Use of Bone Scanning and Skeletal Radiography in the Diagnosis of Bone Metastasis

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The radionuclide bone scan is becoming increasingly useful for evaluating a wide variety of bone and joint disorders. However, the commonest application is still the detection of skeletal metastases in the patient with known or suspected neoplastic disease. The role of this examination relative to other well established methods of evaluating these patients, especially the radiographic skeletal survey, is not clear to all physicians. We hope in this communication to define the role of the radionuclide bone scan and to place in perspective the integral relationship between the "scan" and the "survey," the two radiologic modalities which today are the principal methods of evaluating the skeletal system for metastatic disease.

Radiopharmaceuticals. Historically, numerous agents have been used for bone scanning, but only a small number have been applicable for general clinical use. The first of these were the strontium isotopes, strontium-85 and strontium-87m. Subsequently, fluorine-18 and, most recently, the technetium-99m-labeled phosphate compounds have been used.

Strontium. Strontium is an analogue of calcium and, as such, is incorporated into the hydroxyapatite crystal by an ion-exchange process with calcium (1). Unfortunately, the plasma clearance of strontium is slow due to partial binding with plasma proteins (2, 3). Excretion occurs by both urinary tract and bowel (4).

Strontium-85 nitrate was one of the first agents used for imaging of bone lesions. Its long physical half-life of 65 days severely limited the administered dose, which was usually 100 microcuries. The presence of bowel activity in the first few days following injection necessitated cleansing enemas and/or long delays between isotope administration and scan. Its 514 kev photon was also much higher than ideal for nuclear imaging instrumentation. Nevertheless, ^{85}Sr was a clinically useful bone scanning agent.

Strontium-87m has a considerably shorter physical half-life (2.8 hours) and lower photon energy (388 kev) making it a physically more desirable agent. Unfortunately, the high body-background during the first 12 hours following injection results in less than optimal clinical images (2) and, therefore, this agent has not been widely used for bone imaging.

Fluorine-18. Fluorine-18 is a hydroxyl analogue which is incorporated into bone by an ion-exchange process forming a fluorapatite crystal (1, 5). Bone has a very high affinity for fluorine with most of the radionuclide extracted from the blood on the initial transit (2, 5). The renal extraction efficiency is also high and, therefore, plasma clearance of ^{18}F is the most rapid of any of the clinically useful bone scanning radionuclides (6,7). Excellent bone-to-background ratios can be obtained with ^{18}F at 1 to 2 hours following intravenous injection (3, 6). The half-life is very short (1.8 hours) which is advantageous from the standpoint of patient dose. However, the short half-life of ^{18}F is also a problem because it is cyclotron-produced (8) and, therefore, its use is limited to those locations in close proximity to a cyclotron. The 511 kev annihilation radiation from ^{18}F makes imaging with the gamma camera difficult. The best images are obtained with a rectilinear scanner or special positron camera (5, 9). Transportation

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problems and cost, both related to the short half-life of ^{18}F, have inhibited its clinical use.

Technetium-99m-labeled compounds. This group of compounds contains the phosphate polymers, pyrophosphate and polyphosphate, and their organic analogues, the diphosphonates. These agents localize in bone crystal by surface chemisorption rather than ionic exchange (10,11). The terminal phosphate groups of the ^{99m}Tc-labeled compound react with the "phosphate gaps" which are present in the imperfect bone crystals. (The ^{99m}Tc acts only as a label unlike ^{18}F and the Sr isotopes). Plasma clearance varies

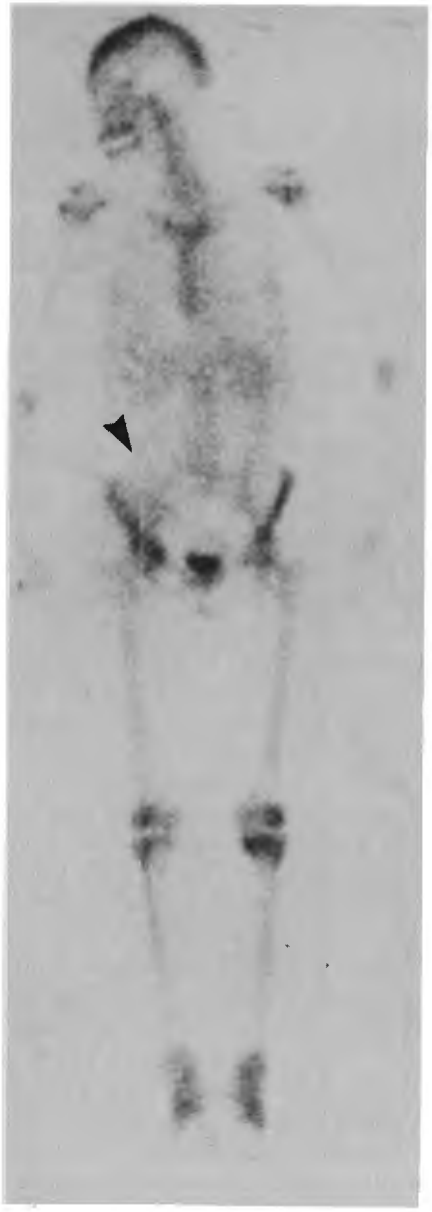

Fig 1—Decreased uptake in Ilium (*arrow*) in patient with metastatic bone lesion. Such "photopenic" lesions occur as a result of lack of hyperemic response to tumor due to debilitation, failure of tumor to provoke response, or radiation to region of lesion.

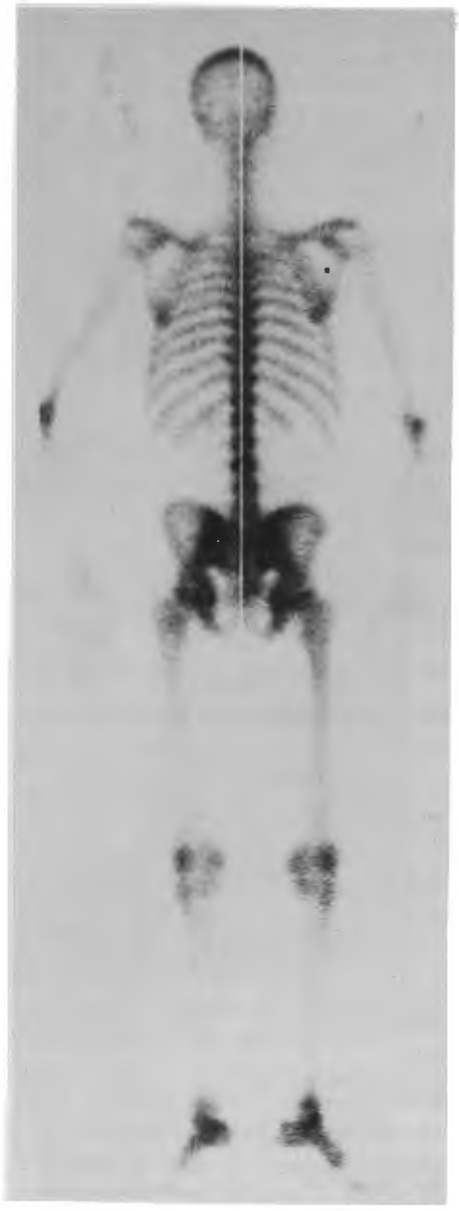

Fig 2—Diffuse increase in skeletal activity denoted by "absence" of renal activity. In addition to diffuse metastasis, the absent kidney sign may also be seen in severe renal disease, hyperparathyroidism and hypermetabolic states.

TABLE 1
Bone Scans vs. Skeletal Survey for the Detection of Metastatic Lesions to Bone

Radionuclide	Source	No. of pts.	+scan −x-ray	−scan +x-ray
Sr	DeNardo (1966) DeNardo et al. (1972)	84	38%	4%
	Briggs (1967)	83	20%	1%
	Bessler (1968)	104	15%	1%
	Harmer et al. (1969)	47	41%	6%
	Legge et al. (1970)	186	13%	2%
	Gnekow et al. (1972)	353	8%	2%
^{18}Fl	Harmer et al. (1969)	112	31%	3%
	Blau et al. (1972)	239	15%	4.5%
	Hopkins et al. (1972)	104	20%	4%
	Merrick (1973)	119	13%	0
^{99m}Tc	Desaulniers (1973)	100	9%	1%
	Pendergrass (1973)	259	20%	2%
	Citrin et al. (1974)	70	10%	0
	Barrett and Smith (1974)	90	71% (of lesions)	2%

among the principal agents comprising this group with the diphosphonates being cleared most rapidly, pyrophosphate cleared somewhat less rapidly, and polyphosphates being cleared least rapidly (7). The bone-to-background ratios achieved with the diphosphonates at 3 hours is almost comparable to that achieved with ^{18}F at 1 to 2 hours (6, 7). Other advantages of this group of agents are the short half-life of ^{99m}Tc (6 hours) which permits the safe administration of millicurie doses and near optimal gamma energy (140 kev) and high photon flux which make possible rapid performance of the procedure and good spatial resolution with the gamma camera, the most widely used nuclear imaging device. The ready availability and easy preparation from commercial kits with a long shelf-life also make them ideal for general clinical use. The ^{99m}Tc-labeled compounds are the current agents of choice for bone scanning. The availability of these excellent and convenient agents has fostered the recent widespread clinical popularity of bone scanning.

TABLE 2
Bone Scan vs. Skeletal Survey For Specific Tumor Types

Source	# of pts.	+scan −x-ray	−scan +x-ray
Breast			
Sklaroff and Charkes (1968)	64	16%	0
Galasko (1969) Galasko (1971)	100	29%	0
Marty and Hoffman (1972)	164	26%	—
Lung			
Sauerbrum et al (1972)	82	30%	0
Shirazi et al (1973)	206	7%	1%
Prostate			
Morgan and Mills (1968)	66	42%	0
Williams et al (1968)	70	21%	0
Roy et al (1971)	30	53%	0
Shearer et al (1974)	61	12%	1%
Bisson et al (1974)	81	27%	1%
Lymphoma			
Weber et al (1968)	19	74%	0
Harbert and Ashburn (1968)	51	12%	4%
Moran et al (1973)	80	5%	0

"Scans Signs" of Tumor. Considerable laboratory data has accumulated over the past years indicating that the two principal factors involved in the uptake of bone-seeking radionuclides into the bone are 1) bone blood flow and 2) metabolic activity of the bone (10,12,13). Recent evidence has indicated that for ^{18}F and the ^{99m}Tc-labeled phosphate compounds, bone blood flow is the most important factor (10).

The detection of metastatic tumor in bone is based on the premise that the destructive and reparative events that occur in the bone as a result of a metastatic deposit cause a localized increase in blood flow and bone turnover. This in turn results in localized increased uptake of the bone scanning agent which is imaged as a "hot spot" on the bone scan. This "hot spot" can usually be easily recognized by an alteration in the bilateral symmetry or, as with the axial skeleton, an alteration of the homogeneous uptake in the spine. A second "scan sign" of tumor involvement is a localized area of decreased uptake of the bone scanning agent (Fig 1). This has been referred to as a "photon deficient" or "photopenic" abnormality and occurs in cases where there is replacement of a portion of bone by tumor with little or no reparative response on the part of the host because of the nature of the tumor or the debilitated state of the patient (14). (Similar findings noted by R. S. Hattner, MD, unpublished data.) This is a distinctly less common sign of skeletal involvement than a localized area of increased uptake. A third "scan sign" of metastatic involvement of the skeleton is diffuse but uniform increased uptake which does not alter the bilateral symmetry and may only be recognized by the decrease in renal activity (Fig 2) (15). Normally, the kidneys in adult patients can be clearly identified at

3 to 4 hours following administration of the ^{99m}Tc compounds. The absence of renal activity is a rare but important manifestation of metastatic skeletal involvement which occurs when so much of the radionuclide is deposited in bone that virtually none is available to be localized in the kidney. In some reported series, this "scan sign" was unrecognized and such cases were termed false-negative (16, 17).

Comparison of Bone Scan to Bone Survey. Many clinical studies have been performed comparing the relative sensitivity of the radionuclide bone scan and the radiographic skeletal survey for the detection of skeletal metastases. In earlier reports, ^{85}Sr and ^{87m}Sr were the isotopes used for radionuclide bone scanning, but in more recent reports ^{18}F and ^{99m}Tc-labeled phosphate compounds have been employed. These studies are summarized in Table 1 (5, 18-28). All of these studies indicate that the radionuclide bone scan is more sensitive than the radiographic skeletal survey for detecting skeletal metastases. Some reports indicate that the results with ^{99m}Tc-labeled phosphate compounds are even better than with ^{18}F or the Sr agents (26-31). For certain common neoplasms, a particularly large experience has accrued over the years to compare the two techniques of bone scanning and skeletal survey on a tumor-oriented basis. These comparisons are summarized in Table 2 (32-45) and as noted by E. M. Moran, MD (oral communication, June, 1973).

Although it is quite clear that the radionuclide bone scan is more sensitive than the radiographic skeletal survey for detecting skeletal metastases, it is important to remember that the examination is nonspecific in nature. Focal areas of increased radionuclide uptake in bone are invariably due to some skeletal abnormality; however, it must be noted that the scan can be "positive" in numerous conditions other than neoplasm (Fig 3*A* and 3*B*) (46, 47). Table 3 is a list of non-neoplastic conditions which cause focal increase in radionuclide uptake in bone. The radiograph, on the other hand, while not as sensitive, is quite specific and may exhibit characteristic patterns which allow for a more accurate etiologic diagnosis. For these reasons, a radiograph is always necessary to assess the significance of a scan abnormality.

False-negative radionuclide bone scans occur infrequently, in approximately 0.4% of patients in most of the recent studies as noted in Tables 1 and 2. These have been seen to occur in certain specific situations (17,48-50). They are: 1) Some patients with myeloma; 2) some patients with tumor of anaplastic cell type; 3) some severely debilitated patients with poor host response; 4) patients with diffuse disease uniformly involving the whole skeleton; 5) patients with pelvic lesions obscured by a high level of activity in the bladder; 6) lesions that have been irradiated. As to the incidence of false-positive bone scans, in

Fig 3*A*—Abnormal bone scan revealing increased radionuclide uptake in the left clavicle and proximal right tibia.

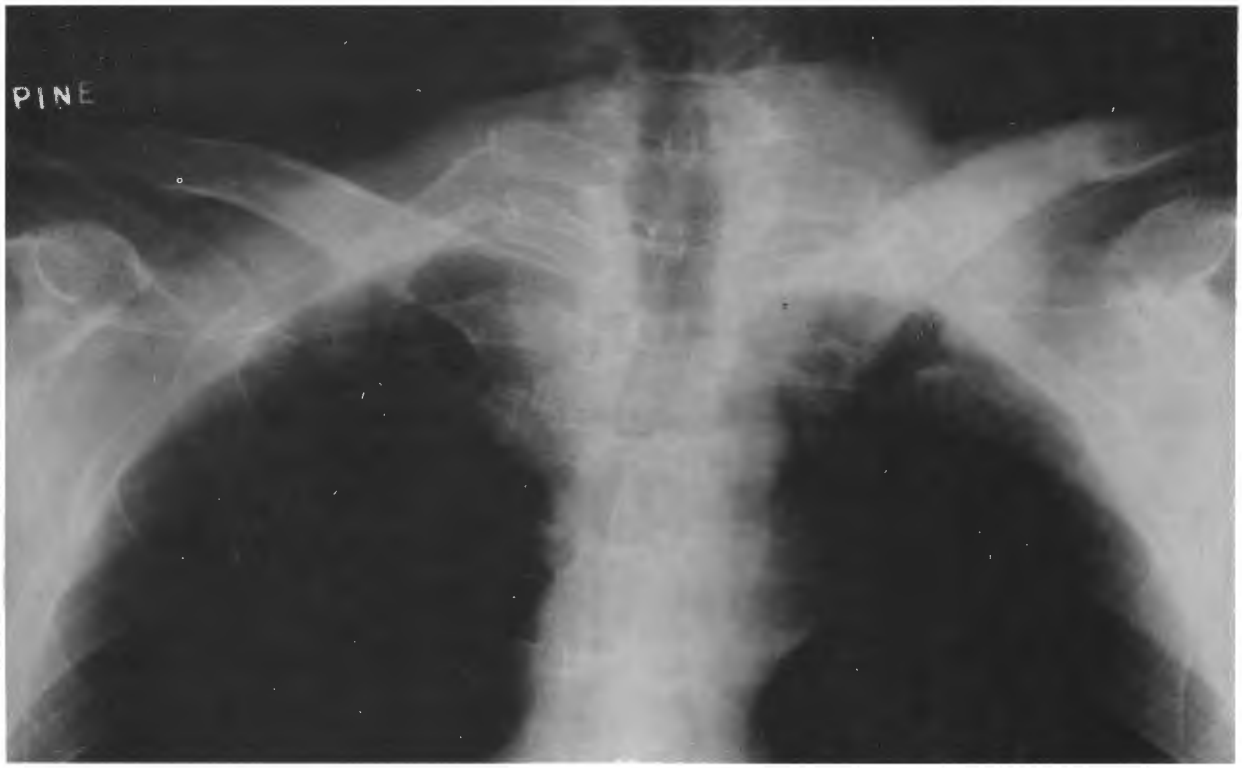

Fig 3*B*—Radiograph of clavicle reveals coarsened trabecular pattern and sclerosis typical of Paget's disease.

those clinical studies in which lesions detected by scan but not by x-ray were evaluated by follow-up x-rays, biopsy, or autopsy, no actual false-positives have occurred (20,24,39,49).

TABLE 3
Non-Neoplastic Causes of *Positive* Bone Scan

Traumatic
Fracture
Slipped epiphysis
Metabolic
Paget's
Renal osteodystrophy
Hypertrophic pulmonary osteoarthropathy
Gout
Rickets
Inflammatory
Arthritis (any type)
Osteomyelitis
Tendinitis
Miscellaneous
Aseptic necrosis
Osteitis pubis
Hyperostosis frontalis interna
Post-thoracotomy

The Unified Radiologic Approach. Because of the already high and ever increasing cost of medical care, we need to reassess the manner in which bone scans and radiographs are utilized so that the patient may benefit from minimum waste and duplication of effort. To this end, we have developed a unified radiologic approach to the detection of skeletal metastases (51). An appropriate examination is "tailored" individually for each patient according to the scheme outlined in Figure 4 which is based on an extensive review of the literature as noted above.

Because of the extensive experience in patients with primary neoplasms of breast, lung, and prostate, and also lymphoma, it is reasonable to perform the bone scan as the primary study in these patients. It has even been suggested that the bone scan completely replace the skeletal survey in the evaluation of all patients for skeletal metastases (52). This may shortly come to pass; however, reported experience with primary neoplasms other than those mentioned is not yet great enough. Therefore, we believe that in those patients it is still necessary to perform both complete examinations. It is much more efficient, nevertheless, to perform the scan as the initial study,

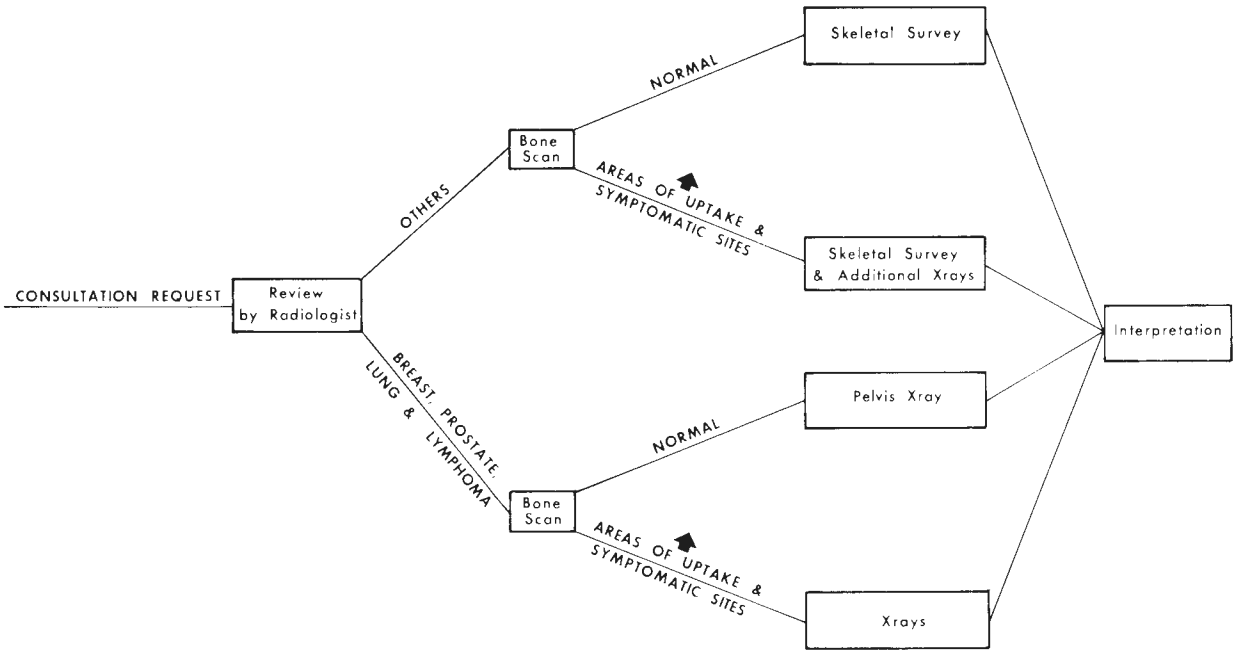

Fig 4—Scheme for radiologic examination of patients with suspected bone metastasis.

even in the latter group. This is because the radionuclide bone scan, as generally performed, is an evaluation of the entire skeleton whereas the radiographic skeletal survey, as generally performed, covers only the axial skeleton. Thus, any sites outside the axial skeleton which may be positive on the scan, can be radiographed at the time the skeletal survey is obtained, thereby eliminating wasted time and effort. This approach is feasible only if false-negative, and to a lesser extent, false-positive bone scans occur infrequently. False-negative scans occur infrequently and usually in specific circumstances as described above. To further minimize this possibility, however, we have incorporated into our approach a radiograph of the pelvis even if the scan is normal. As explained above, false-positive bone scans are, for practical purposes, almost nonexistent.

The efficacy and practicability of the unified approach was determined in a trial period during which it was applied to all patients referred to the radiology department for either radionuclide bone scan or radiographic skeletal survey for the detection of skeletal metastases. A comparison of the individually "tailored" examination actually performed with the examination (or examinations) requested by the clinical service revealed malutilization of these radiologic modalities; that is, superfluous, inadequate or inappropriate studies were requested in almost half the patients examined (51).

Conclusions.

1. Technetium-99m-labeled phosphate compounds are currently the agents of choice for radionuclide bone scanning.

2. Metastatic involvement of bone is most frequently identified by a localized area of increased uptake. Uncommon signs of skeletal metastasis are a localized area of decreased uptake and generalized symmetrically increased uptake with reduced renal excretion.

3. Radionuclide bone scanning is much more sensitive than the radiographic skeletal survey for the detection of skeletal metastases.

4. Since the findings on the bone scan are nonspecific, all abnormal areas should be radiographed to determine the nature of the abnormality.

5. The incorporation of the radionuclide bone scan and the radiographic skeletal survey into a single unified examination for the detection of skeletal metastases, formulated and coordinated by the radiologist, is desirable, practicable, and efficacious.

Table 1 and Table 2 reprinted with permission from *Radiology*, Vol. 117, No. 1.

Figure 4 reprinted with permission of *Radiology*, Vol. 117, No. 1.

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