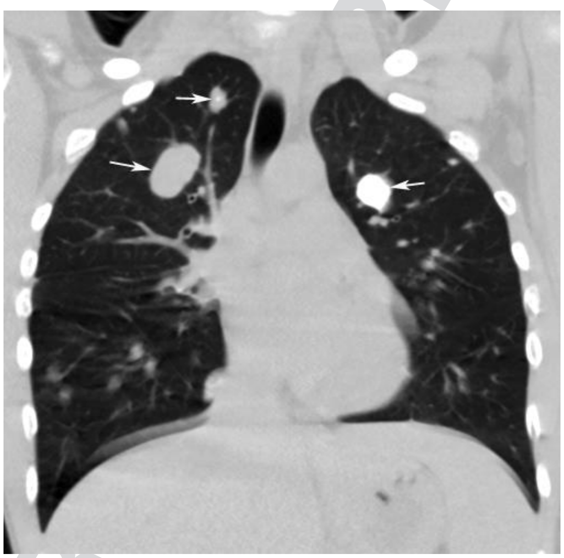


Fig. 2 A 12-year-old girl with tibial osteosarcoma. Chest CT demonstrates multiple large nodules (arrows) measuring >5mm in size consistent with pulmonary metastases. The lesion on the left is completely calcified.

Fig. 3 A 32-year-old female with scapular osteosarcoma. Chest CT demonstrates a partially calcified peripheral nodule (arrow) measuring >5mm in size. Histologically confirmed pulmonary metastasis.

Fig. 4 A 36-year-old female with recurrent scapular high-grade chondrosarcoma. Chest CT demonstrates a large lobular calcified pulmonary nodule (arrow) measuring >10mm in size. Histologically confirmed pulmonary metastasis.

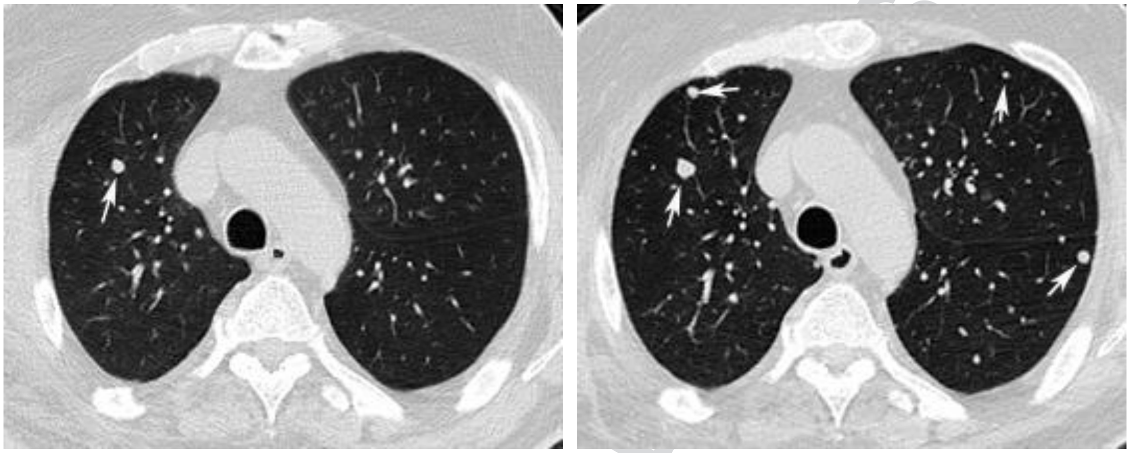


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Fig. 5 A 61-year-old male with previously resected right scapular grade 2 chondrosarcoma. (a) Chest CT 13-months after diagnosis demonstrates a single <10mm pulmonary nodule (arrow) which is indeterminate in nature. (b) Chest CT 23 months after diagnosis shows growth of the indeterminate nodule and at least 3 new nodules (arrows) consistent with pulmonary metastases.

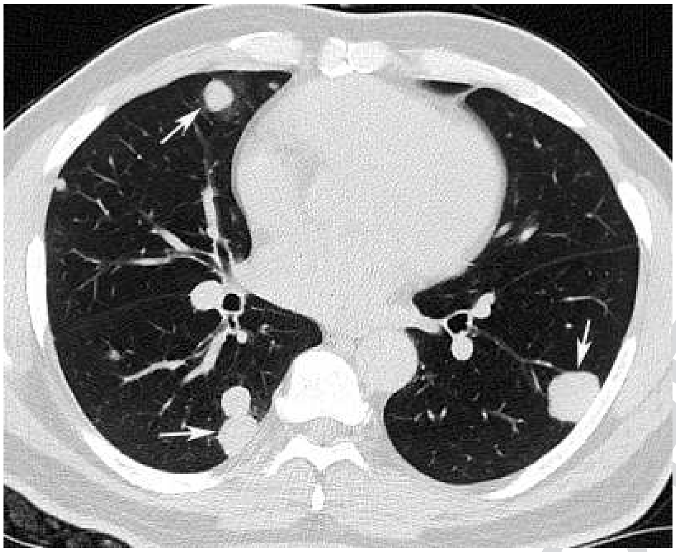

Fig. 6 A 63-year-old male with undifferentiated pleomorphic sarcoma of the thigh. Chest CT demonstrates multiple peripheral pulmonary nodules (arrows) measuring >10mm in size consistent with pulmonary metastases.

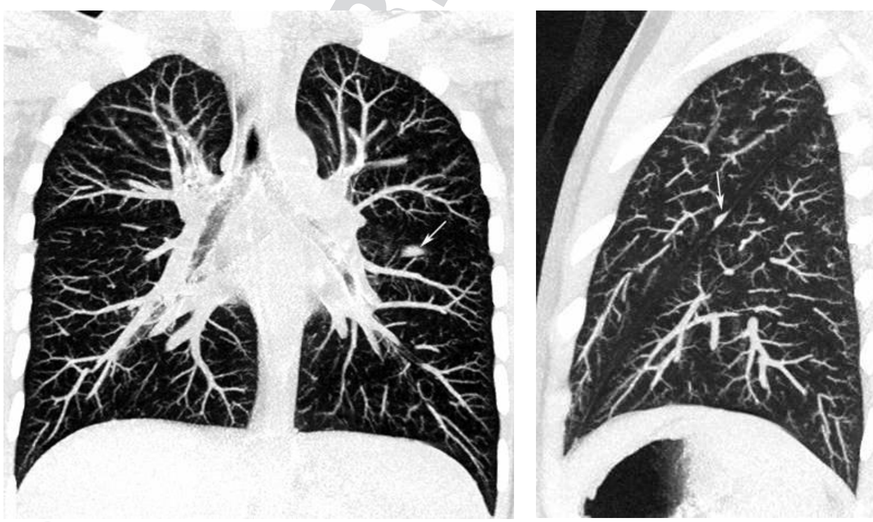

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Fig. 7 A 10-year-old boy with fibular Ewing sarcoma. (a) Coronal and (b) sagittal chest CT images demonstrate a single oval pulmonary nodule (arrows) related to the left oblique fissure consistent with an intra-pulmonary lymph node.

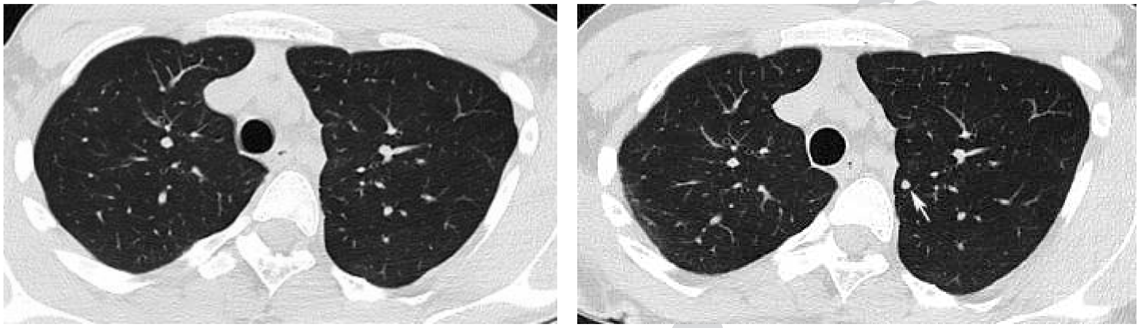

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Fig. 8 A 16-year-old boy with right scapular Ewing sarcoma. (a) Chest CT at presentation shows no evidence of metastases. (b) Chest CT 22-months later demonstrates a single left para-mediastinal pulmonary nodule (arrow) thought to be consistent with development of a pulmonary metastasis as there was an increase in size 5 months later from 3 to 5mm. However, histology revealed a benign inflammatory lesion.

Figure 1

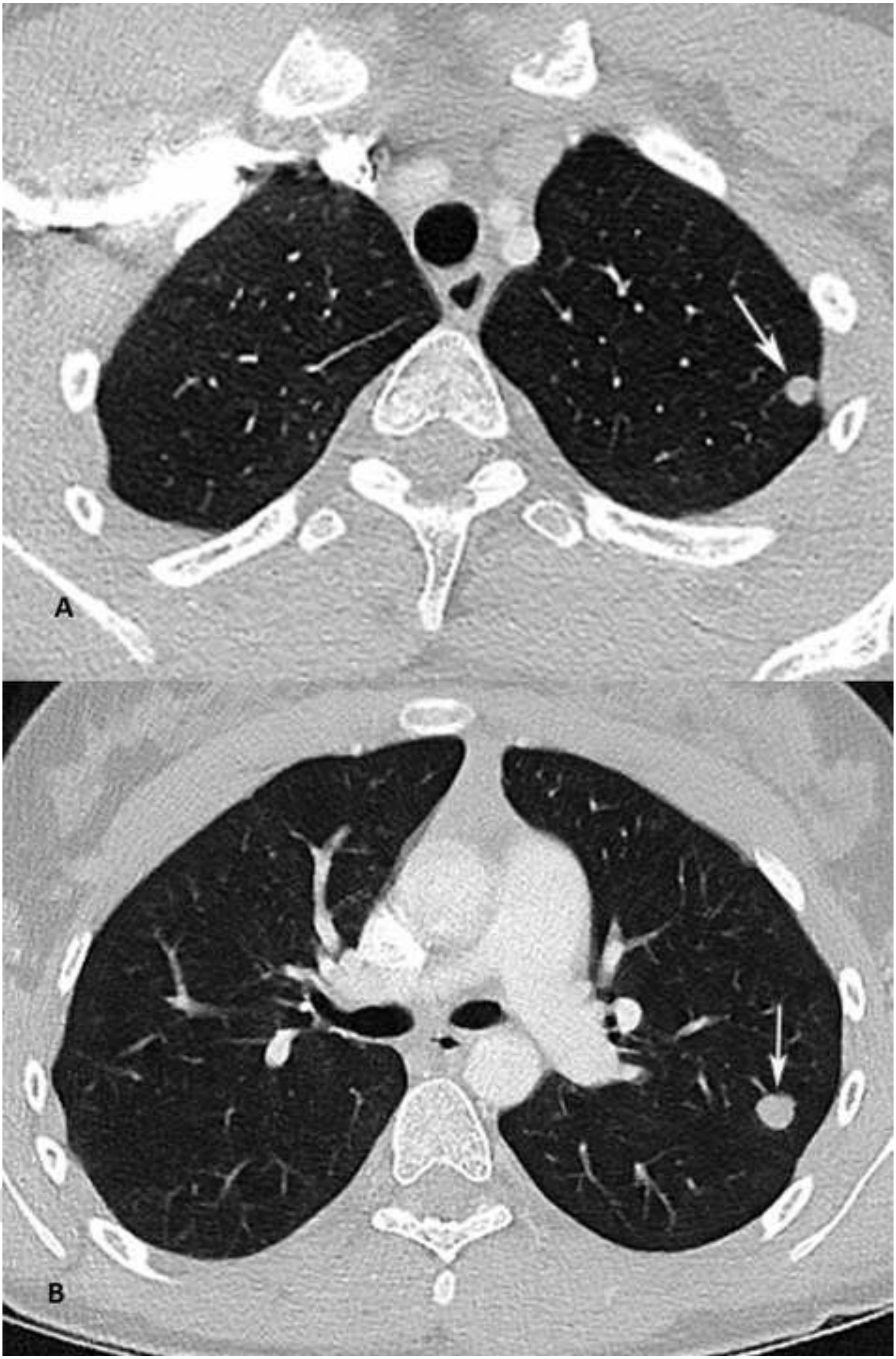

Figure 2

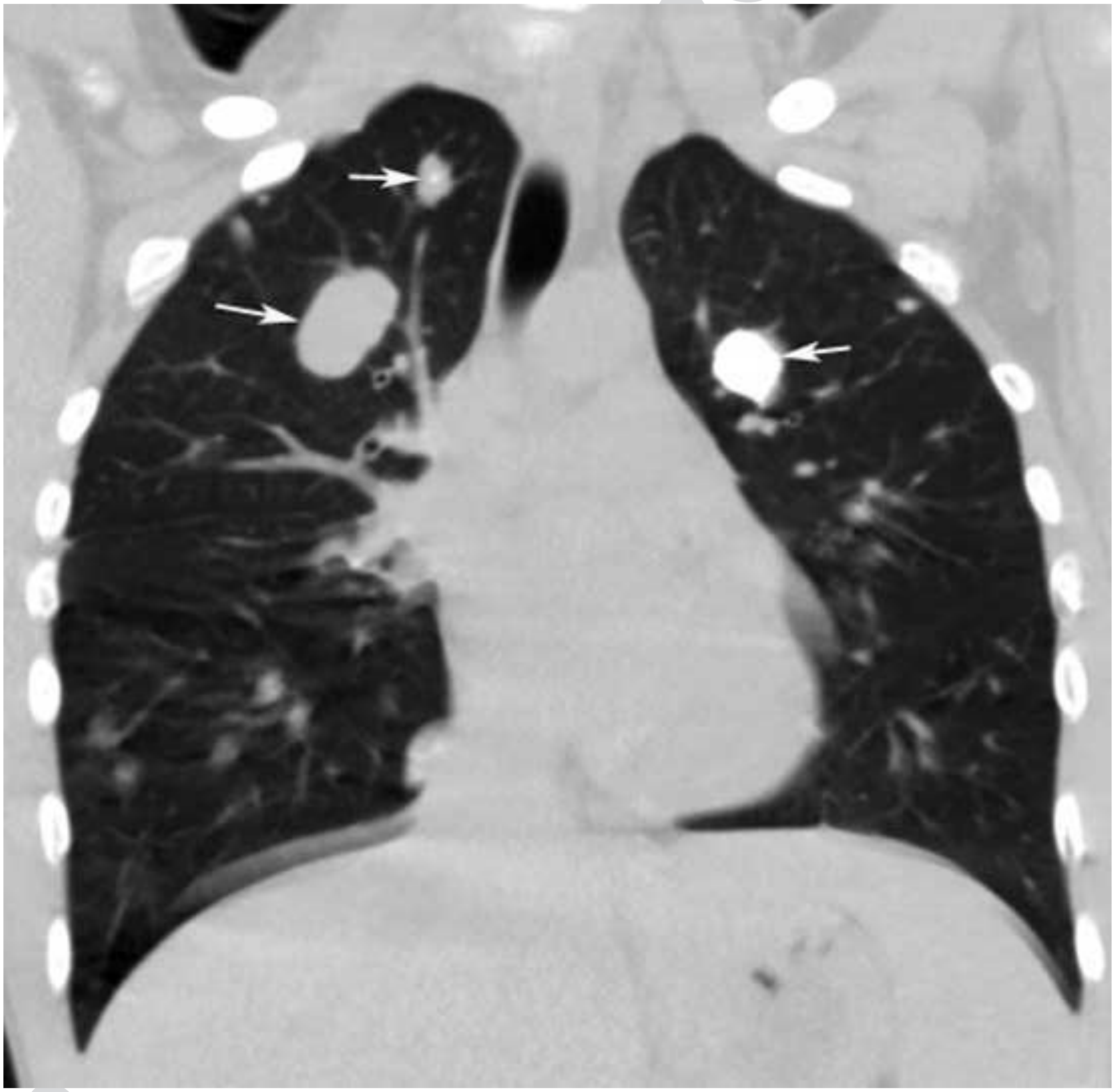

Figure 3

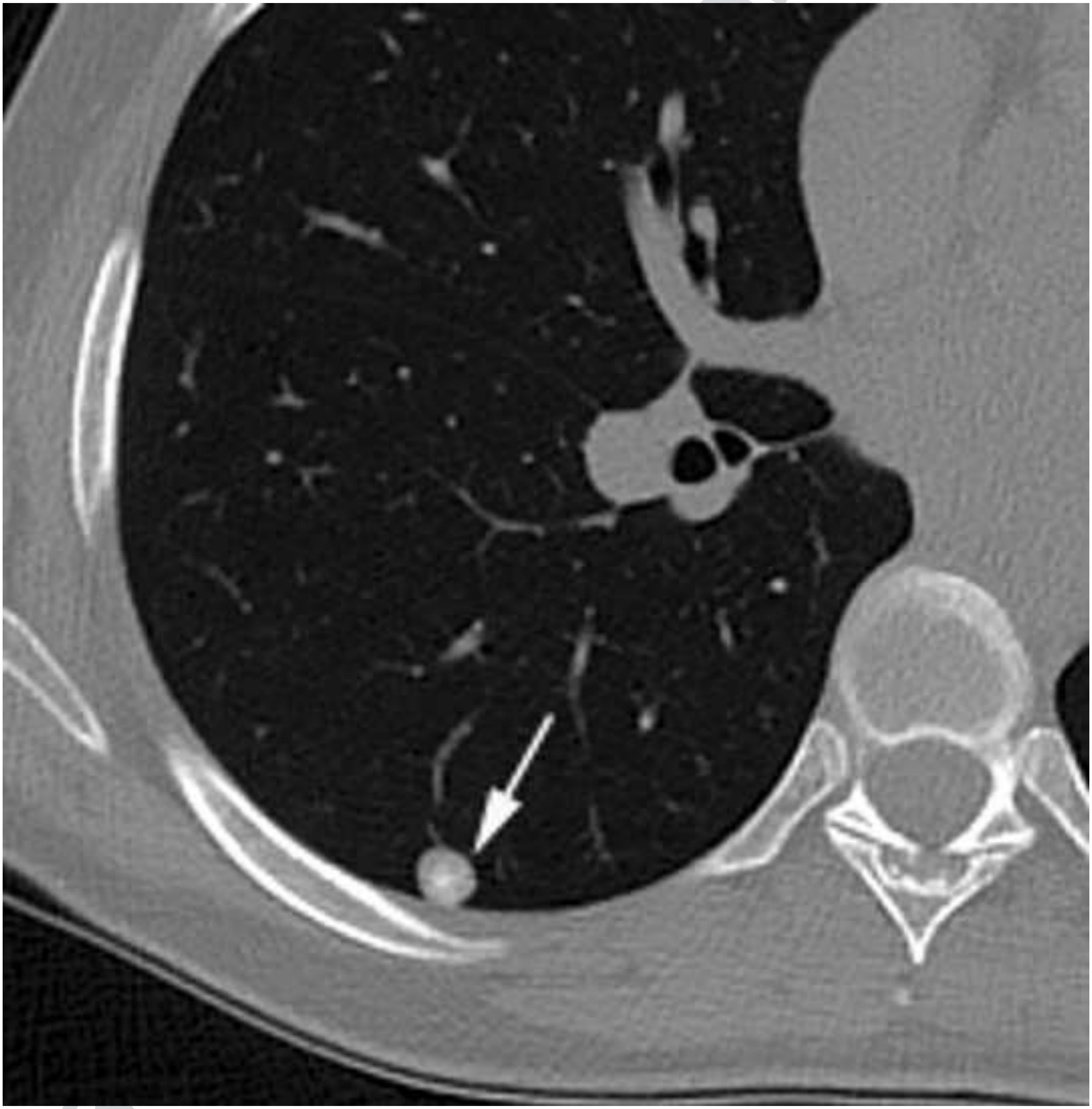

Figure 4

Figure 5

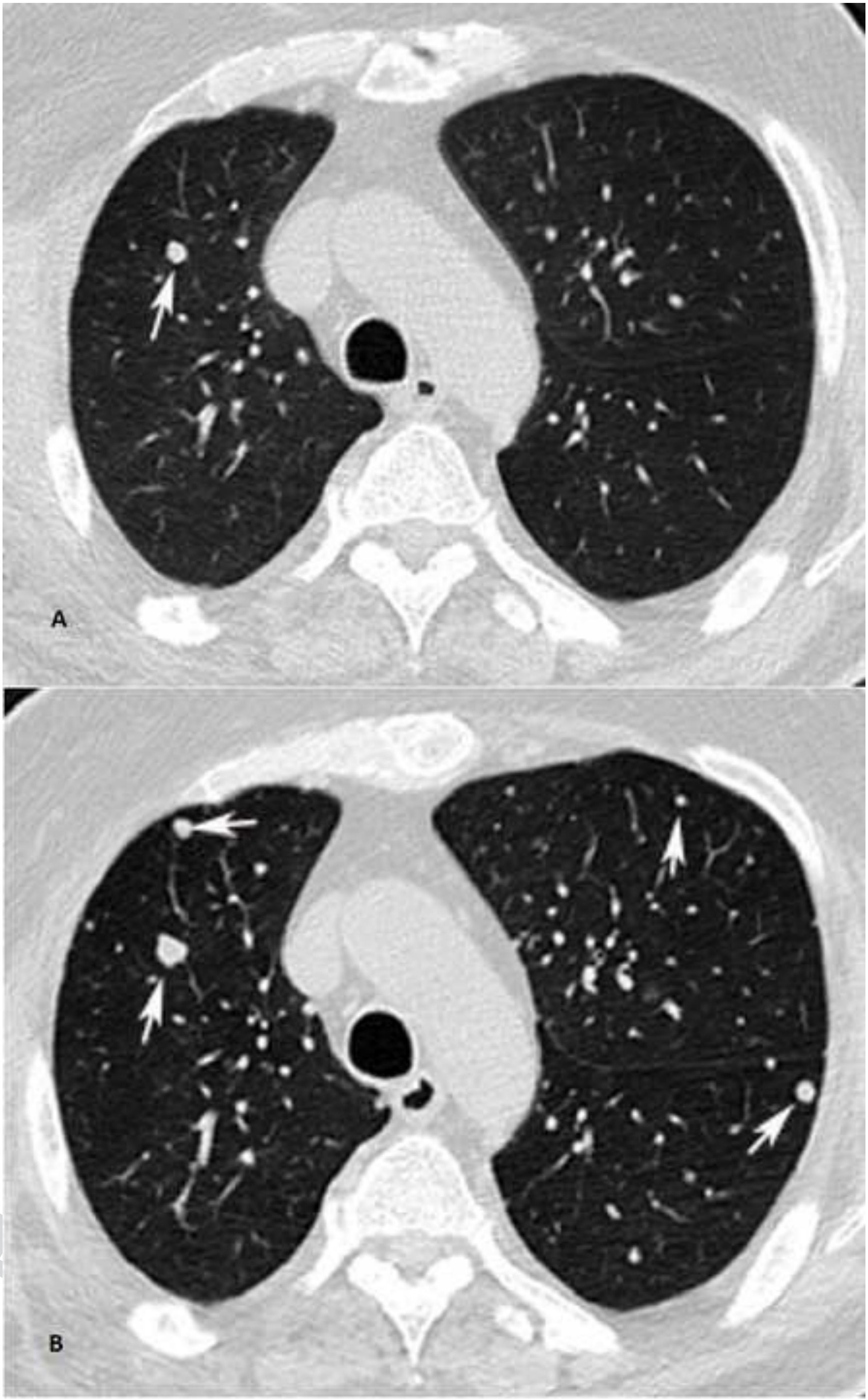

Figure 6

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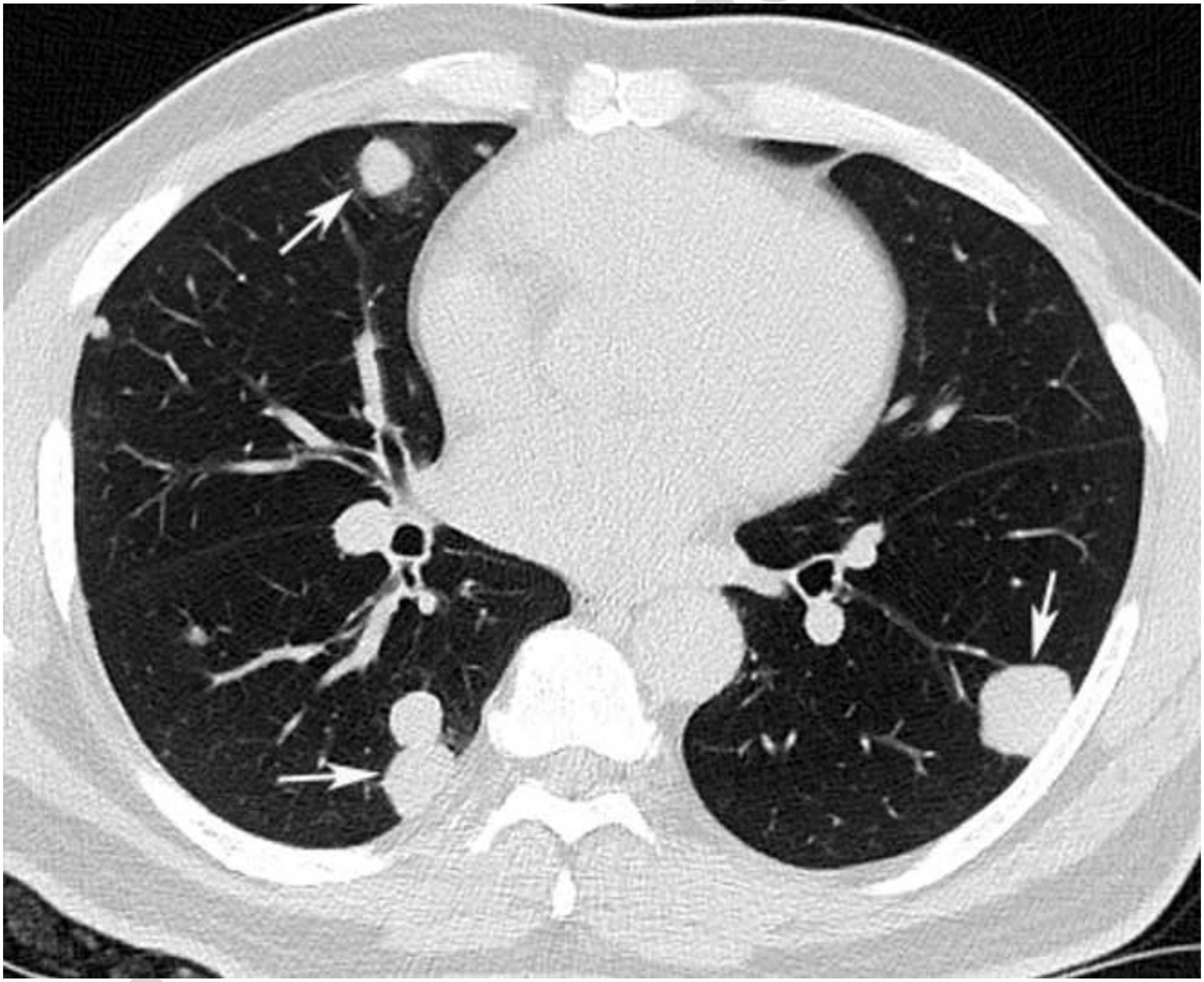

Figure 7

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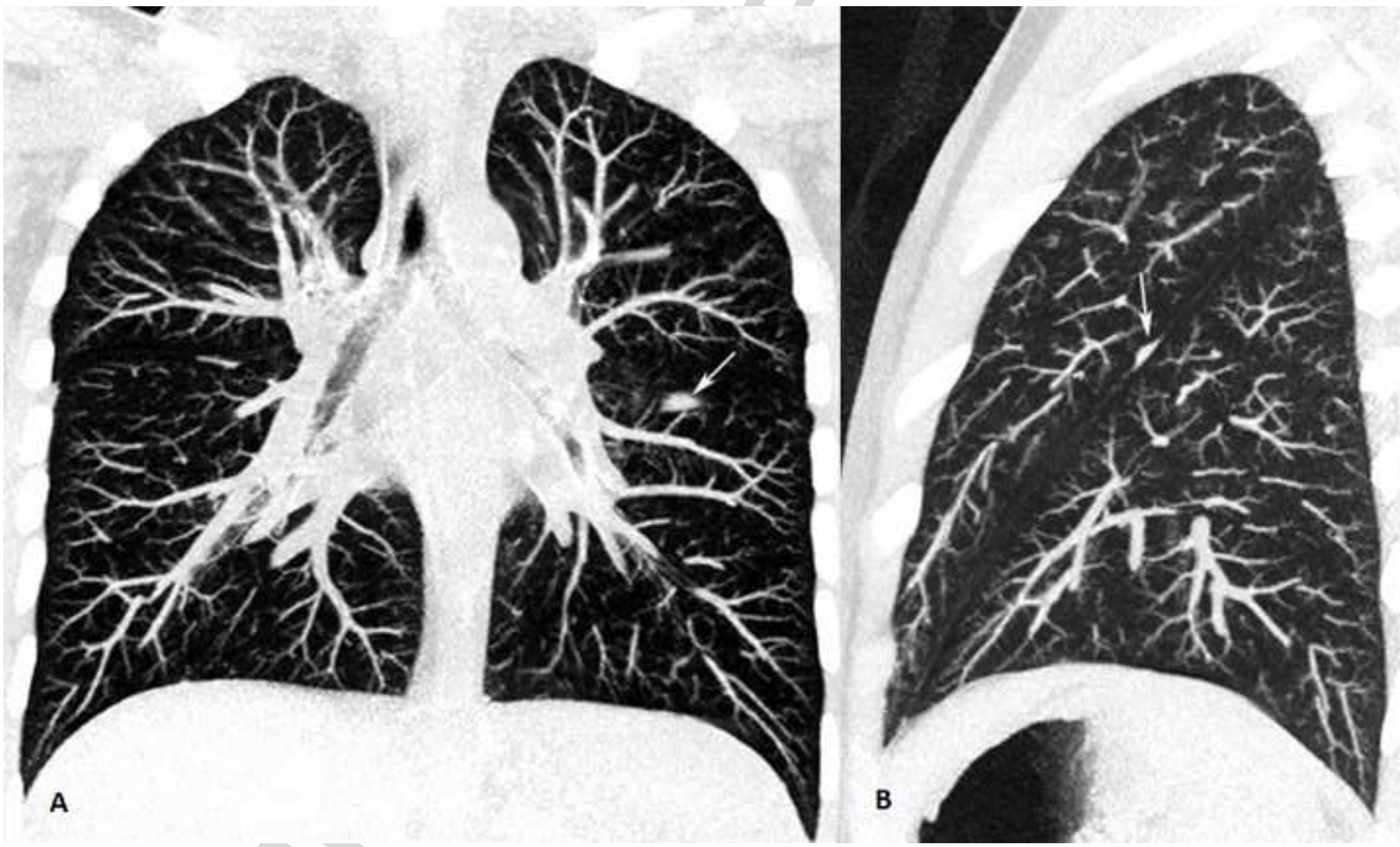

Figure 8

Tables

Table 1. Summary of features of pulmonary metastases on chest CT for osteosarcoma.

Features of pulmonary metastases in osteosarcoma
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Table 2. Summary of features of pulmonary metastases on chest CT for chondrosarcoma.

Features of pulmonary metastases in chondrosarcoma
Nodule size >10mm: • ~92% metastatic • Particularly in HG-CD and DD-CS Nodule size <10mm: • ~77% non-metastatic • Low-grade CS • But more likely metastatic in HG-VS or DD-CS

Table 3. Summary of features of pulmonary metastases on chest CT for soft tissue sarcoma.

Features of pulmonary metastases in soft tissue sarcoma
Features likely indicative of metastases: • Nodule size >5mm (~92% metastatic; median size of metastases 6.1mm)) • New nodules at follow-up (~70% metastatic) Features likely indicative of benign nodules: • Nodule size <5mm (~67% non-metastatic; median size of benign nodules 3.5mm) • Nodule size <3mm (~80% non-metastatic) • No increase in size or number after 1-year follow-up

Table 4. Summary of CT features of benign intra-pulmonary lymph nodes.

Features of benign intra-pulmonary lymph nodes
• Sub-pleural in location (46%) • Oval in shape (67%) • Located in the lower lungs (81%) • Lymphatic distribution (75%)