Bone Scintigraphy: Part 1. Oncology and Infection

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This article and the following two articles are a part of the continuing education series in the *Journal*. The goal is to provide a state-of-the-art review of topics in bone scintigraphy as they relate to clinical practice. This article discusses the bone scan in oncology and infection. The second article is a review of metabolic bone disease and will include comments on bone mineral densitometry. The final article in this series deals with common orthopedic problems and the usefulness of the bone scan in their work-up.

The bone scan has now been with us for over 30 yr. There has been significant improvement in radiopharmaceuticals and instrumentation in that time and by optimizing technical factors (*1*) exquisite images can be obtained, which allow a high degree of sensitivity with accurate anatomic localization necessary to provide our clinical colleagues with the information they seek.

ONCOLOGY

The earliest use of bone scintigraphy was in the evaluation of patients with primary and metastatic bone lesions. Bone scanning continues to play an important role, albeit one that is changing, in the evaluation of patients with soft-tissue or osseous neoplasms. One of the major advantages of the bone scan is it allows a total body survey. This remains very important because approximately 20% of lesions are in the distal appendicular skeleton or skull (*2*) and because routine x-rays are significantly less sensitive for the early detection of metastatic disease than the bone scan.

In a patient with a known malignancy, solitary lesions on a bone scan are often problematic. Data from several series (*3–11*) reveal that between 60% and 70% of solitary lesions in the central skeleton are due to metastatic disease where a smaller number, between 40% and 50%, of lesions in the extremities or skull are due to metastatic disease. A solitary rib lesion is much less likely to be metastatic in origin. A recent article on solitary rib lesions showed that approximately 10% of these are due to metastatic disease in patients with known malignancies (*11*). An isolated sternal lesion in a patient with breast carcinoma has a probability of almost 80% of being due to metastatic disease (*5*).

The development of the solitary bone lesion in a patient with a known soft-tissue malignancy is not uncommon. In a review of 160 consecutive cases of patients with breast cancer, Boxer et al. showed that approximately 20% of patients relapsed with a solitary bone lesion, most commonly in the spine (*3*). These studies were performed every 6 mo and presumably, if the scans had been performed more frequently, a higher incidence of solitary lesions may have been found. When the bone scan shows a solitary lesion in a patient with a known malignancy, it is important to undertake further evaluation with plain films, CT or MRI.

Another finding seen in the evaluation of patients with metastatic disease is the "flare phenomenon," where there is worsening, or even new lesions, on the bone scan during the first several months following new chemotherapy, while the patient's clinical condition improves (*12–16*). This also occurs in patients following orchiectomy (*17*) and radiation therapy (*18*). A repeat bone scan will show marked improvement after several months. The flare phenomenon occurs in up to 20% of patients; however, the frequency obviously depends on tumor type, therapeutic regimen and the interval between therapy and the bone scan.

PRIMARY TUMORS AND MYELOMA

Bone scintigraphy remains an important part of the work-up and as a means of following patients with primary bone tumors (*19,20*). Both Ewing's sarcoma and osteogenic sarcoma can metastasize to bone. The frequency of osseous metastases is higher in Ewing's sarcoma. The limitations of bone scintigraphy in multiple myeloma has again been confirmed in a recent study by Feggi and colleagues

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(*21*). This is due to the purely lytic nature and the lack of a reparative osteoblastic response in myeloma. Although bone scintigraphy is not as sensitive as plain film radiography in detecting the typical lesions of myeloma, the bone scan can be helpful in certain areas, such as in the ribs and sternum, that are difficult to evaluate with x-rays and it can also be helpful in patients with bone pain and normal radiographs.

Soft-Tissue Tumors

Bone scintigraphy is very useful in the care of patients with common soft-tissue malignancies such as breast cancer, prostate cancer, etc. In breast carcinoma, routine bone scintigraphy in Stage 1 and possible Stage 2 disease is unwarranted due to the low true-positive yield (*22–26*). Bone scintigraphy is useful in the preoperative or postoperative setting in Stages 3 and 4 breast carcinoma and in patients who are symptomatic. Bone scintigraphy is also useful in following patients with breast cancer, especially those who become symptomatic or have positive laboratory studies.

As bone metastasis usually start in the marrow, a marrow imaging agent may be more sensitive than bone scintigraphy. In a recent study by Duncker and colleagues (*27*) using a radiolabeled antigranulocyte monoclonal antibody which has a marrow distribution, they were able to detect metastatic disease in 78% of patients where the bone scan performed at the same time showed only 53% of patients having metastatic disease. In patients that had positive studies on both the bone scan and marrow scan, the marrow scan demonstrated more lesions (*27*). Marrow scintigraphy showed a significantly greater extent of metastatic disease than bone scintigraphy in patients with lymphoma, breast cancer and multiple myeloma and to a lesser but still significant degree in other malignancies in another study (*28*). This was also true in a study of patients with breast cancer and lymphoma (*29*) and in a study of patients with small-cell lung cancer where defects on the marrow scan were helpful in evaluating metastatic disease to bone marrow (*30*). Although marrow scintigraphy is promising, more work is needed to show that disease is detected earlier than on the bone scan before this can be considered a standard clinical test.

The bone scan remains very important in the care of patients with prostate carcinoma. Recently, PSA (prostate-specific antigen) has been shown to be a useful marker of prostatic cancer. PSA is more specific than prostatic acid phosphatase (*31*) and correlates well with the bone scan (*32*). In patients with a low serum PSA level, there was a very low likelihood of having a positive bone scan. In their study, PSA levels of less than 20 ng/ml had a negative predictive value of 99.7% (*32*). In another study by Freitas et al. (*33*), patients with PSA values of less than or equal to 8 ng/ml rarely had a positive bone scan, with a negative predictive value of 98.5%.

This finding of a negative predictive value in patients with low levels of PSA is true in newly diagnosed patients and in patients who have had some forms of therapy, but it is not true in patients who have had hormonal treatment. Leo and colleagues (*34*) showed that patients with well documented metastatic disease who had had anti-androgen treatment often had normal levels of PSA. They concluded that PSA levels in patients with hormonal treatment of prostatic carcinoma had a significantly different meaning than PSA levels in patients with other forms of therapy.

Patients who have had postradical prostatectomy should have bone scintigraphy performed when PSA levels start to rise or when patients become symptomatic (*35*). Osterling et al. (*36*) state that in newly diagnosed prostate cancer, patients who have no skeletal symptoms and have a PSA level of 10 ng/ml or less do not need a staging bone scan. However, this applied to only 39% of their patients.

Merrick and Merrick (*37*) studied patients with lung cancer. In their study, bone scintigraphy had a sensitivity of 89% and an accuracy of 78% for metastatic disease. Both the findings of bone pain, and an abnormal bone scan, were independently associated with a significant reduction in patient survival. They conclude that bone scanning was indicated in patients with unexplained symptoms and where staging was required. These results were unrelated to the patient's age, sex or the cell type of lung cancer. In the initial staging of nonsmall-cell lung cancer, the bone scan should be reserved for patients with symptoms or laboratory evidence of bone metastases (*38*).

In summary, the bone scan is a valuable tool in the care of patients with a soft-tissue or osseous malignancy. Table 1 suggests how the bone scan maybe used for the oncologic patient.

OSTEOMYELITIS

Musculoskeletal infections can be considered in several categories. These include: soft-tissue infections such as cellulitis and myositis; osteomyelitis, either hematogenous or by direct extension from other sites of infection and either in "virgin" bone or in bone with superimposed disorders such as fractures, orthopedic appliances, diabetic osteopathy, etc.; joint space infections and disc space infections. Bone scintigraphy plays an important role in the workup of musculoskeletal sepsis. It is helpful in the differentiation of cellulitis from osteomyelitis and it is also an important tool in the workup of complicated osteomyelitis in conjunction with the other nuclear medicine studies such as labeled leukocytes or ^{67}Ga-citrate.

In a recent review article, Schauwecker (*39*) did an excellent survey of the field. In his review of the literature, he showed that the bone scan had a high sensitivity (94%) and specificity (95%) for osteomyelitis in both children and adult patients with normal radiographs. The limitation of bone scintigraphy is in patients who have conditions that cause increased bone turnover. In Schauwecker's review (*39*), the sensitivity remained high, approximately 95%, but the specificity drops significantly to 33% in patients with conditions that cause abnormal bone scans. To im-

TABLE 1
Uses for Bone Scan in Oncology Patients

	Staging	Follow-up
Prostate carcinoma	Bone pain PSA >10 ng/ml	Patients with antiandrogen therapy. Any PSA if the patient's status is postradical prostatectomy. PSA >8–20 ng/ml or new bone pain.
Breast carcinoma	Clinical Stage III or IV disease Bone pain or suspicious laboratory values	Bone pain or suspicious laboratory values. 6–12 mo for poor prognosis patients (T4, >4+ lymph nodes, inoperable).
Other carcinomas (lung, colon, miscellaneous)	Bone pain or suspicious laboratory values	Bone pain or suspicious laboratory values.

prove the accuracy in this setting, additional studies are required. Historically, ^{67}Ga was the agent of choice, but recently ^{111}In-labeled leukocytes and now ^{99m}Tc-HMPAO-labeled leukocytes have been used with great success. The sensitivity for gallium scanning was 81% with a specificity of 69%, and the sensitivity of indium-labeled leukocytes was 88% with a specificity of 85% (*39*). The same results were obtained for such diverse processes as fracture nonunion, diabetic osteopathy and in orthopedic appliances.

To add to the specificity of ^{111}In-leukocyte scintigraphy in areas that contain marrow, a bone marrow scan should be performed because labeled white blood cells localize normally in marrow-containing bone. This can be especially problematic in the proximal femurs and humeri and wherever there is marrow expansion (*40–42*). The concept is that when ^{111}In-white cell localization is incongruent with the marrow scan there is likely to be infection (Fig. 1).

Patients with diabetic osteopathy and foot ulcers can present a special problem because the underlying condition will cause abnormal findings on bone scintigraphy and there is little if any tissue between the ulcer crater and bone. Many studies have attempted to use the three-phase bone scan to improve specificity and accuracy with limited success (*43–45*). A meta-analysis of 10 reports meeting the following criteria was recently reported: bone scanning in patients with diabetes, vasculopathy or neuropathy and an ulcer or soft-tissue inflammation and patients suspected of having osteomyelitis of the foot (*46*). The results showed a false-positive rate in the range of 10%–20% with sensitivities between 70% and 80%. The consensus was that even small increases in sensitivity caused large sacrifices in specificity (*46*). Indium-111-leukocyte scanning had better specificity and overall accuracy (*44,47–50*). A recent article, in a relatively small series of patients, showed that the labeled white blood cell study was better than MRI in detecting patients with diabetic osteopathy (*51*). The improvement in specificity seen with ^{111}In-leukocytes also appears to be true for ^{111}In-labeled nonspecific immunoglobulin (*52*).

Technetium-99m-HMPAO labeled white cells have also shown excellent results in suspected osteomyelitis (*53*), and recent articles on the use of indium-labeled IgG report excellent results using this labeled nonspecific human gamma globulin in osteomyelitis (*52,54,55*).

For disc space infections, although the bone scan is often positive, gallium scintigraphy is the preferred method (*56,57*). Indium-111-leukocytes have been shown to be of limited value in the diagnosis of disc space infection (*58*), although some authors feel that the labeled white cell scan can be of benefit especially if the cold (photon deficient) lesions are considered diagnostic of disc space infection (*59*).

In summary, bone scintigraphy remains a very important component of the diagnostic armamentarium for both oncologic disease and in problems related to musculoskel-

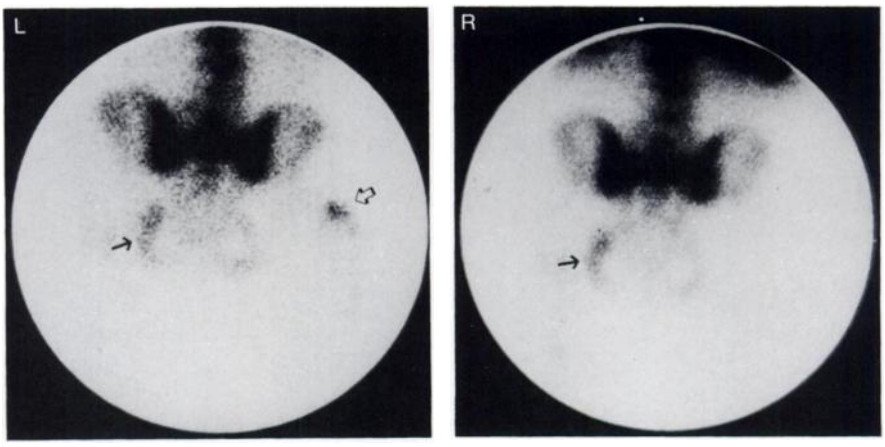

FIGURE 1. The left panel shows an ^{111}In-leukocyte scan with focal uptake in the proximal portion of a right girdlestone (arrowhead) and moderate increase uptake in the left ischium (arrow). The marrow scan (right panel) shows a similar distribution in the left ischium, indicating more reactive bone marrow in this location where there is no corresponding uptake in the girdlestone, indicating this as a site of infection. This activity was surgically proven to be an infection in the proximal girdlestone of the right hip.

etal infections. The following articles will show its role in metabolic bone disorders and in orthopedic disorders.

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