Role of skeletal scintigraphy in soft tissue sarcoma: Improving the diagnostic yield

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ABSTRACT

Background: The presence of skeletal metastases significantly influences the therapeutic strategy adopted for soft tissue sarcoma. However, literature on the prevalence of skeletal metastases in soft tissue sarcoma is limited and none of the available data is based on the Indian patient population.

Aim: To determine the prevalence of skeletal metastases at presentation in patients of soft tissue sarcoma and to rationalise the use of preoperative skeletal scintigraphy in such patients.

Methods and Material: Preoperative bone scans were evaluated in 122 patients with soft tissue sarcoma (median age, 34 years; range, 4-83). The scans were classified into 3 grades: Grade 1: metastases very likely; Grade 2: equivocal; Grade 3: normal or benign lesion. In all the patients studied, the ability of the patient to localize the site or sites of pain was recorded and that was correlated with the site of metastases in scintigraphy.

Result: Seventeen (13.9%) patients had Grade 1 scan; 16 of them had bony pain that was not readily explainable by trauma or other local factors. Ten (8.1%) patients had Grade 2 scan, five of them had bony pain which was not readily explainable by trauma or other local factors. Ninety-five patients (77.8%) had Grade 3 scan. Of these, 9 had localised bone pain which could be definitely associated with trauma or joint degeneration.

Conclusion: The prevalence of skeletal metastases at presentation in patients with soft tissue sarcoma is low (13.9%). The low rates of skeletal metastases in bone pain-free patients (0.9%) versus the high rate in symptomatic patients (76.1%) supports the use of bone scanning in symptomatic patients only.

KEY WORDS: Skeletal metastases, scintigraphy, soft tissue sarcomas

Soft tissue sarcomas are a heterogeneous group of malignancies arising from mesenchymal structures accounting for around 1% of all cancers.[1] They are locally aggressive and frequently invade the surrounding structures. The therapeutic strategy adopted for their treatment depends on the type of tumour, its site and presence of local invasion or distant metastasis.[2] At presentation, systemic spread of the disease is not very common, with frequencies ranging from 7%-25%.[3-5] The most common site of metastasis is the lung but bones are also involved.[6] The presence of skeletal metastases significantly influences the therapeutic strategy adopted. However, there is limited literature estimating the prevalence of skeletal metastasis in patients with soft tissue sarcoma and none of it is based on the Indian patient population. As genetic, ethnic and racial factors are known to influence the incidence and behaviours of several malignancies, a study was undertaken to determine the prevalence of skeletal metastasis at presentation in Indian patients with soft tissue sarcoma and to rationalise the use of preoperative skeletal scintigraphy in such patients.

Materials and Methods

Preoperative bone scans were performed in 122 consecutive patients of soft tissue sarcoma (median age, 34 years; range, 4-83) who had undergone skeletal scintigraphy between 1999 and 2003. Thirty-six patients were under the age of eighteen. Patient and tumour characteristics are presented in Table 1. Pathological diagnosis was based on tumour material obtained from a diagnostic biopsy or during therapeutic resection. Bone scan was performed before resection of tumour as a part of standard metastatic work-up along with skeletal survey, CT scanning of chest and ultrasound of abdomen. The presence or absence of skeletal pain and location of pain were evaluated and recorded in the pre-scan clinical examination.

Bone scan was performed 3 hours post-intravenous administration of 185–1000 MBq (5-27m Ci) of Tc99m-Methylene diphosphonate (Tc99m-MDP) using a dual head single photon emission computed tomography system fitted with low-energy high resolution collimator (Varicam and millennium VG from General Electric, Milwaukee, USA). Dose was calculated as body surface area divided by 1.73 and then multiplied by the adult dose of 1,000 MBq. Whole body acquisition was done using step and shoot method with 180 seconds per view. For any spinal lesion, single photon emission computed tomography (SPECT) of the involved vertebral lesion was performed.

Bone SPECT was acquired in a 128 x 128 matrix with 90 views at every 4° for 25 seconds per view were obtained. Projection data was prefiltered before back projection and reconstruction performed with a two-dimensional hanning filter (cut off=0.23 cm, P=50). Attenu-

Table 1: Demographic and other characteristics of the study subjects (n=122)

Characteristic	Number (%)
Gender	
Male	68 (55.7)
Female	54 (44.2)
Age (Yr.)	
Median	38
Range	4-83
Tumour site	
Head Neck	17 (13.9)
Upper limb/ shoulder	9 (7.3)
Chest	5 (4.09)
Trunk	3 (2.45)
Abdomen	26 (21.3)
Retroperitoneum/pelvis	25 (20.4)
Lower limb/hip	37 (30.3)
Tumour Histology	
Rhabdomyosarcoma	37 (30.3)
Chondrosarcoma	19 (16.3)
Fibrosarcoma	18 (14.7)
Sarcoma otherwise not specified	17(13.9)
Synovial sarcoma	10 (8.1)
Malignant nerve seethe tumour	5 (4.09)
Kaposi's sarcoma	2 (1.6)
Alveolar soft part sarcoma	3 (2.4)
Angiosarcoma	2 (1.63)
Liposarcoma	4 (3.2)
Hemangiopericytoma	3 (2.4)
Hemangioendothelioma	1 (0.81)

ation correction was done by Chang's method.[7] No scatter correction was done. Reconstructed images had a slice thickness of 7 mm and were displayed and analysed using transverse, sagittal and coronal views.

Two experienced nuclear medicine physicians evaluated the scan findings independently and both of them were blinded to the findings of other investigators but were aware of the primary disease and its location. Abnormally increased radiotracer uptake away from joints, which is not readily explainable by trauma or other local factors, was considered as skeletal metastasis. Scans were classified into three Grades: Grade 1 (high probability scan for skeletal metastases), Grade 2 (definite characterisation as malignant or benign lesion not possible), or Grade 3 (normal or certainly benign lesions).

The presence or absence of bone metastases was determined based on the combination of bone scan findings, the results of other investigations (absence or presence of typical sclerotic lesions on X-rays, appearance of tumour tissue in bone, bone cortex defect, or signal changes as visible in CT or magnetic resonance imaging [MRI]), and a follow-up bone scan whenever available.

Results

Grade 1 scans were found in 17 of 122 patients (13.9%); all bone metastases were confirmed by additional investigations (Figure 1). Sixteen of these patients reported pain and the site of pain could not be definitely associated with trauma or joint degeneration. One patient had no pain or discomfort over any of the sites of skeletal metastasis.

Grade 2 (definite characterisation as malignant or benign lesion not possible) scans were present in 10 of 122 patients

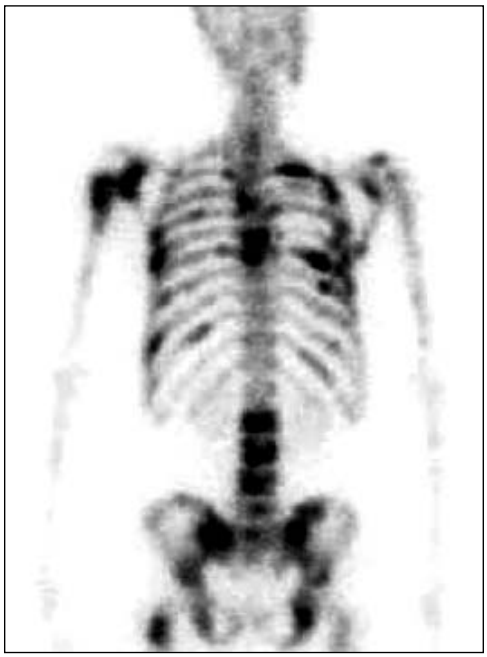

Figure 1: A Grade 1 scan with multiple areas of intense uptake of Tc99m-MDP, highly suggestive of skeletal metastases.

(8.1%). All these patients underwent further investigations, which excluded skeletal metastases. In 3 patients the equivocal lesion was in the same bone region involved but was distinctly separated from the primary soft tissue mass. Seven patients had increased tracer uptake over vertebra, but the intensity of increased tracer uptake was not sufficient to place them into Grade 1. MRI of spine, performed in these patients revealed only degenerative changes (Figures 2a, 2b). Five patients with Grade 2 scan complained of bone pain which could not be readily explained by trauma or joint degeneration.

Grade 3 (normal) bone scans were found in 95 patients (77.8%) (Figure 3). Lesions described as 'almost certainly benign' were usually the result of degenerative disease of the spine or clearly

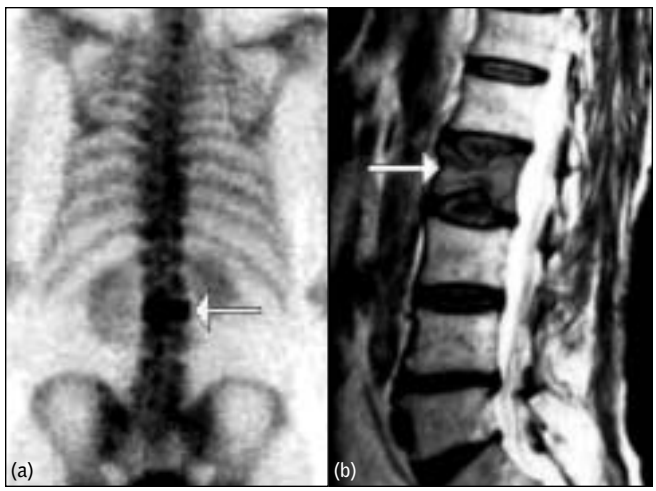

Figure 2: (a) A Grade 2 scan with moderately increased uptake of Tc99m-MDP in the L2 vertebra. **(b)** MRI of lumbar vertebra of the patient showing collapse of L2 vertebra (Patient was later diagnosed to have tuberculosis of spine).

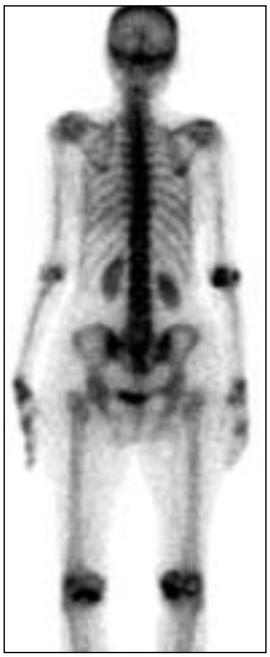

Figure 3: A Grade 3 scan with intense uptake of Tc99m-MDP over both the medial condyles of femur: highly suggestive of degenerative changes.

caused by recent trauma (focally increased rib uptake over the site of pleural tap in 2 patients). Nine of these patients also had localised bone pain but that could be definitely associated with trauma or joint degeneration, and hence excluded from further analysis of results. Skeletal survey performed in these patients excluded any skeletal metastases.

Overall, in 3 cases (3.06%), there was a difference in interpretation between two observers as Grade 2 versus Grade 3 and that was resolved by consensus.

Overall, bone pain was present in 22 patients (excluding those patients where pain was due to trauma and degenerative joint disease). Of these, in 16 patients (72.7%) (Table 2), this pain could be correlated to bone metastases. Hence skeletal metastases were present in 76.1% patients with bone pain as against only in 0.9% patients without bone pain.

Discussion

In this study, routine bone scan had a relatively low yield. Therefore, if bone scan had been obtained only in the 21(17.2%) patients with bone pain, 101(82.7%) bone scans could have been avoided. In that case bone metastases would have been missed in one patient without bone pain. This patient had clinically advanced disease with lung and brain metastasis. Bone scans in this patient revealed extensive skeletal metastases. Therefore, the clinical yield would have been almost the same if bone scan had been performed only in patients with bone pain and would have saved 101 unnecessary bone scans.

Table 2: Grading of the tumour as per bone scans and the association with bone pain of recent onset

Scan reading	Total	Patients with bone pain
Grade 1	17 (13.9)	16 (94.1)
Grade 2	10 (8.1)	6 (60.0)
Grade 3	95 (77.8)	0 (0)

Figures in parentheses indicate percentages

As a method to detect skeletal metastases, skeletal scintigraphy proved to be accurate. All cases of Grade 1 scan indeed had skeletal metastases, as evidenced by other imaging studies whereas all cases with a Grade 3 reading were free of bone metastases. The equivocal group (Grade 2 reading) was relatively small (8.1%) and no bony metastases were found.

Several investigators have reported a low incidence of skeletal metastases in soft tissue sarcoma (STS) patients. Yoshikawa et al reported an incidence of 9.4% in a series of 320 patients.[8] Jager et al reported an incidence of 7% in a series of 109 patients.[9] Our study revealed a slightly higher prevalence (13.9%) of skeletal metastases as compared to other studies. This could be partly due to referral bias and partly due to a larger proportion of those tumours, which produce skeletal metastases more frequently like rhabdomyosarcoma and poorly differentiated soft tissue sarcoma. Isolated skeletal metastases were present in 5 patients. However, lung metastases were more common than bone metastasis. Twenty-one patients had lung metastases and one patient had cerebral metastasis.

There is no widely accepted view on the level of incidence of skeletal metastases that justifies routine bone scan in all patients. Skeletal scintigraphy is a very sensitive modality for the detection of skeletal metastases but has poor specificity. Trauma, degenerative disease, and inflammatory disease also cause increase in tracer uptake which can sometimes mimic skeletal metastasis. However, the pattern of abnormalities together with detailed clinical history increases the specificity of bone scan. In case of multiple lesions randomly spread all over the skeleton, the likelihood of bone metastasis is very high. Conversely, if the bone scan is normal it virtually rules out the possibility of skeletal metastasis. In many cases the pattern of abnormalities does not follow a specific pattern and further investigations are required to exclude the possibility of skeletal metastasis. Bone scanning with its high sensitivity and low specificity is cost- effective only when applied to a subgroup of patients with increased risk of skeletal metastases. Bone pain of relatively recent onset has been suggested as a predictor of the presence of skeletal metastasis.[9] Our study also demonstrates the utility of bone pain of recent onset as a predictor of the presence of skeletal metastasis; 76.1% patients with bone pain had skeletal metastasis whereas only 0.9% of patients without bone pain had skeletal metastasis.

Apart from the use in staging the disease, bone scan is also performed to detect local bone involvement by the soft tissue sarcoma. However, MRI and CT scan studies have been demonstrated to be more precise, especially CT scans which reliably detect defects in the bone cortex.[10-11] A bone scan can be false positive in this scenario due to tumour-associated local hyperemia, though bone scan is occasionally performed when anatomical imaging studies are equivocal.

A limitation of the study was the absence of follow-up bone scan in Grade 3 patients. However, bone metastases were not confirmed in any of the patients with even more abnormal bone scan (Grade 2) who did have extensive metastatic work-up and serial follow-up bone scan.

It could be concluded that skeletal metastases at presentation in soft tissue sarcoma patients are low (13.9%). The low rates of skeletal metastases in bone pain-free patients (0.9%) versus the high rate in symptomatic patients (76.1%) supports the use of bone scanning in symptomatic patients only.

References

1. Storm HH. Cancers of the soft tissues. Cancer Surv 1994;19:197-217.
2. Coindre JM, Terrier P, Guillou L, Le Doussal V, Collin F, Ranchere D, et al. Predictive value of grade for metastasis development in the main histologic types of adult soft tissue sarcomas: Study of 1240 patients from the French Federation of Cancer Centers Sarcoma Group. Cancer 2001;91:1914-26.
3. Rydholm A, Gustafson P, Alvegard TA, Saeter G, Blomqvist C. Prognostic factors in soft tissue sarcoma. A review and the Scandinavian Sarcoma Group experience. Acta Orthop Scand Suppl 1999;285:50-7.
4. Zagars GK, Ballo MT, Pisters PW, Pollock RE, Patel SR, Benjamin RS, et al. Prognostic factors for patients with localised soft-tissue sarcoma treated with conservation surgery and radiation therapy: An analysis of 225 patients. Cancer 2003;97:2530-43.
5. Pisters PW, Leung DH, Woodruff J, Shi W, Brennan MF. Analysis of prognostic factors in 1,041 patients with localised soft tissue sarcomas of the extremities. J Clin Oncol 1996;14:1679-89.
6. Gustafson P. Soft tissue sarcoma. Epidemiology and prognosis in 508 patients. Acta Orthop Scand Suppl 1994;259:1-31.
7. Chang LT. A method for attenuation correction in radionuclide computed tomography. IEEE Trans Nucl Sci 1978;25:638-43.
8. Yoshikawa H, Myoui A, Ochi T, Araki N, Ueda T, Kudawara I, et al. Bone Metastases from Soft Tissue Sarcomas. Semin Musculoskelet Radiol 1999;3:183-90.
9. Jager PL, Hoekstra HJ, Leeuw J, van Der Graaf WT, de Vries EG, Piers D. Routine bone scintigraphy in primary staging of soft tissue sarcoma; Is it worthwhile? Cancer 2000;89:1726-31.
10. Heslin MJ, Smith JK. Imaging of soft tissue sarcomas. Surg Oncol Clin N Am 1999;8:91-107.
11. Ozaki T, Inoue H, Taguchi K, Sugihara S. Gadolinium-DTPA enhanced magnetic resonance imaging of bone and soft-tissue sarcomas in comparison with pathological findings. Acta Med Okayama 1992;46:471-7.

Expert's Comments

Bone scintigraphy in oncology

Bone scintigraphy has been in use for approximately 30 years now. It is one of the main nuclear medicine procedures performed in every department around the world. Although competing modalities, such as whole body MRI are coming up, even pessimists do not foresee a rapid disappearance of this established technique. The reasons for the success of bone scintigraphy are simple: the procedure is simple, patient-friendly, relatively cheap and reliably provides relevant clinical information in an early phase where radiographs are frequently still normal. Also, there is a vast body of knowledge available worldwide on virtually every thinkable application.

In oncology, the place of bone scintigraphy is rather well established, and the method has found its place in many algorithms. Bone scintigraphy is sensitive for any abnormality in bone that causes an osteoblastic reaction (and most do), yet it is rather unspecific. This important characteristic requires that the pre-test chance of finding an abnormality, e.g. bone metastases, should not be 'too low', in order to avoid false positive findings caused by other (benign) pathology. This is nicely illustrated by the yield of bone scintigraphy in staging breast cancer patients, in which the percentage of abnormal bone scans rises from 0.3%, 3%, 8% to 13%, in T1, T2, T3 and T4 tumours.[1] In early stage breast cancer therefore, there is no place for routine bone scintigraphy.

The pre-test chance rises considerably, when other factors are present, the most important being bone pain and increased alkaline phosphatase (AP) or calcium levels. In lung cancer staging most algorithms advise bone scans only in patients with pain or high AP, as the yield of positive bone scans is 40-74% in those patients, versus 4-19% in asymptomatic patients,[2,3,4] although this has recently been questioned.[5] In prostate cancer the yield of bone scintigraphy rises strongly when PSA levels are increased (e.g. >20 ng/ml).

This kind of information is however not available in all types of cancers. In this issue of the journal, Barai et al[6] have studied the yield of routine bone scintigraphy in soft tissue sarcoma. Probably due to its rarity, very few have focussed specifically on the issue of routine bone scanning in these patients, and they reached the same conclusion as another report, with approximately 1% bone metastases in asymptomatic patients, versus 76% in those with bone pains, at an incidence of 13%.[7] It therefore appears safe to check for pain, and when absent avoid the routine demand for a bone scan.

What incidence of the searched abnormality should be present to justify routine searching for it? It is intuitively clear that 1% is not enough, 100 scans to find one positive, is a waste of resources. Many agree, again intuitively, that 10% or more, is worthwhile, but what about 5%? These questions are difficult to answer in general, and also require an estimation of the therapeutic consequences of a positive scan, and the context of the patient, e.g. the presence of other than bone metastases (like lung metastases in sarcoma). Naturally, when lung metastases are found, the detection of asymptomatic bone metastases becomes less relevant. This complicated reasoning and weighing is the daily work of physicians around the world. Basic information, such as provided by Barai et al, helps in developing sound algorithms in the work-up of tumours, and helps individual reasoning, even after 30 years of bone scintigraphy.

With exciting new modalities coming up, such as whole body

MRI, FDG PET, and especially sodiumfluoride-18 PET with their own new individual properties with regards to sensitivity, specificity, intra- and interindividual variation in reading, relation to bone scintigraphy, costs, availability and knowledge. the very same basic questions will come up again.

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References

1. Coleman RE, Rubens RD, Fogelman I. Reappraisal of the baseline bone scan in breast cancer. J Nucl Med 1988;29:1045-9.
2. Hooper RG, Beechler CR, Johnson MC. Radioisotope scanning in the initial staging of bronchogenic carcinoma. Am Rev Respir Dis 1978;118:279-86.
3. Mountain CF, Dresler CM. Regional lymph node classification for lung cancer staging. Chest 1997;111:1718-23.
4. Spiro SG, Porter JC. Lung cancer—where are we today? Current advances in staging and nonsurgical treatment. Am J Respir Crit Care Med 2002;166:1166-96.
5. Schirrmeister H, Arslandemir C, Glatting G, Mayer-Steinacker R, Bommer M, Dreinhofer K, et al. Omission of bone scanning according to staging guidelines leads to futile therapy in non-small cell lung cancer. Eur J Nucl Med Mol Imaging 2004;31:964-8.
6. Barai S, Bandopadhayaya GP, Chumber S, Gupta DK, Patel CD, Dhanpati H. Role of skeletal scintigraphy in soft tissue sarcoma: Improving the diagnostic yield. J Postgrad Med 2004;50:180-5.
7. Jager PL, Hoekstra HJ, Leeuw J, van Der Graaf WT, de Vries EG, Piers D. Routine bone scintigraphy in primary staging of soft tissue sarcoma; Is it worthwhile? Cancer 2000;89:1726-31.