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Radionuclide evaluation of skeletal metastases: Practical considerations*

Richard H. Gold, M.D., and Lawrence W. Bassett, M.D.
Department of Radiological Sciences, UCLA School of Medicine, Los Angeles, California, USA

Abstract. The indications for radionuclide bone scanning to evaluate possible metastatic disease are reviewed. The causes of false-positive and false-negative interpretations are discussed and illustrated. Since breast cancer leads all malignant tumors in incidence of skeletal metastases found at autopsy, the efficacy of preoperative bone scans in patients with breast cancer is analyzed in detail. A routine preoperative bone scan for patients with Stage I breast cancer produces negligible immediate benefits, but may serve a useful purpose as a baseline to enhance the detection of subtle changes that could represent metastases in a subsequent scan. However, the clinical usefulness of this screening procedure for Stage I disease must be balanced with its cost. Clinical Stage II is a grey area and may include patients with large primary tumors and axillary nodal involvement, implying a greater chance for the occurrence of skeletal metastases and hence a significant yield in bone scans. Patients with clinical Stages III or IV disease have the greatest chance of harboring metastases and should have an extensive diagnostic evaluation including bone scans prior to definitive treatment. Selected radiographs of sites of abnormally increased radionuclide activity and an anteroposterior radiograph of the pelvis should be correlated with the scan to permit a single comprehensive diagnostic impression.

Key words: Radionuclide bone scan – Radioisotope bone scan – Scintigraphy of skeletal system – Skeletal metastases – Bone metastases – Breast cancer – Metastatic breast cancer

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Address reprint requests to: Richard H. Gold, M.D., Department of Radiological Sciences, UCLA Medical Center, Los Angeles, CA 90024, USA

No technique in general use today is more sensitive than the radionuclide bone scan in imaging the earliest skeletal metastases of most primary tumors [14]. A breakthrough in radionuclide bone scanning occurred in the early 1970s with the introduction of ^{99m}Tc agents. Since ^{99m}Tc does not emit beta rays and has a half-life of only six hours, it yields a low radiation dose. Among the various compounds that have been labeled with ^{99m}technetium, the diphosphonates are the ones most readily cleared from the blood pool. This results in low activity in the blood and extraskeletal tissues, leading to an improved image and hence greater diagnostic accuracy. Technetium-labeled disphosphonate is taken up by chemisorption onto the phosphorus groups of calcium hydroxyapatite, the basic crystal of bone. Although the exact mechanism by which such isotopes are deposited remains unknown, increased blood flow to bone and to areas of abnormal bone turnover are known to accelerate their accumulation. To increase the effectiveness of radionuclide bone scanning it is appropriate to consider some practical aspects related to its use.

Indications

Indications for bone scanning of the patient with cancer include: staging of disease in the asymptomatic patient; evaluation of persistent pain that is thought to be skeletal in origin despite equivocal or negative radiographs; determination of the extent of skeletal metastases when radiographs are abnormal; investigation of areas that are difficult to evaluate by conventional radiographic techniques, such as the sternum and scapula; differentiation of pathologic from traumatic fracture by disclosing additional sites of involvement not detected in radiographs; planning of radiation portals; determination of response to hormonal,

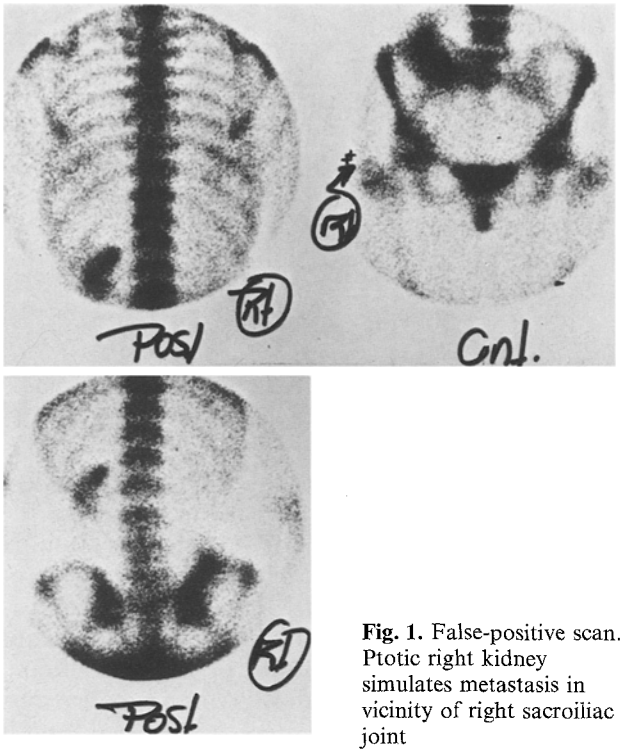

Fig. 1. False-positive scan. Ptotic right kidney simulates metastasis in vicinity of right sacroiliac joint

chemical, or radiotherapy; and periodic evaluation of the asymptomatic patient who is clinically free of disease.

False-positive scans

Bone scans, while highly sensitive to localized skeletal abnormalities, are nonspecific as to the cause of the increased radionuclide uptake. At least one-third of solitary abnormalities detected in the scans of patients with primary malignant disease result from benign processes or normal variations (Figs. 1–5) (Table 1) [6]. Recognition of the normal scan image and its variations is essential to avoid interpretive errors which may be responsible for false-positive diagnoses. Benign disorders which may result in positive scans include: benign cartilage tumors, arthridities, Paget disease, fibrous dysplasia, bone infarct, osteomyelitis, and soft-tissue inflammation. Previous surgery or fracture may be associated with an increased uptake of isotope for as long as one to three years after the incident. Bone scans performed up to several months after mastectomy may reveal increased ac-

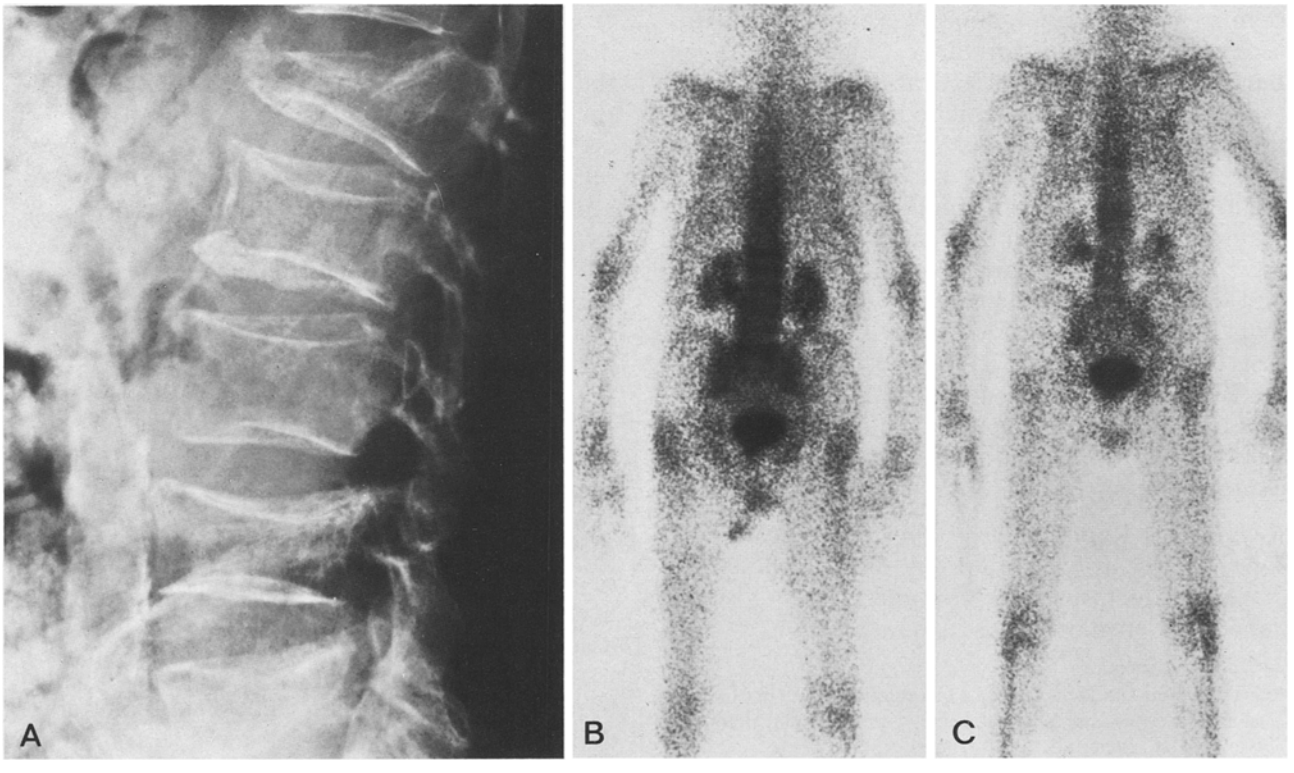

Fig. 2A–C. False-positive scan resulting from osteoporotic spine with multiple compression fractures that simulate metastases. **A** Lateral radiograph. **B** Scan shows increased activity in lumbar region. **C** Activity has returned almost to normal after healing of fractures

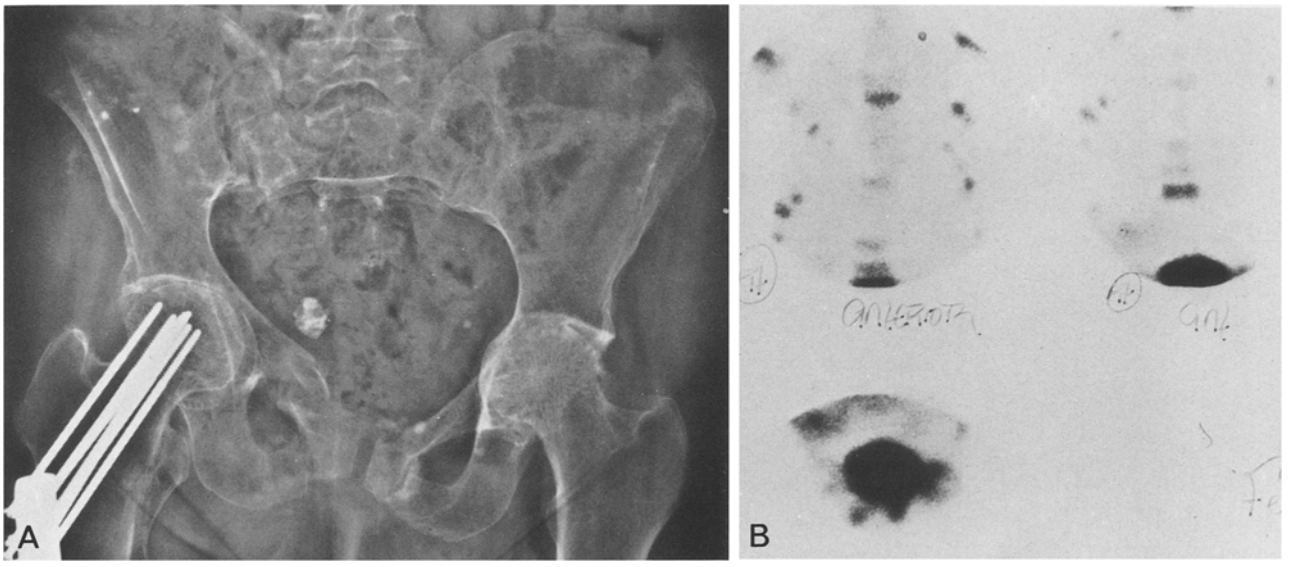

Fig. 3A, B. False-positive scan caused by multiple insufficiency fractures in woman with rheumatoid arthritis. **A** Radiograph reveals fractures of both pubic bones and right femoral neck, and uniform narrowing of hip joints and protrusio acetabuli secondary to rheumatoid arthritis. **B** Scan reveals increased activity at sites of numerous fractures in spine, ribs, and pelvis. Fractures of pubic bones are partially obscured by radioisotope-filled urinary bladder

cumulation in the region of the ipsilateral shoulder and upper chest.

Breast cancer leads all malignant tumors in incidence of skeletal metastases found at autopsy [1]. Fifty percent of patients with breast cancer have their first recurrence in bone. Moreover, bone metastases tend to occur rapidly; 50% develop by 12 months and 74% within 18 months of diagnosis of the primary tumor [13]. Since so many radionuclide bone scans specifically directed toward the detection of metastatic disease are performed on patients with breast cancer, it is pertinent to discuss the value of the scans for these patients.

Many published reports on the efficacy of bone scans in patients with breast cancer are difficult to evaluate because some of the scans have been classified not as positive or negative, but rather as suspicious. The rate of such suspicious findings has varied from 1% [12] to 14% [10]. In some series suspicious findings were considered as negative [4, 7] while in others they were considered as positive [10] and in all likelihood included some false-positive interpretations. Some and perhaps most false-positive scans may have resulted from review of the scan independent of the review of corresponding radiographs. It is likely that were the scan and radiographs concomitantly reviewed and correlated, the problem of false-positives could have have been largely resolved.

To improve specificity we have found it useful to correlate the foci of increased radionuclide uptake with selected radiographs of the same sites. The scan is immediately reviewed, and if there are no recent radiographs of any abnormal foci of increased activity these are promptly acquired. An anteroposterior radiograph of the pelvis is obtained for every patient in order to decrease instances of a false-negative scan occurring because pelvic lesions have been obscured by the radionuclide activity in the superimposed urinary bladder (Figs. 6 and 7).

The scan and radiographs are subsequently analyzed at a daily correlative conference attended by experts in nuclear medicine and skeletal radiology, and a single comprehensive diagnostic impression is recorded. There are several advantages to this combined review: it eliminates excessive, inappropriate, and inadequate radiographic examinations, thereby reducing both radiation and financial burdens; the referring clinician receives a single definitive opinion rather than two sometimes vague reports which may be at odds with one another; and by performing the two examinations concurrently, the need for a return visit to obtain corroborative radiographs is avoided.

When a patient with cancer manifests an abnormal focus of increased radionuclide activity that cannot be explained by a radiographically evident benign abnormality, it must be assumed to be a metastasis until proved otherwise. Three alternatives are available to determine the origin of the scan abnormality: Repeat the scan in four to six weeks and if it is still abnormal repeat the radiographs; minor trauma may result in a "hot

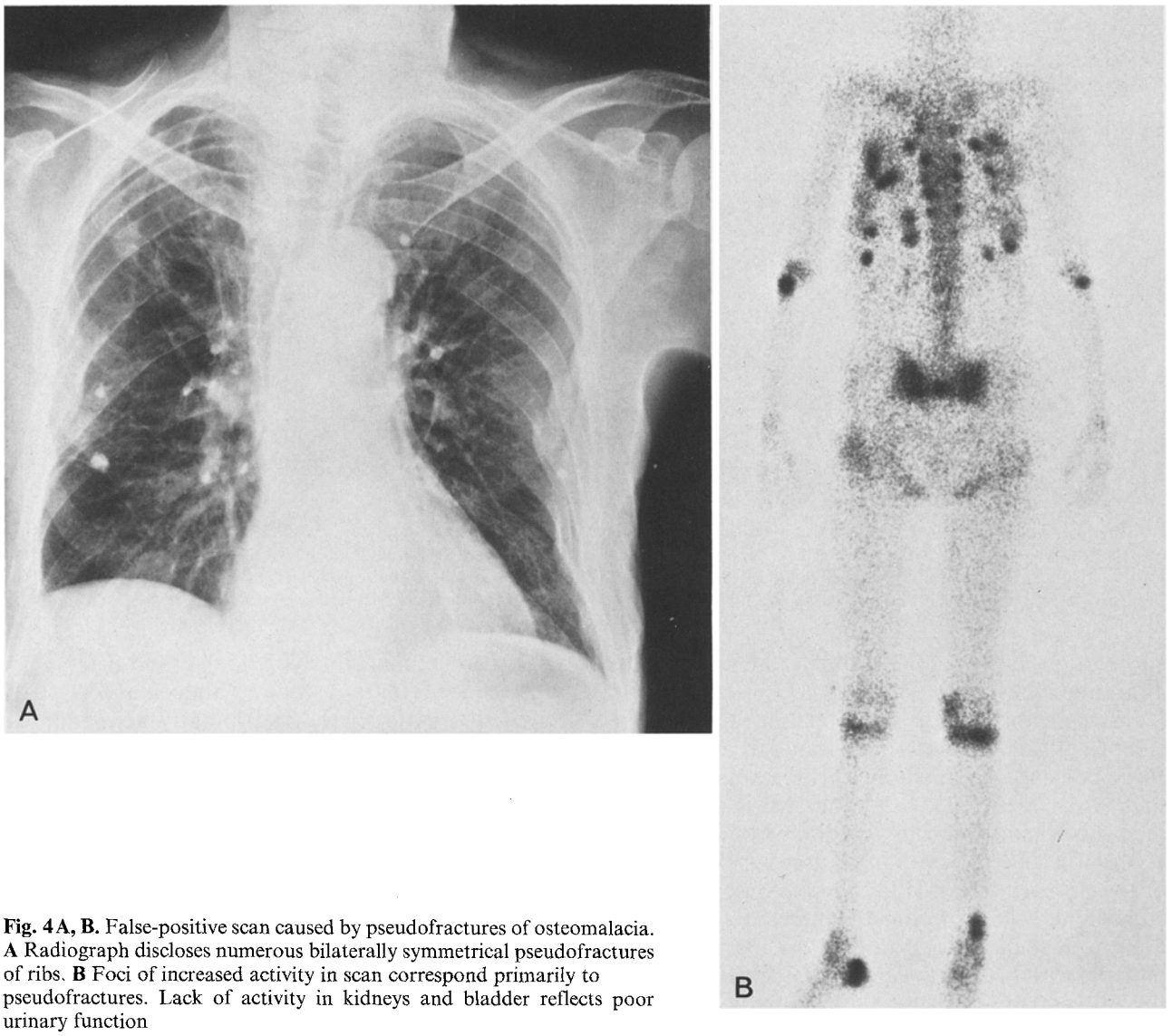

Fig. 4A, B. False-positive scan caused by pseudofractures of osteomalacia. **A** Radiograph discloses numerous bilaterally symmetrical pseudofractures of ribs. **B** Foci of increased activity in scan correspond primarily to pseudofractures. Lack of activity in kidneys and bladder reflects poor urinary function

spot" and the radiographic changes may not be evident for weeks (for example, as with a stress fracture), or the scan abnormality may resolve without the appearance of any radiographic change. Another alternative is to follow the abnormal scan site with radiographs alone; radiographic changes of metastasis may be delayed for as long as 18 months from the time of the earliest scan abnormality [8]. The last means to determine the origin of the scan abnormality is to perform a percutaneous needle biopsy, a relatively innocuous and productive procedure, especially useful when an immediate therapeutic decision must be made.

False-negative scans

Accumulation of isotope in the urinary bladder may obscure abnormal isotope activity in portions of the ischia, pubic bones, and sacrum (Figs. 6 and 7). Rarely, at sites of extremely aggressive metastases the scan, instead of manifesting increased activity, shows normal, or even diminished isotope accumulation (Figs. 8 and 9). "Cold" or photopenic metastases are found most often in association with lung or breast carcinoma or soft-tissue sarcoma. Multiple myeloma is notorious for its association with negative and sometimes photopenic bone scans. Barium in the gut may absorb gamma rays emanating from the underlying spine to such an extent on an anteroposterior view as to simulate an aggressive cold metastasis (Fig. 10).

In diffuse metastatic disease the isotope accumulation occasionally may be so uniform as to give a false-negative impression (Fig. 11). One clue to the true state of affairs is the presence of a greater than normal intensity of isotope uptake in

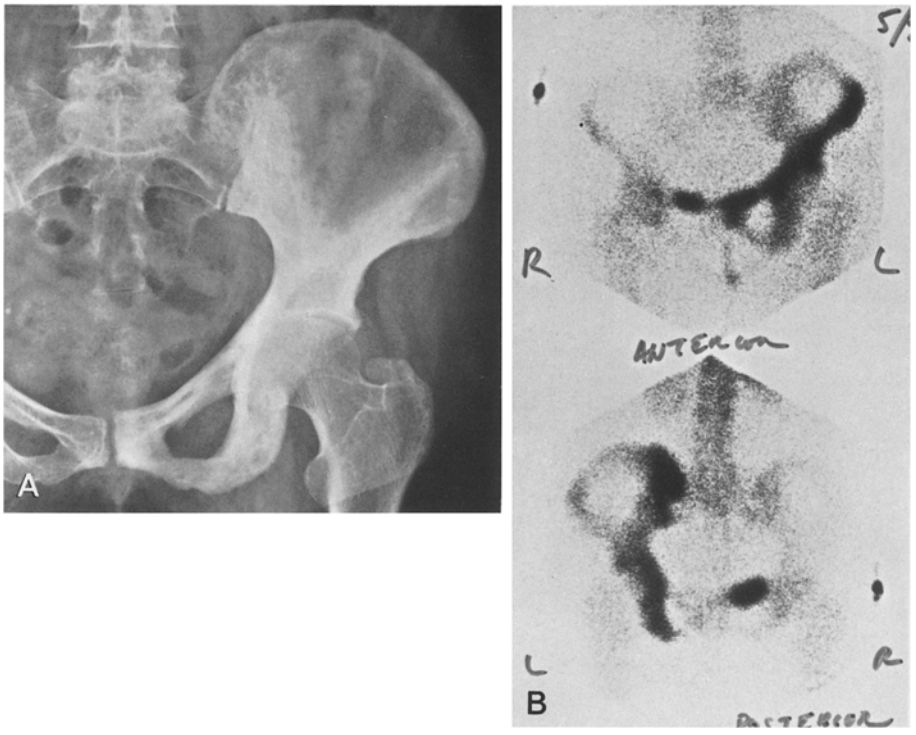

Fig. 5A, B. False-positive scan resulting from Paget disease involving left hemipelvis. **A** Radiograph reveals cortical thickening and increased breadth of entire left hemipelvis. **B** Scan discloses corresponding characteristically intense and extensive radionuclide activity

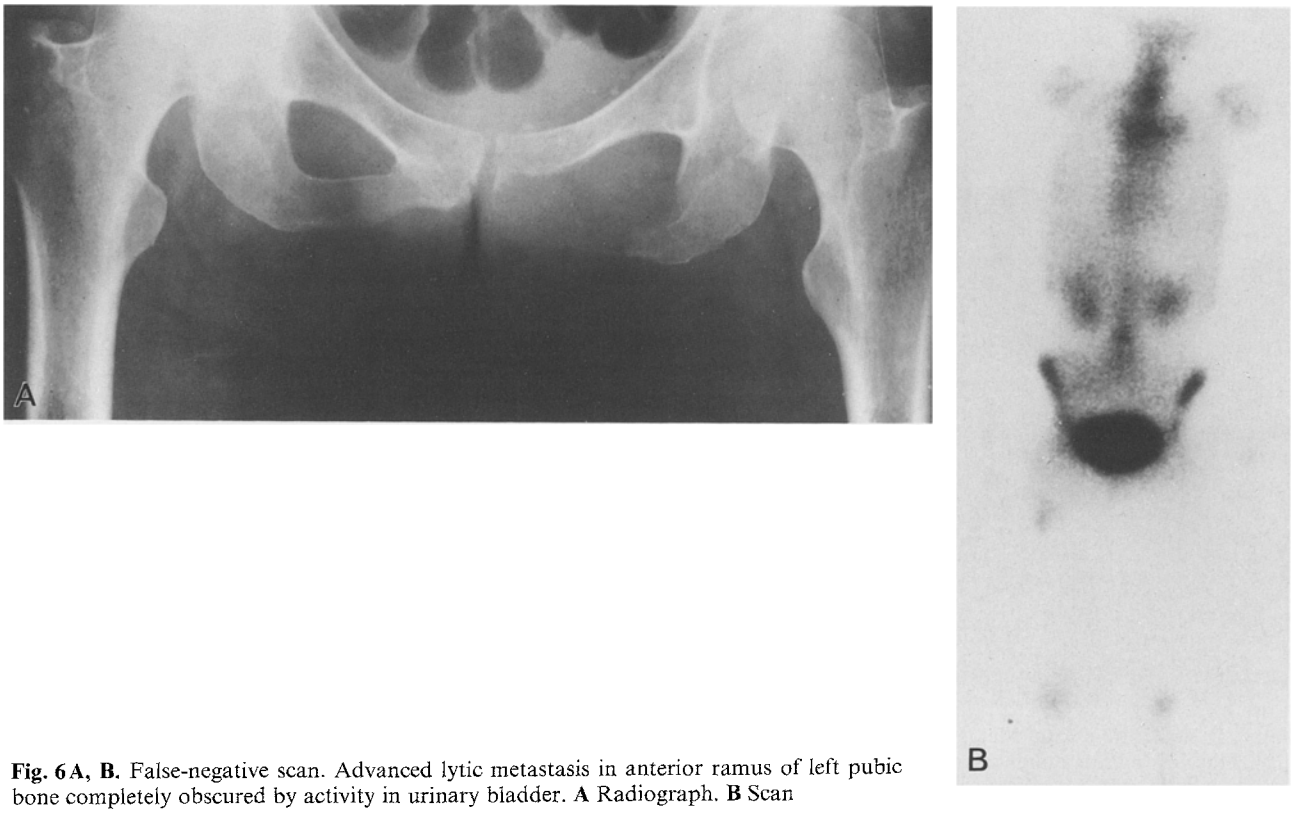

Fig. 6A, B. False-negative scan. Advanced lytic metastasis in anterior ramus of left pubic bone completely obscured by activity in urinary bladder. **A** Radiograph. **B** Scan

Table 1. Nonmalignant causes of increased activity in radionuclide bone scans

Normal structures
Base of skull
Calcified thyroid cartilage
Costochondral junctions
External occipital protuberance
Paranasal sinuses
Inferior tip of scapulae
Spinous processes of vertebrae
Sternum
Stenoclavicular joints
Sternomanubrial joint
Thyroid
Sacroiliac joints
Unfused epiphyses
Benign soft tissue abnormalities
Calcific tendinitis
Cellulitis
Injection site of scan agent
Myositis ossificans
Operative site
Benign osseous abnormalities
Benign cartilage tumors
Bone infarct
Fibrous dysplasia
Healing fractures
Hyperostosis frontalis interna
Hypertrophic pulmonary osteoarthropathy
Inflammatory arthritis
Metabolic bone disease
Osteoarthritis
Osteoid osteoma
Osteomyelitis
Paget disease
Spondylosis and degenerative disease
Surgical or biopsy site

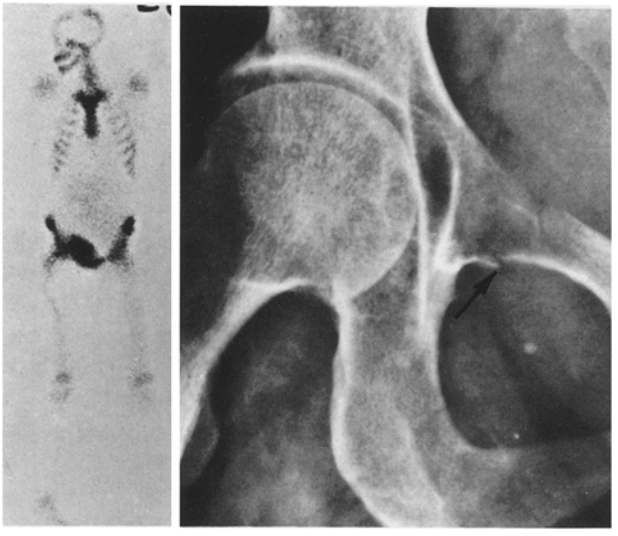

Fig. 7. False-negative scan. Metastasis and pathologic fracture at junction of inferior ramus of right pubic bone and ischium is obscured in scan by activity in urinary bladder displaced to right by pelvic mass

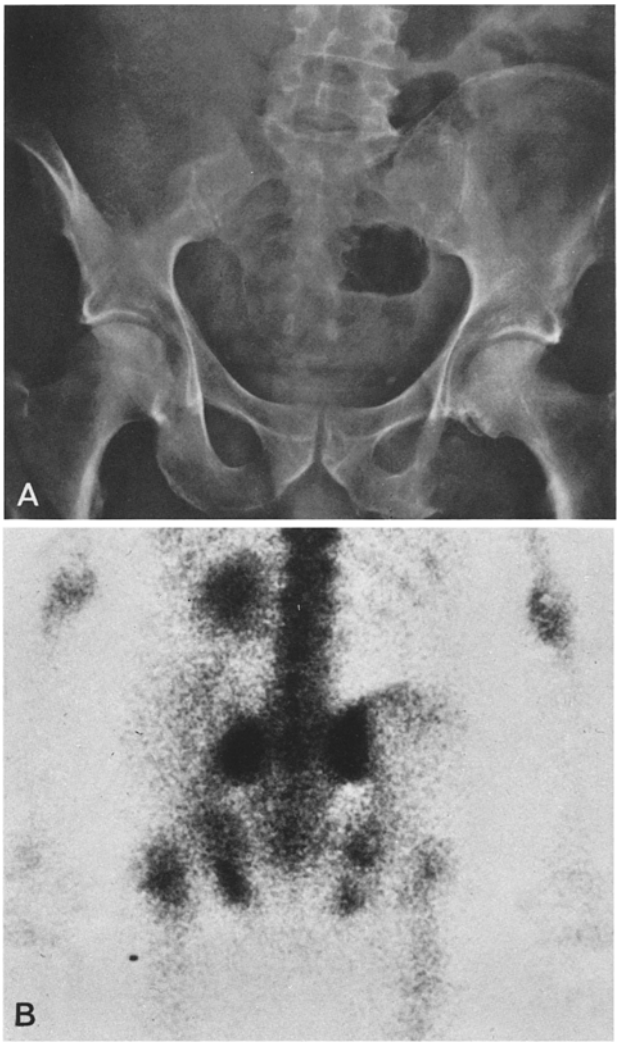

Fig. 8A, B. Negative scan associated with superaggressive metastases of renal cell carcinoma. **A** Radiograph reveals extensive lytic "blown out" metastases in right ilium and left ischium. **B** Scan reveals that huge right ilial metastasis has relatively low level of radionuclide activity while left ischial metastasis is less active than normal right ischium. Metastatic lesion in the right proximal femur with moderate activity is depicted on scan but not in radiograph

the skeleton, producing a so-called "superscan". Another clue is the scant or absent radionuclide activity in the kidneys, bladder, and soft-tissue. In infants and children, the normal increase in activity in unfused epiphyses may mask adjacent metastases such as those of neuroblastoma (Fig. 12).

Preoperative bone scans

What is the value of routine preoperative bone scanning in asymptomatic patients with known primary malignant disease? It might be argued that

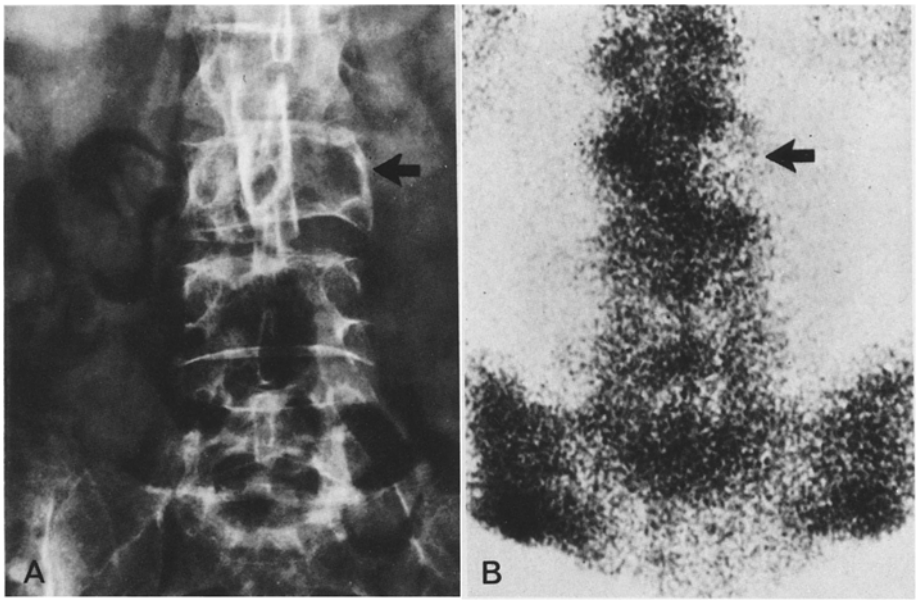

Fig. 9A, B. False-negative scan in woman with breast carcinoma. **A** Radiograph reveals lytic metastatic lesion of body and left pedicle of third lumbar vertebra (*arrow*). **B** Scan discloses corresponding deficit in isotope activity (*arrow*)

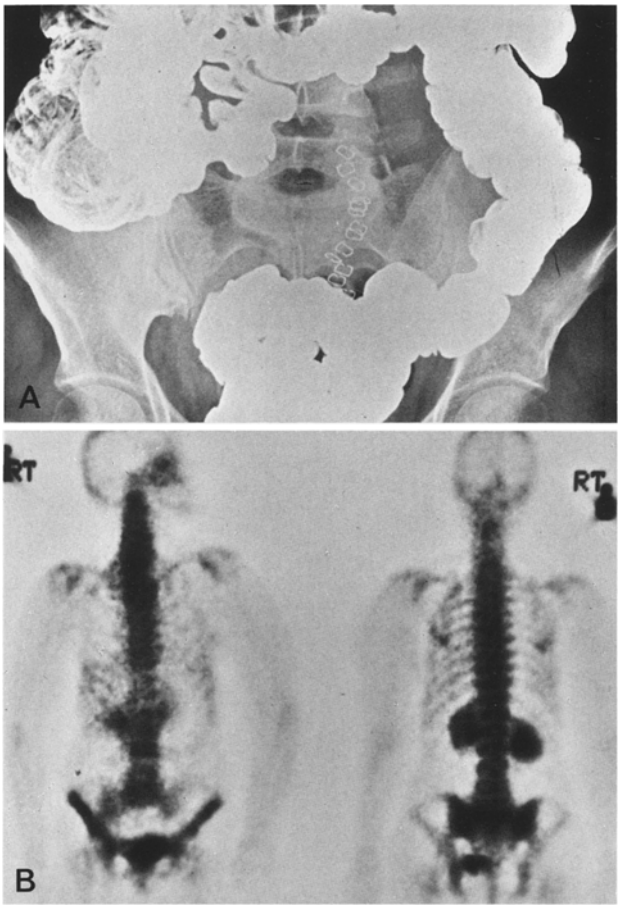

Fig. 10A, B. Deficiency in isotope activity on anteroposterior scan resulting from overlying barium-filled colon. **A** Radiograph shows residual barium from gastrointestinal tract examination on previous day. **B** Anterior view shows photopenic foci in lumbar spine, but posterior view, with barium-filled colon no longer interposed between spine and detector, reveals normal activity

the use of bone scans as a screening procedure for metastasis must be guided by the same principle that applies for any other screening procedure: there must be a reasonably high likelihood of finding a significant number of positive cases in asymptomatic patients. An effective opposing argument, however, might stress the usefulness of the scan as a baseline with which future scans could be compared in order to detect evolving metastases as near to their inception as possible. Nevertheless, the clinical usefulness of any baseline screening procedure must be balanced with its cost. Whereas the cost of a bone scan in some communities in the United States may run as high as 400 dollars, too high perhaps to justify its use as simply a baseline indicator, the cost in other communities is below 150 dollars, making it eminently cost-effective.

Breast cancer patients with Stage III disease preoperatively show a consistent and significant increased incidence of positive bone scans. In a study by McNeil et al. the yield from bone scans was 0/37 patients in Stage I, 4% in Stage II, and 16% in Stage III [13]. These results led McNeil to conclude that preoperative bone scans in patients with clinical Stage III breast cancer revealed significant numbers of unsuspected metastases, but that the value of bone scans in patients with Stages I or II disease lay primarily in providing a baseline evaluation. Baker reported 10/41 patients or 24% with Stage III disease had evidence of bone metastasis detected by preoperative bone scan, whereas only 1/64 patients with Stages I or II breast cancer had a positive scan [2]. Based on these and other investigations, the need for preoperative bone

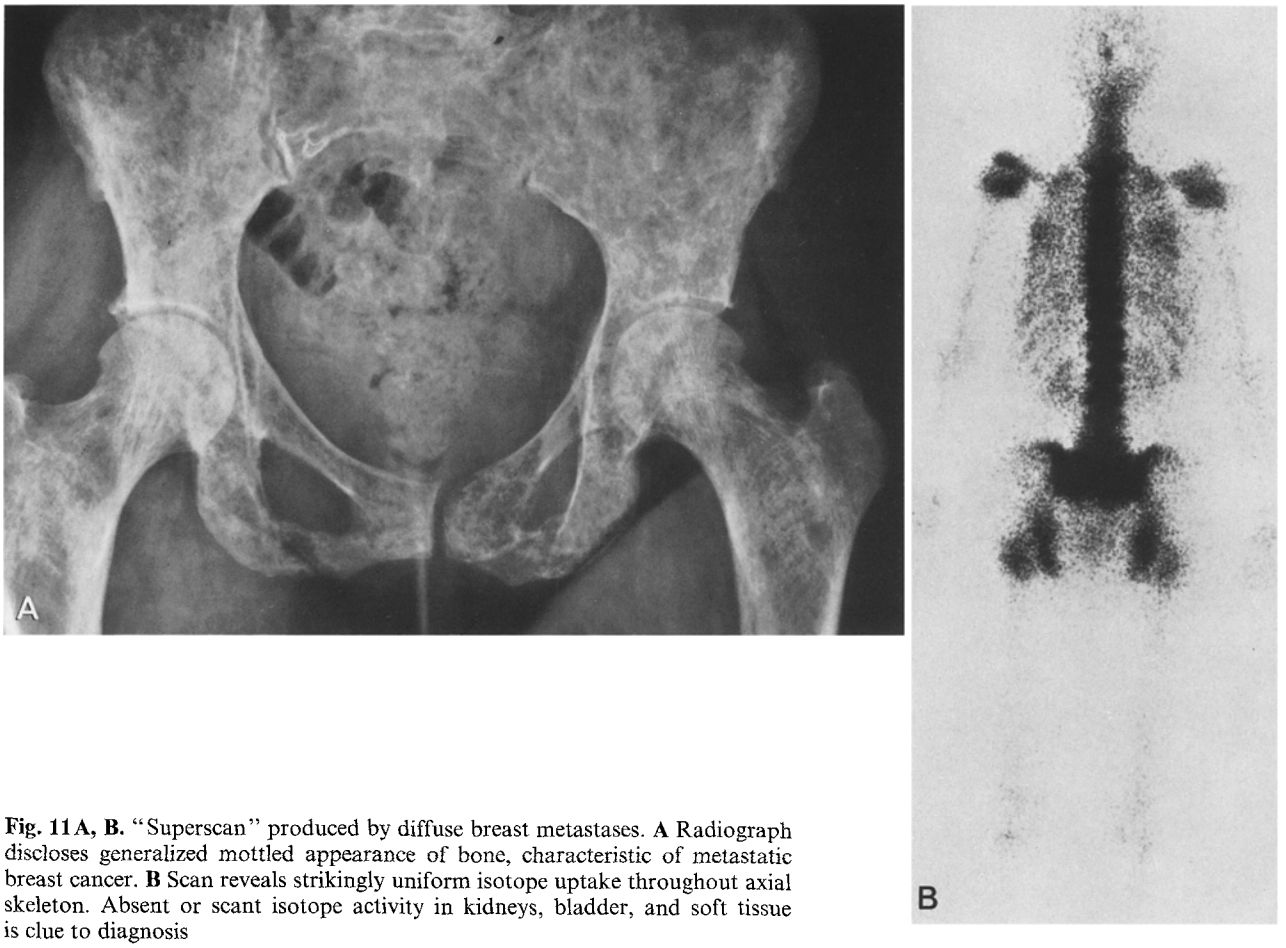

Fig. 11A, B. "Superscan" produced by diffuse breast metastases. **A** Radiograph discloses generalized mottled appearance of bone, characteristic of metastatic breast cancer. **B** Scan reveals strikingly uniform isotope uptake throughout axial skeleton. Absent or scant isotope activity in kidneys, bladder, and soft tissue is clue to diagnosis

scans in patients with clinical Stage III disease has been well established.

In women with Stages I or II breast cancer, preoperative bone scans have yielded a wide variation in results. Hoffman and Marty [11], Citrin et al. [5], and Sklaroff and Sklaroff [15] reported an incidence of positive bone scans in patients with Stages I or II breast cancer of 40%, 14%, and 14%, respectively. Conversely, Baker indicated that out of 64 patients with Stages I or II breast cancer, bone scans were positive for metastases in only one, an incidence of 1.5% [2]. Gerber et al. performed bone scans on 122 women with biopsy-proved breast carcinoma [9]. Only two of their 110 patients with Stages I or II disease had preoperative scan abnormalities interpreted as bone metastases. However, of 55 women with normal preoperative scans, 20 had changes suggestive of bone metastases on subsequent scans, most of them within two years of operation. Five of the 23 women with potential surgical cures, i.e., negative lymph nodes, had bone metastases within two years of mastectomy. These results imply that although the preoperative scans produced negligible immediate benefit, they could have served as useful baselines with which to compare a significant number of subsequent positive scans.

The diversity of opinion regarding the usefulness of bone scans in Stages I or II breast cancer may reflect variations within these stages [3]. According to the TNM classification proposed by both the American Joint Committee on Cancer and the International Union Against Cancer, patients with Stage I disease have lesions that are classified as T1, N0, M0. Patients with Stage II disease have lesions that are classified as T1, N1, M0 or T2, N1, M0. Thus, Stages I and II actually represent a diversity of tumor sizes and nodal involvement. The size of the tumors may vary from one too small to palpate and detectable only by mammography, to one as large as 5 cm. A patient with Stage II disease may even have movable homolateral axillary lymph nodes that are considered clinically to contain metastases. Consider for example a patient who is clinical Stage II with a T2 lesion 5 cm in diameter, found to manifest

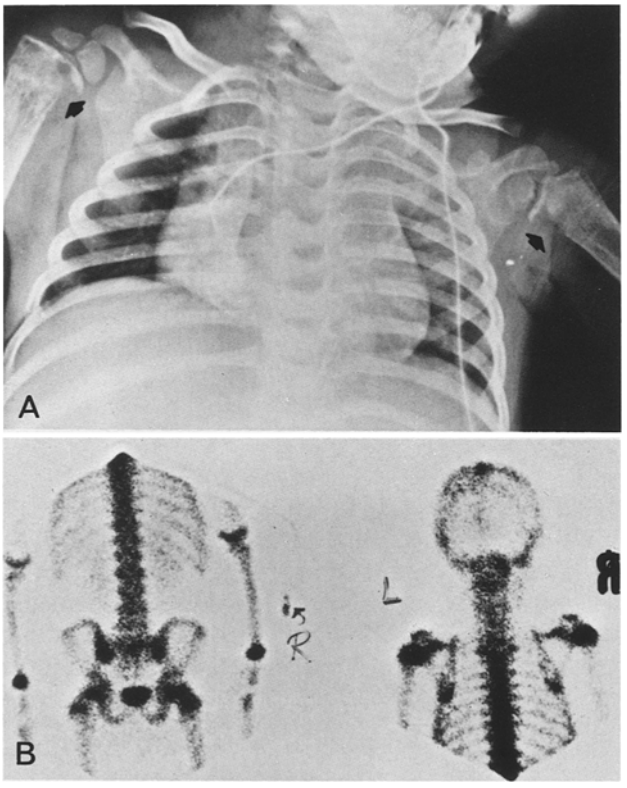

Fig. 12A, B. False-negative scan resulting from metastatic neuroblastoma. **A** Radiograph reveals bilaterally symmetrical destruction of proximal humeral metaphyses (*arrows*). **B** Resultant activity is difficult to distinguish from normal increased activity in unfused epiphyses

poorly differentiated histology, and located in the medial hemisphere of the breast. The patient also has movable, firm, enlarged homolateral axillary lymph nodes. The yield of occult metastases in a group of such patients could be considerable.

Follow-up scans

Follow-up bone scans are valuable for monitoring the progression or regression of metastatic disease. In the early stage of healing, metastatic lesions may undergo a paradoxical increase in activity, but this will eventually diminish and may even return to normal. The bone scan is particularly useful in evaluating the response of blastic metastases which on healing may become even more sclerotic in radiographs, giving a false X-ray impression of progression.

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