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Imaging strategy for detecting lung metastases at presentation in patients with soft tissue sarcomas ☆

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ABSTRACT

Purpose: To identify the risk of lung metastases at the time of diagnosis in patients with soft tissue sarcomas (STS) and to establish the optimum imaging strategy for the diagnosis of these metastases and whether this affects outcome.

Materials and methods: A retrospective review of an orthopaedic oncology database identified 1170 patients with newly diagnosed STS during a 7.5-year period (1996–2004). The patient demographics, tumour type, size, depth, histology grade and presence of metastatic disease at presentation were studied. The chest radiograph (CXR)/computed tomography of the chest (CT chest) findings, performed as part of the initial staging study, were available in all patients. We estimated the efficacy of CXR in identifying pulmonary metastatic disease compared with CT chest and whether this affected patient survival.

Results: The incidence of metastases at diagnosis was 10% (116 patients), 8.3% (96 patients) had lung metastases on chest CT and 1.7% (20 patients) had metastases elsewhere. The risk of having lung metastases at diagnosis was 11.8% in high grade tumours, 7% in intermediate grade and 1.2% in low grade tumours. CXR alone detected 2/3 of all lung metastases. The positive predictive value of the CXR was 93.3%, the negative predictive value 96.7%, the sensitivity 60.8% and the specificity 99.6%. The accuracy was 96.9%. CT overestimated metastases in 4% with a sensitivity of 100%, specificity of 99.6% and accuracy of 99.6%. Median survival of patients with lung metastases at diagnosis was 11 months and there was no significant difference in survival between those who had metastases detected on CXR or purely on CT.

Discussion: We recommend that all patients with a suspected STS should have a CXR at presentation, prior to histological diagnosis. CT of the chest should then be performed in those patients with an abnormality on the presentation CXR and routinely in those patients who have large, deep seated or high/intermediate grade tumours and in certain histological subtypes where the incidence of lung metastases at diagnosis is known to be high. In our experience, this strategy will detect 93% of all chest metastases. With current treatment strategies for metastases, outcome is not likely to be affected by any delay in diagnosis.

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1. Introduction

Soft tissue sarcomas are rare tumours in adulthood. The most common pattern of disease spread is haematogenous, in particular to the lungs.[1] Certain soft tissue sarcomas (epithelioid sarcoma, synovial sarcoma, rhabdomyosarcoma, clear cell sarcoma and angiosarcoma) have a higher propensity for lymph node metastases (10–20%).[2] Staging studies typically include magnetic resonance imaging (MRI) for local tumour staging and operative planning. Imaging of the chest is performed to detect the presence of pulmonary metastases. The aim of these studies is to provide adequate and accurate information about the status of the disease so that the prognosis can be established and a treatment strategy formulated.

Chest radiographs (CXR) are readily available, cheap and easily performed. Chest CT is relatively more expensive with a significantly higher radiation dose and may give false positive results in the presence of small lung nodules (<5 mm).[3] This has not altered significantly with the advent of modern multi-slice techniques, and the problem has increased with smaller lesions being more readily identifiable. When the chest CT is correlated with open thoracotomy findings of lesions <6 mm in size, only 60% of this group is correctly identified as metastases.[4] The optimum method of staging patients with STS for the presence of pulmonary metastatic disease, therefore, remains uncertain. It is a common practice for patients with suspected soft tissue sarcoma to undergo a routine CT chest as a staging investigation before the histological diagnosis is established. Even though the histological diagnosis is obtained, the Royal College of Radiologists of the United Kingdom still recommends routine chest CT for the staging of all soft tissue sarcomas.[5] We postulated that there may be groups of patients who are unlikely to present with chest metastases and therefore do not benefit from a routine chest CT. This would potentially avoid a significant radiation dose to certain patient groups and enable resource use to be streamlined.

The aim of this study was to identify the risk of patients with soft tissue sarcoma of having lung metastases at presentation and to try to provide guidance on an appropriate imaging strategy for the detection of chest metastases. We also wished to assess if failure to detect metastases at diagnosis may have led to a worse outcome or unnecessary debilitating surgery.

2. Materials and methods

A retrospective review of our Orthopaedic Oncology database was performed to identify all patients with newly diagnosed soft tissue sarcomas over a 7.5-year period (1996-mid-2004). The patient demographics, maximal tumour size at diagnosis, depth, Trojani grade and the CXR and CT chest imaging findings were available in all the cases. We used the International Union against Cancer/American Joint Committee on Cancer (UICC/AJCC) staging system to identify the stage of the tumour assuming there were no metastases identified.[6] We identified all patients where the CXR or CT chest indicated the presence of lung metastases at presentation. This enabled us to provide an estimated risk of lung metastases at presentation for the study criteria. Lung metastases were diagnosed on either CXR or chest CT as the presence of multiple, non-calcified, ovoid or round soft tissue masses within the lungs.

3. Results

1170 patients were identified with newly diagnosed soft tissue sarcomas during the study period. The age of our patients ranged from 3 to 94 years (median 46 years). The maximal tumour diameter ranged from 2 to 45 cm (mean 9.6 cm). 367 patients presented with T1 tumours (tumours 5 cm or less in diameter), and 803 patients had T2 tumours (tumours greater than 5 cm in diameter). There were 255 (21.7%) low grade, 321(27.3%) intermediate grade and 594(50.7 %) high grade lesions. 328 (28 %) tumours were superficial to the fascia and 842 (71.9 %) were deep to the fascia.

The most common diagnoses were pleomorphic sarcoma 234 (20.1%), liposarcoma 159 (13.6%), leiomyosarcoma 137 (11.7%), malignant peripheral nerve sheath tumour 105 (9%) and synovial sarcoma 119 (10.2%). Table 1 documents the histological subtypes of tumour and the percentage with lung metastases at diagnosis. 116 (10%) patients had metastases at diagnosis. Of these, 96 (83%) had lung metastases and 20 (17%) patients had metastases elsewhere – four patients had bony metastases, one patient had liver metastases, 11 patients had lymph node metastases and five patients had other soft tissue metastases. Of the patients with lung metastases, 60 (62.5%) were detected by a routine CXR and were subsequently confirmed on CT. In 36 (37.5%) patients, the CXR was reported as normal but the CT chest revealed metastases. Table 2 illustrates the comparison of chest radiographs with CT findings (assuming that CT chest acts as the 'gold standard'). CXR is thus very specific (99.6%) but not sensitive (60.8%), although

Table 1 – Details the histological subtypes and the percentage with lung metastases at diagnosis

Diagnosis	Number	% of total	No (%) with lung metastases at diagnosis
Pleomorphic sarcoma	234	20.1	26 (11.1)
Liposarcoma	159	13.6	1 (0.6)
Leiomyosarcoma	137	11.7	11 (8)
Synovial sarcoma	119	10.2	11 (9.2)
MPNST	105	9.0	17 (16.2)
Myxofibrosarcoma	86	7.4	3 (3.5)
MFH	63	5.4	5 (8)
Myxoid Liposarcoma	59	5.0	0
Soft tissue Ewings'	37	3.2	9 (25)
Clear cell sarcoma	23	2	1
Extraskeletal chondrosarcoma	22	1.9	3 (13.6)
Rhabdomyosarcoma	22	1.9	2 (9.1)
DFSP	22	1.9	0
Fibrosarcoma	18	1.5	0
Extraskeletal osteosarcoma	13	1.1	0
Epithelioid sarcoma	10	0.9	1 (10)
Others	41	3.5	6 (14.6)
Total	1170		96 (8.2)

Table 2 – The comparison between the CXR and chest CT findings at presentation

	Mets +ve	Mets –ve	
CXR +ve	56 True +ve	4 False + ve	PPV 93.3%
CXR –ve	36 False –ve Sensitivity 60.8%	1070 True –ve Specificity 99.6%	NPV 96.7%

it has high positive and negative predictive factors. When we analysed the CT chest findings, 4 of the patients who were initially diagnosed as having chest metastases were subsequently restaged (all the other patients either had lesions pathognomonic of metastases or showed progression on subsequent CT). These patients all underwent thoracotomies to remove what later turned out to be histologically benign lung lesions. This gave CT chest a positive predictive value of 95.8%, negative predictive value 100%, sensitivity 100%, specificity 99.6% and accuracy 99.6%. Table 3 illustrates the impact of using only CXR in staging patients with STS and shows which subgroups would be most affected in terms of understaging of their disease. By using only CXR to stage we would miss metastases in 36 patients (that is 37.5% of all patients who were found to have lung metastases on CT). The initial staging would thus be inaccurate in 3.1% of all the cases. The rate of inaccuracy is just as great for all stages (Table 3) but a greater proportion (4.9%) would be incorrectly staged if CXR alone was used in patients with high grade, large deep tumours (UICC grade 3).

Taking staging factors independently – deep lesions had a higher risk of lung metastasis at presentation as opposed to superficial ones (Deep:Superficial 9%:4%) and tumour grade also had an influence on the likelihood of chest metastases. The risk of lung metastases at presentation was 11.8% for high grade lesions, 7.0% for intermediate grade and 1.2% for low grade tumours.

The histological subtype of lesions most frequently associated with lung metastases included alveolar soft part sarcoma (33%), extraskeletal Ewing's sarcoma (25%), MPNST (16%) and Triton tumour (12%).

We estimated the Kaplan Meier survival of all 92 patients with proven lung metastases at diagnosis finding that the median survival was 11 months and there was a 24% survival at 2 years. Not surprisingly, patients with a higher UICC grade tended to do worse but due to small numbers this was not statistically significant. When split by whether the metastases had been visible on CXR or just on CT scan there was very little difference (Fig. 1). Patients whose metastases were not visible on CXR had a median survival of 14 months compared to 10 months for those detected on CXR but this was not statistically significant. The whole group with metastases had 11% survival at five years.

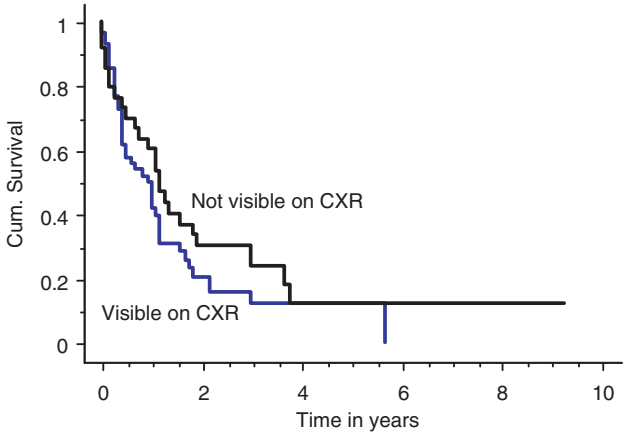

Fig. 1 – Kaplan Meier graph showing the survival curves for patients with metastases at diagnosis split by whether the metastases were visible on chest X-ray alone or only on CT scanning. There was no significant difference in survival ($p = 0.21$).

4. Discussion

Soft tissue sarcomas are a rare, heterogeneous group of solid tumours that arise primarily from embryonic mesoderm. They form approximately 1% of all new adult cancers in the UK per annum, roughly 1500 cases[7] and can occur anywhere in the body – 59% occur in the extremities, 19% in the trunk, 15% in the retroperitoneum and 9% in the head and neck. The 5-year survival for soft issue sarcomas of all stages is between 50% and 60%.[8] Pretreatment imaging is essential for assessing the local extent of the tumour, staging and guiding biopsies.[2,9]

Table 3 – Illustrates the percentage of metastases which would be missed in individual subgroups of patients if chest radiographs alone were used for staging

UICC stage	Number	No and % with metastases identified on CT scan	No and % missed by CXR alone	% inaccuracy for that stage
1a	96	1 (1.04)	1 (1.04)	100
1b	22	0	0	0
2a	137	2 (1.46)	1 (0.73)	50
2b	255	10 (3.92)	3 (2.7)	30
2c	109	7 (6.42)	3 (2.75)	43
3	551	76 (13.8)	27 (4.9)	36
Total	1170	96 (8.25)	36 (3.1)	37.5

In this study, we are aiming to assess the best method of screening for lung metastases at diagnosis in patients with a soft tissue sarcoma. We have examined the risk of lung metastases at presentation and the accuracy of CXR compared to CT chest in their identification. A screening test can be evaluated by five criteria. Is the test able to identify pathology in the asymptomatic patient, is the intervention acceptable to the patient, is it accurate in establishing a diagnosis, is it affordable and can a positive result lead to a change in the outcome?[10] Currently, the most common practice is to use CT chest as the screening tool of choice – as it fulfils most of the screening test criteria. Critics may argue that CXR fails on one of the most important criteria of a good screening test – accuracy in establishing a diagnosis. One naturally assumes that CT is much more accurate. However, the difference in accuracy was not as great as may be expected, and showed CXR to be 96.9% accurate in comparison to CT with an accuracy of 99.6%. So whilst our study does confirm the fact that CT will identify a greater number of patients with metastatic lung disease, it also demonstrates that CT will detect a subgroup of patients with indeterminate nodules. In a series of 146 patients with extra-thoracic malignancy, Chalmers and co-workers found 13% of chest CTs detected nodules not seen on CXR. However, 80% of these nodules were benign on biopsy.[11] We had four patients with a false positive CT scan of the chest who underwent thoracotomies to remove what later turned out to be histologically benign lung lesions. In a further study comparing intra-operative palpation with helical CT chest findings, CT had a sensitivity of 78% with 22% more malignant nodules detected intra-operatively.[12] So CT is by no means infallible and in fact it could be argued that the detection of indeterminate nodules may lead to unnecessary investigations/procedures with its associated morbidity.

Staging is all important in the management of soft tissue sarcomas and has a direct bearing on the prognosis. The current UICC/AJCC staging criteria for soft tissue sarcomas relies on the histological grade, the tumour size and depth and the presence of distant or nodal metastases.[6] Of these, the most important prognostic criteria is the histological grade. The next most important criteria are the tumour size and location, i.e. its relationship with the fascia. Larger tumours (>5 cm) and those deep to the investing fascia have a significantly worse outcome and are more likely to develop distant metastases.[13] This is also reflected in our data where we found that the higher the tumour grade the more likely the patient was to have lung metastases at presentation – 11.8% of our patients with high grade disease had distant metastases at diagnosis *versus* 1.2% of patients with low grade disease. Similar findings were seen with regard to tumour depth – 9% of deep tumours had metastases at presentation *versus* 4% of superficial tumours. If we look at our figures for lung metastases at diagnosis per UICC/AJCC grade, we see that there is a significant increase in the risk of metastasis between the grades 2a and 2b, a change from 1.5% to 4%. This translates to 2% of patients with grade 2a disease having lung metastases at diagnosis *versus* 11% of grade 2b.If CXR was used as the only screening tool this would result in metastases being missed in 4.9% of high grade, deep tumours, greater than 5 cm in size . This is arguable an unacceptably high rate. However, less than 0.5% of metastases would be missed if patients with low grade, superficial tumours equal to or less than 5 cm in size had CXR alone. These findings are borne out by a previous similar study, where less than 1% of patients with T1 soft tissue sarcomas had pulmonary metastases detectable on CXR at presentation. No patients had CXR occult metastases detected on CT.[14]

We therefore propose that all patients with a suspected soft tissue sarcoma have a CXR. Only those patients with an abnormality on CXR or with high/intermediate grade, deep tumours greater than 5 cm (Stage 2b/3) in size should undergo a CT chest routinely. Patients with specific histological subtypes of soft tissue sarcoma where the incidence of lung metastases at diagnosis is known to be high, for example, extra skeletal Ewings sarcoma and MPNST, should also routinely undergo a CT chest.

The next question is does early diagnosis of lung metastases matter and does it influence the treatment of soft tissue sarcoma patients? Patients with large, often unresectable pulmonary metastases might not be offered radical and extensive surgery, i.e. a hind quarter amputation, because of the generally poor prognosis. The emphasis in these patients is on palliation and radiotherapy might be employed rather than surgery. CXR will pick up these large lung lesions and a CT of the chest is not always needed. Lung lesions below 5mm in diameter will be missed on CXRs and will only be identified on CT. The vast majority of these patients are completely asymptomatic and will therefore often be offered radical surgery despite the presence of lung metastases especially if these lung lesions are accessible to surgical excision. The success of pulmonary metastectomy for soft tissue sarcoma is well documented with a 5-year survival of 52.7% following a complete metastectomy.[15] If these patients were in a physically poor condition, radical surgery would most likely not be performed.

Our figures for survival following the diagnosis of metastases are consistent with the 11.6 month median survival reported by Billingsley.[1] They found that ability to resect the metastases and a long disease-free interval were the most important prognostic factors. Size of the metastases does not seem to have been important and this would fit with our results. The difference in survival we identified between the groups with CXR identified and CT only identified metastases was not statistically significant but may fit with the possible difference in the size of the metastases likely to have been identified, as CT will pick them up when they are much smaller.

We did not assess the treatment of this group of patients for this study as that was not the aim, but in general patients were offered surgical excision and chemotherapy when appropriate. Despite this, the survival was only 11% at five years and this again would fit with the poor prognosis reported for patients with a short disease-free interval (in this case, zero).

One of the potential limitations of this study is that in most cases we have no histological data to correlate the findings on CXR and chest CT. It is, however, not feasible or indeed safe to biopsy all indeterminate nodules detected on CT. In these patients, a 'wait and see approach' with interval scanning is frequently used – though this may be associated

with a poorer outcome in some cases.[16] Other possible limitations include the fact that as a tertiary referral centre some of the imaging is performed in other institutions and then referred to us for opinion. This results in two potential issues – one that different imaging protocols may be used, for instance the use of 5mm collimation as opposed to our standard of 2.5mm. This could potentially miss some small nodules. The second pitfall is that outside imaging in the study period was often reported from hard copy rather than from a work station. In both situations the lesions missed, if any, would be small and unlikely to have a significant impact in the immediate treatment decision for the patient.

We suggest that every patient with a newly diagnosed soft tissue sarcoma should routinely have a CXR during staging. Following diagnosis, patients with a high risk of lung metastasis, i.e. patients with large, deep and high/intermediate grade tumours, as well as patients with suspicious CXR appearances will also require a CT of the chest. The current thinking, that the biopsy is the last step in the diagnostic chain, should be revised. A CT scan of the chest ought to be done after the biopsy results are available and its routine use should be limited to a selected group of patients as outlined above. In our series this would have resulted in 563 of the 1170 patients having a CT (48%) but all having a CXR. Only 9 patients with metastases visible on CT but not on CXR would be missed, giving an accuracy of 99.4%. This study shows that the CXR still has an important role to play in the initial evaluation of patients with soft tissue sarcomas and in certain cases is sufficient as the only screening tool for lung metastases. Omitting a CT scan on all patients will save radiation exposure, cost and time with a 1.6% risk of not detecting a metastasis at diagnosis. There is no proof that this delay affects outcome adversely.

Conflicts of interest statement

None declared.

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