Establishing a Clinical Role for Bone Scans

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We are not going to be the first to this party, but we are going to be the best.
—Steve Jobs

The initial tracer used to study bone metabolism (*1*,*2*) was the artificially produced radionuclide ^{32}P. The tracer, made as described in the note below, was fed orally to rats. The tracer localized in multiple organs, with a preponderance in bone. ^{32}P is a pure β-emitter and is not suitable for imaging human subjects. Table 1 lists some of the bone scan candidates, their physical half-life, and major photons that were considered for bone scanning. Although ^{99m}Tc was considered, it was in the form of pertechnetate, which did not have significant retention in bone. It was not until 1971 that Subramanian and McAfee discovered ^{99m}Tc-polyphosphate as a technetium-labeled agent that localized in bone.

TABLE 1
Selected Bone-Seeking Radionuclides Circa Early 1960s

Nuclide	Half-life	Energy
^{140}Ba	12.8 d	0.306- and 0.540-MeV γ and 0.48-MeV β
^{47}Ca	4.7 d	1.31-MeV γ and multiple β
^{68}Ga	1.13 h	0.511-MeV annihilation radiation
^{85}Sr	64 d	0.51-MeV γ
^{87m}Sr	2.8 h	0.388-MeV γ

A major rationale for pursuing a tracer technique to image bone metabolism was to improve the sensitivity for detecting osseous metastases in patients with a diagnosis of cancer. Plain radiographs are relatively insensitive, requiring a lesion at least 1 cm in diameter

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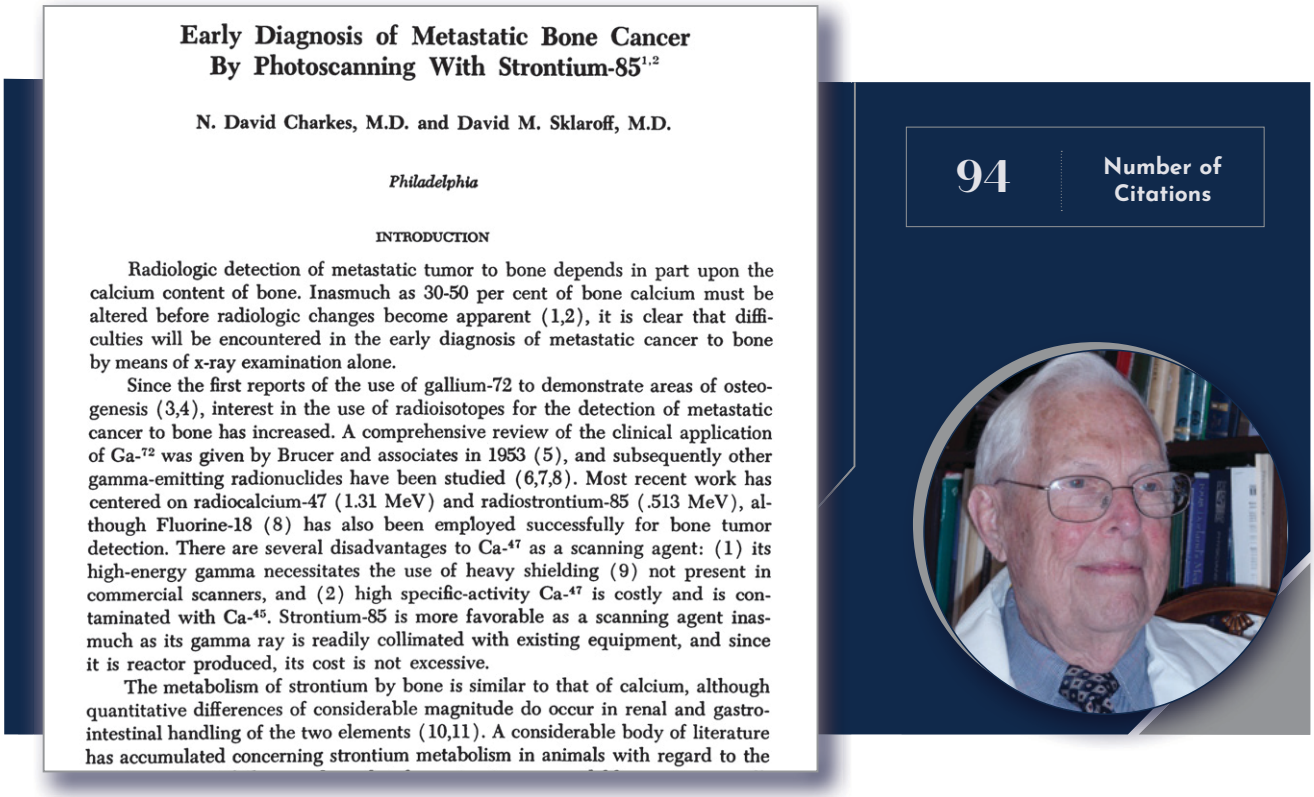

Early Diagnosis of Metastatic Bone Cancer By Photoscanning With Strontium-85[1,2]

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INTRODUCTION

Radiologic detection of metastatic tumor to bone depends in part upon the calcium content of bone. Inasmuch as 30-50 per cent of bone calcium must be altered before radiologic changes become apparent (1,2), it is clear that difficulties will be encountered in the early diagnosis of metastatic cancer to bone by means of x-ray examination alone.

Since the first reports of the use of gallium-72 to demonstrate areas of osteogenesis (3,4), interest in the use of radioisotopes for the detection of metastatic cancer to bone has increased. A comprehensive review of the clinical application of Ga-72 was given by Brucer and associates in 1953 (5), and subsequently other gamma-emitting radionuclides have been studied (6,7,8). Most recent work has centered on radiocalcium-47 (1.31 MeV) and radiostrontium-85 (.513 MeV), although Fluorine-18 (8) has also been employed successfully for bone tumor detection. There are several disadvantages to Ca-47 as a scanning agent: (1) its high-energy gamma necessitates the use of heavy shielding (9) not present in commercial scanners, and (2) high specific-activity Ca-47 is costly and is contaminated with Ca-45. Strontium-85 is more favorable as a scanning agent inasmuch as its gamma ray is readily collimated with existing equipment, and since it is reactor produced, its cost is not excessive.

The metabolism of strontium by bone is similar to that of calcium, although quantitative differences of considerable magnitude do occur in renal and gastrointestinal handling of the two elements (10,11). A considerable body of literature has accumulated concerning strontium metabolism in animals with regard to the

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and loss of at least 50% of bone mineral mass for lesion detection. Up to 40% of lesions are not identified on plain films (*3*). In these early days of nuclear medicine, several factors came together to permit the development of a high-sensitivity technique to detect osseous metastases. Benedict Cassen had developed an imaging device, the rectilinear scanner, in 1950. By 1965, several commercial vendors were selling improved versions of this instrument, including the Picker Corp. and Ohio Nuclear. A major improvement was the enhanced image quality of the photoscanner, as described by Kuhl et al. (*4*). The photoscanner provided an image on x-ray film that corresponded to the anatomic location of the tracer in the patient. The radionuclide scan could be directly correlated with radiographs.

Charkes and Sklaroff (*5*) built on the studies of Dow and Stanbury (*6*), which confirmed that "^{85}Sr qualitatively parallels ^{45}Ca as an index of skeletal function in metabolic bone diseases." The 64-d half-life of ^{85}Sr limits the intravenously administered dose to approximately 1,850 kBq (50 μCi). This low dose delivers a radiation burden of about 2.28 rad to bone. Because the photon flux from this dose is low, the area scanned was typically limited to the pelvis or spine. Even then, a scan would require about 30–45 min to record a single view. ^{85}Sr is produced in a reactor, making it available at modest cost. ^{87m}Sr, on the other hand, was expensive and had to be prepared by milking the ^{87}Y generator, and the user had to sterilize the eluate.

In the landmark report comparing ^{85}Sr radionuclide bone scans to radiographs, Charkes and Sklaroff described the results of ^{85}Sr bone scans in 90 patients with proven cancer and known or suspected bone metastases. The results of the bone scans were compared with orthoradiograms recorded at a 1.8-m (6-ft) distance. In 35 patients, both radiographs and bone scans were positive for tumor. In some patients, the scans demonstrated more extensive disease. Bone biopsies in 12 of these patients revealed tumor in the areas found to be positive on the scans. In 11 patients, the scan was positive and the radiograph negative. In 6 patients, the scan failed to detect a lesion seen on the radiograph. The scan for one patient was false-positive because the suspected lesion was due to tracer in the cecum, which overlaid the pelvis. Repeated scanning after bowel cleansing revealed that the lesion disappeared.

The authors observed positive scans in patients with both osteolytic and osteoblastic metastases. However, several patients with reticulum cell sarcoma metastatic to bone had negative scans. These pioneering investigators could not have imagined the pivotal role they played establishing the clinical value of radionuclide bone scans. The ultimate development of tracers with a shorter half-life and better imaging characteristics, as well as the development of imaging devices that sample the whole body in a single procedure, continue to make the bone scan a valuable procedure for clinical care.

On a personal note, when I started my medical internship I was searching for a specialty. I visited Larry Silver, head of nuclear medicine at Queens General Hospital. Dr. Silver had an intensely positive ^{85}Sr bone scan on a view box, next to the normal plain film of a patient with lung cancer. That scan showed me the power of nuclear medicine and the tracer technique. I was hooked.

NOTE

Georg Hevesy described how ^{32}P was produced for the rat experiment (*2*). α-particles emitted from ^{222}Rn, which was produced by the decay of ^{226}Ra, produced a large number of neutrons. The neutrons irradiated a solution of carbon disulfide. The ^{32}S in the carbon disulfide solution transmuted to ^{32}P by the (n,p) reaction. After evaporation of remaining carbon disulfide, the ^{32}P was concentrated and fed to the rats.

DISCLOSURE

No potential conflict of interest relevant to this article was reported.

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Negative scans have been obtained in four patients with positive x-rays and in two additional patients with other scan-positive areas. It is of interest that all three of our patients with reticulum cell sarcoma fell into this categoiy. In one other patient, a small, osteolytic rib metastasis was missed, but we have not to date found a negative scan in any area of pathologic fracture with callus formation, whether in a rib or elsewhere. With the dose employed (50 μc) and the line spacing which we routinely use (0.4 cm) it is possible to miss certain small areas such as osteolytic rib metastases unless fracture with callus formation has occurred. Osteoblastic reaction has been noted in wide variety of metastatic tumors and in primary bone tumors as well. Two patients with metastatic thyroid carcinoma to bone had very little osteogenic reaction.

It is of interest that both osteolytic and osteoblastic metastases may give positive scans, although all of our negative scans were obtained in patients with osteolytic lesions. It is apparent that the roentgenogram, which depicts the net local calcium balance, may not reflect increased accretion and resorption when they occur simultaneously. The scan therefore supplements the roentgenogram by depicting areas of augmented osteogenesis, and the combination of the two techniques affords maximum knowledge of local bone metabolism.

The bone dose from 50 μc of Sr-^{85} has been calculated by Fleming and associates as approximately 2.3 rads. Inasmuch as the bone dose (and the body dose as well) is primarily from the gamma photons (a 13 kev x-ray is also emitted in Sr-^{85} decay), it is apparent that estimation of the geometry factor *g* will play an important role in calculation of the radiation dose. Fleming *et al* have apparently used a whole-body *g* of approximately 125. Calculation of the bone dose with estimated values for bone composition given by the International Commission on Radiological Protection (22) gives a radiation dose of 0.80 rads per 50 μc. It is apparent, therefore, that the calculation of Fleming *et al.* represents a maximum dose, whereas ours is a minimum dose.

SUMMARY

Photoscans of bone utlizing 50 μc of strontium-85 have been made in 90 patients with cancer, with proven or suspected metastases to bone. In 11 patients the scan was positive and the x-ray negative, and in 75 other patients there was good agreement between the scan and the roentgenogram. The scan, however, frequently showed greater involvement than was apparent on x-ray. These results were confirmed by bone biopsy in 14 patients. Phantom studies were carried out which indicated that there is good correlation between the scan and known isotopic volumes within bone. Bone tissue counts of radiostrontium content were also correlated with biopsy findings and lend further support to the validity of the method.

It is therefore clear that the Sr-^{85} photoscan can detect early metastatic cancer to bone prior to observable roentgenographic changes. Not only have these scans been of value in diagnosis, but they have allowed the radiation therapist to plan treatment portals more effectively.

ADDENDUM

Since this paper was submitted for publication, a negative Sr-85 scan was obtained in a patient with widespread osteoblastic metastases from breast carcinoma on roentgenogram. The disease was stationary 7 years post-operatively and the patient asymptomatic. No systemic therapy had been administered. Similar findings have been previously reported with calcium-47 (Greenberg, E., in discussion of "Sr-85 and Ca-47 in the Study of Bone" by G.C.H. Bauer, in Radioisotopes and Bone, F. C. McLean, P. Lacroix, and A. M. Budy, eds. Philadelphia, 1962, F. A. Davis, p. 102).

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