Title
An Integrated Approach to the Evaluation of Metastatic Bone Disease

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An Integrated Approach to the Evaluation of Metastatic Bone Disease

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The most common sources of skeletal metastasis are, in order of decreasing incidence, carcinomas of the breast, prostate, and lung.[1] Most cases of metastatic disease affect the middle-aged and the elderly. The most commonly involved bones are those rich in red marrow, and are, in decreasing order of incidence, the thoracolumbar spine and sacrum, pelvis, ribs, sternum, proximal femoral and humeral shafts, and skull.[7] We first discuss and compare the advantages and drawbacks of the various imaging modalities in the detection and evaluation of skeletal metastases, and we then present an algorithm that features a practical step-by-step approach to the workup of these metastases.

CONVENTIONAL RADIOGRAPHY OF SKELETAL METASTASES

Compared with most other imaging modalities, conventional radiography is relatively insensitive for metastatic bone disease. Although minor alterations of the compact cortical bone are easily discernible, even far-advanced destruction of the spongy, cancellous bone may go undetected when unaccompanied by reactive new bone or cortical involvement. This is especially true of the osteopenic bones of those people with the greatest frequency of metastatic disease, the elderly.[17] Moreover, because cortical bone is responsible for most of the bone density depicted in a radiograph, it easily masks underlying pathology in the cancellous bone. This lack of sensitivity is compounded by the fact that the cancellous bone in the medullary canal is usually the first site of skeletal metastasis. In contradistinction, because even small intracortical osteolytic metastases appear in high contrast to the dense compact bone that surrounds them, they are easily detected in conventional radiographs. Similarly, once a metastasis in the cancellous bone extends to the cortex, the resultant endosteal cortical scalloping is easily perceived. Thus, conventional radiographs are useful for determining integrity of cortical bone, and especially for depicting impending or early pathologic fractures. Large scalloped destructive metastatic lesions of the external cortical surface have been termed *cookie bite* metastases, and originate most often from bronchogenic carcinoma (Fig. 1).[4] Lymphatic spread of carcinoma of the uterine cervix may result in scalloped erosions of the bony pelvis and lumbar spine, especially on the left side, from invasion by nodal tumor deposits (Fig. 2).[6] A distinction must be made between the radiographic features of osteolytic metastases and those of plasma-cell myeloma. Multiple metastases usually vary in size, whereas the lesions of myeloma tend to be more uniform. Moreover, destruction of vertebral pedicles occurs more frequently with metastases.

Although conventional radiography is relatively insensitive to the presence of bone metastases, it is the best modality for characterizing them. The response of bone to the presence of metastases can be classified as osteolytic, osteosclerotic, or mixed. Metastases that usually produce an osteolytic response may arise from carcinomas of the thyroid, kidney, bladder (if the prostate gland remains uninvolved), and parts of the gastrointestinal tract, and also include metastases from Ewing sarcoma and melanoma (Fig. 3). Metastases that usually produce an osteo-
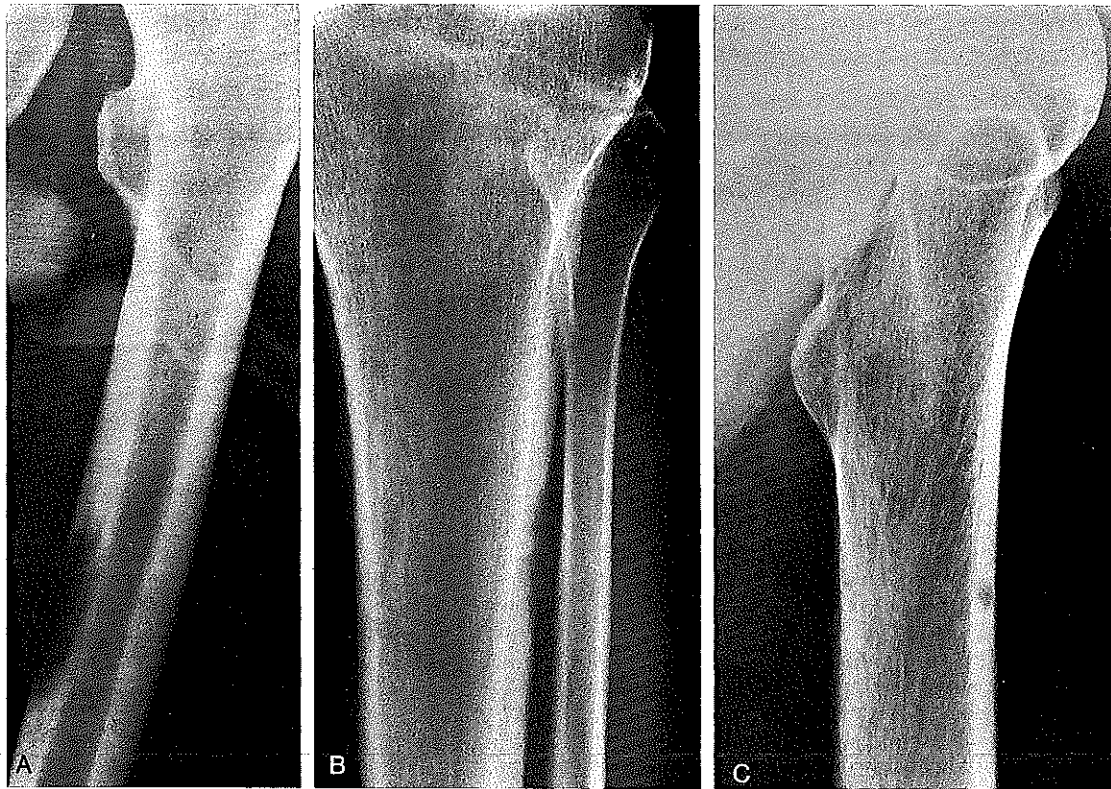
Figure 1. Intracortical metastases from bronchogenic carcinoma. *A,* "Cookie bite" sign in the femur of a 50-year-old man. *B,* Tibial lesion in a 48-year-old man. *C,* Femoral lesion in same patient as *B.*

sclerotic response arise from carcinomas of the prostate, stomach and nasopharynx, mucinous carcinoma of the colon, bladder carcinoma that involves the prostate gland, carcinoid tumor, and medulloblastoma (Fig. 4). A mixed response may be associated with metastases arising from carcinomas of the breast, lung, cervix, ovary, and testis (see Fig. 8). Osteolytic lesions that are geographic (well-circumscribed) and do not breach the cortex are usually less aggressive than those that are moth-eaten or permeative (poorly defined) with extensive cortical disruption. Collapse of an upper thoracic vertebra is more likely to be caused by metastasis than osteoporosis. Other clues to metastatic vertebral involvement include an associated soft-tissue mass and an angular or irregular deformity of the affected vertebral endplates.

Radiographic Evaluation of the Response to Therapy

Valuable information regarding the response to treatment may be obtained by correlating the radiographic changes with radionuclide imaging and clinical and biochemical data.[13, 14, 23] The initial radiographic manifestation of healing of an osteolytic metastasis is a sclerotic rim of reactive bone (Fig. 5). Progressive healing results in increased sclerosis that advances from the periphery of the lesion toward its center, eventually becoming uniform, then smaller, and finally disappearing.[23] With healing, bones that harbored metastases but were radiographically normal may show sclerotic foci at the sites of the occult lesions. On the other hand, progression of osteolytic metastases is signified by increased size of the lesions, appearance of new lesions, or both. Mixed osteolytic-osteosclerotic lesions demonstrate a successful response to therapy by gradually becoming uniformly sclerotic, whereas disease progression is reflected in increased osteolysis.[16]

The effect of treatment on purely osteosclerotic metastases may be difficult to evaluate. A decrease in size or a complete disappearance of the sclerotic metastasis signifies disease regression, whereas increasing size and progressive destruction imply progression. It is essential to use previous radiographs for comparison, so that a distinction can more easily be made between osteosclerotic metastases that are becoming progressively osteolytic, signifying disease progression, and a gradual and uniform disappearance of sclerotic metastases, signifying a favorable response to therapy.[24] Also difficult to differentiate are an increasing number of osteosclerotic foci, signifying progression, versus a sclerotic healing response of lesions that were not previously identifiable.[25] Furthermore, sclerotic metastases may remain unchanged even while undergoing remission.[25] To reiterate, these problems are more easily resolved
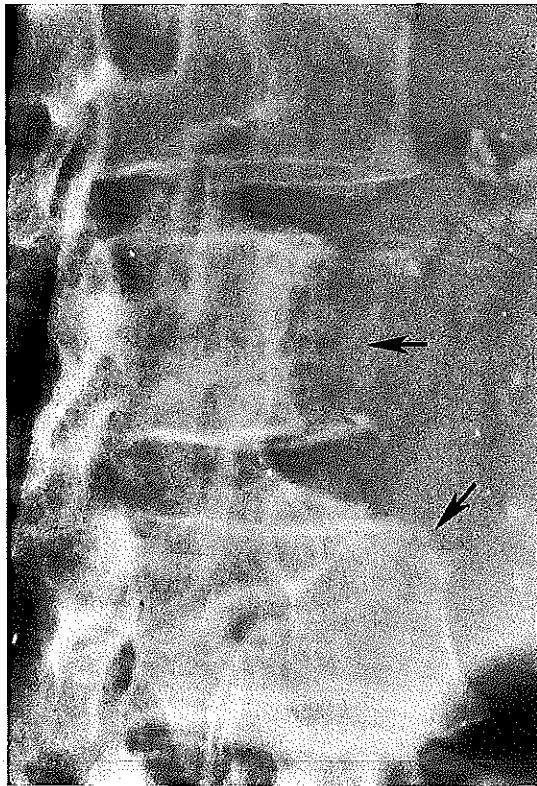
Figure 2. Oblique projection of lumbar spine showing scalloped anterolateral erosions *(arrows)* of second and third lumbar vertebrae, resulting from invasion by lymph node metastases from carcinoma of uterine cervix in a 62-year-old woman.

when the radiographic changes are correlated with radionuclide, clinical, and biochemical findings.

Radiographic Survey for Skeletal Metastases

Although its use is currently considered archaic by most authorities, the avowed purpose of the radiographic survey has been to detect the greatest number of metastases with the fewest possible radiographs. The survey emphasizes the axial skeleton, where metastases predominate. A typical survey might consist of an anteroposterior view of the pelvis; anteroposterior and lateral views of the thoracic, lumbar, and sacral spine; lateral view of the cervical spine; lateral view of the skull; anteroposterior view of the thorax for rib detail; and anteroposterior view of the femurs and humeri. Such surveys were popular in the past. Current opinion tends to question both their usefulness and cost effectiveness,[20] and most authorities now favor the radionuclide bone scan to demonstrate possible metastatic disease, with the scan then serving as a guide to ordering those radiographs that would be most appropriate for further evaluation. Although as a screening test for metastatic disease the radiographic skeletal survey has been supplanted by the radionuclide bone scan, it is still considered a necessity for evaluation of plasma-cell myeloma, the lesions of which may not be evident on radionuclide bone scans because of the lack of associated bone turnover.

RADIONUCLIDE EVALUATION OF SKELETAL METASTASES

No imaging modality is more effective in screening the whole body for skeletal metastases than the radionuclide bone scan. Among the various compounds that have been labled with technetium-99m (^{99m}Tc), the diphosphonates are the most readily cleared from the blood pool. This clearing leads to low activity in the blood and extraskeletal tissues, an improved image, and hence greater diagnostic accuracy. Technetium-labeled methylene diphosphonate (^{99m}Tc MDP) is taken up by chemisorption onto the phosphorus groups of calcium hydroxyapatite, the basic crystal of bone. Although the exact mechanism by which the isotope is deposited remains unknown, increased blood flow to abnormal bone and reactive bone turnover are known to accelerate its accumulation.

The indications for bone scanning include staging of the 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 show abnormal findings; investigation of bones that are difficult to evaluate by conventional radiography, such as the sternum and scapula; differentiation of pathologic from traumatic fractures by disclosing additional sites of involvement not detected radiographically; and determination of the response of metastases to therapy.
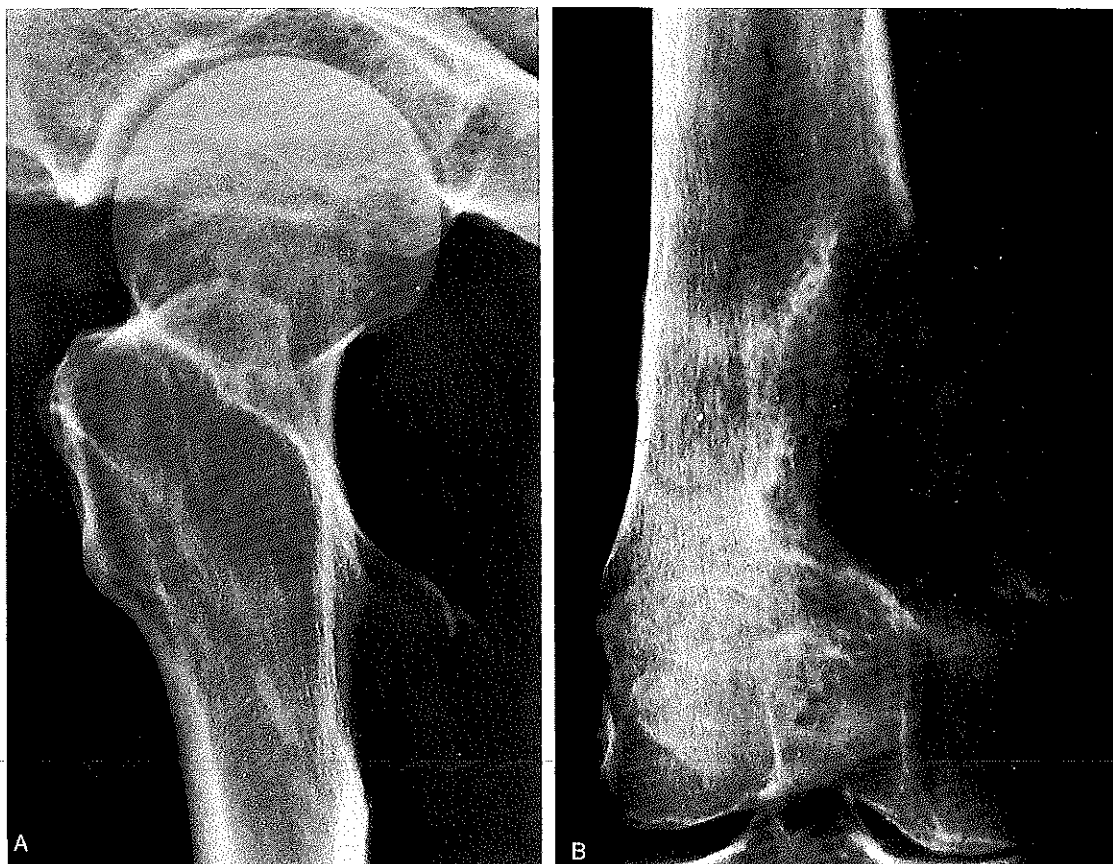
Figure 3. Osteolytic metastases. *A*, Pure osteolytic metastasis of lesser trochanter of the femur of a 50-year-old man with renal cell carcinoma. The cortex is characteristically "blown out." *B*, Osteolytic metastasis to the femur from mucinous adenocarcinoma of the colon in a 79-year-old woman. The cortex is destroyed, and subtle sandlike calcifications, typical of those elaborated by mucin-producing tumors, mimic calcifications of chondrosarcoma.

Bone scans, although highly sensitive to localized skeletal abnormalities, are nonspecific as to the cause of increased radionuclide uptake. At least one third of solitary abnormalities detected in the scans of patients with malignant disease result from benign processes or normal variations (Table 1). Recognition of the normal scan image and its variations is essential to avoid interpretive errors, which may lead to a false-positive diagnosis. Benign disorders that result in positive scans include benign cartilage tumors, arthritis, Paget disease, fibrous dysplasia, bone infarct, osteomyelitis, and soft-tissue inflammation. Previous surgery or fractures may be associated with an increased uptake of isotope for as long as 1 to 3 years after the incident. Bone scans performed up to many months after mastectomy may reveal an increased accumulation of isotope in the ipsilateral shoulder and upper chest in the absence of metastasis. Nonpathologic rib fractures are suggested by two or more nonlinear foci of increased activity in the same location that progressively diminish in activity in subsequent scans. An elongated focus of increased activity that follows the long axis of the rib suggests a metastasis. In about 15 per cent of cases,

metastatic disease initially appears as a single focus rather than as multiple foci. In a series of proved cases of metastatic disease to bone, 80 per cent of solitary "hot spots" in the axial skeleton were found to be due to metastases, but only 17 per cent of solitary "hot spots" in the ribs resulted from metastatic disease.[2]

The number of false-positive scan findings can be decreased if the findings are reviewed concomitantly with corresponding radiographs. Therefore, if there are no recent radiographs of areas where there are abnormal foci of increased activity, they should be acquired promptly. An anteroposterior radiograph of the pelvis should accompany every whole body scan in order to decrease false-negative scan findings caused by obscuration of pelvic lesions by radionuclide activity in the superimposed urinary bladder (Fig. 6).[9] The scan and radiographs should be analyzed together, and a single comprehensive diagnostic impression should be recorded. There are several advantages to this combined review: elimination of excessive, inappropriate, and inadequate radiographic examinations, with resultant reduction of both radiation and financial burdens; the referring
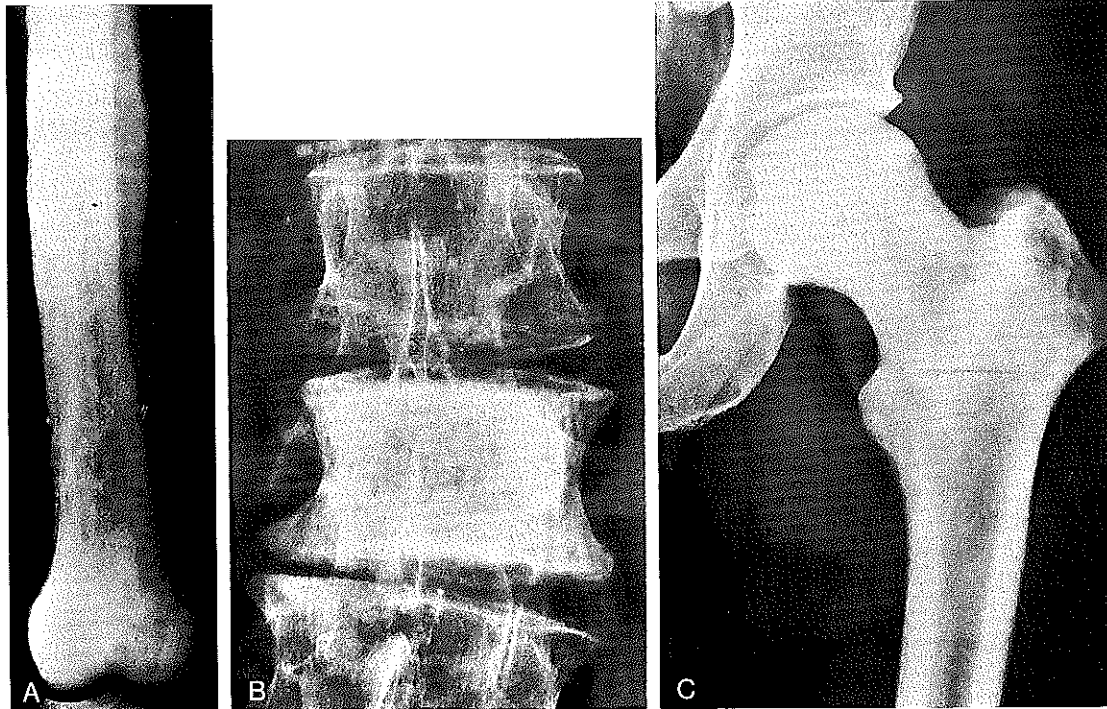
Figure 4. Pure osteosclerotic metastases. *A*, Exuberant osteosclerotic response of femur to metastases from carcinoma of prostate in a 49-year-old man. *B*, "Ivory vertebra" due to osteosclerotic metastasis to L3 from nasopharyngeal carcinoma in a 53-year-old man. *C*, Osteosclerotic metastasis of proximal femur from carcinoid tumor of ileum in a 50-year-old man.

clinician receives a single definitive opinion rather than two sometimes vague and contradictory reports; and concurrent performance of the two examinations precludes the need for a return visit by the patient to obtain corroborative radiographs. Focal scan abnormalities that are associated with normal radiographs usually represent metastases. If radiographs demonstrate a typical benign lesion corresponding in location to the focal scan abnormality, it can be assumed to be responsible for the increase in radionuclide activity.

When a patient with cancer manifests an abnormal focus of increased radionuclide activity that cannot be explained radiographically, it must be assumed to be a metastasis until proved otherwise. Several alternatives are available to determine the origin of the scan abnormality. One alternative is to repeat the scan in 4 to 6 weeks and, if it is still abnormal, to repeat the radiographs; minor trauma such as a stress fracture may result in a "hot spot" and the radiographic changes may not be evident for weeks, or the scan abnormality may resolve without the

Table 1. *Nonmalignant Causes of Increased Activity in Radionuclide Bone Scans*

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Normal structures	Benign osseous abnormalities
Base of skull	Benign cartilage tumors
Calcified thyroid cartilage	Bone infarct
Costochondral junctions	Fibrous dysplasia
External occipital protuberance	Healing fractures
Paranasal sinuses	Hyperostosis frontalis interna
Inferior tip of scapulae	Hypertrophic pulmonary osteoarthropathy
Spinous processes of vertebrae	Inflammatory arthritis
Sternum	Metabolic bone disease
Sternoclavicular joints	Osteoarthritis
Sternomanubrial joint	Osteoid osteoma
Thyroid	Osteomyelitis
Sacroiliac joints	Paget disease
Unfused epiphyses	Spondylosis and degenerative disease
Benign soft-tissue abnormalities	Surgical or biopsy site
Calcific tendinitis	
Cellulitis	
Injection site of scan agent	
Myositis ossificans	
Operative site	
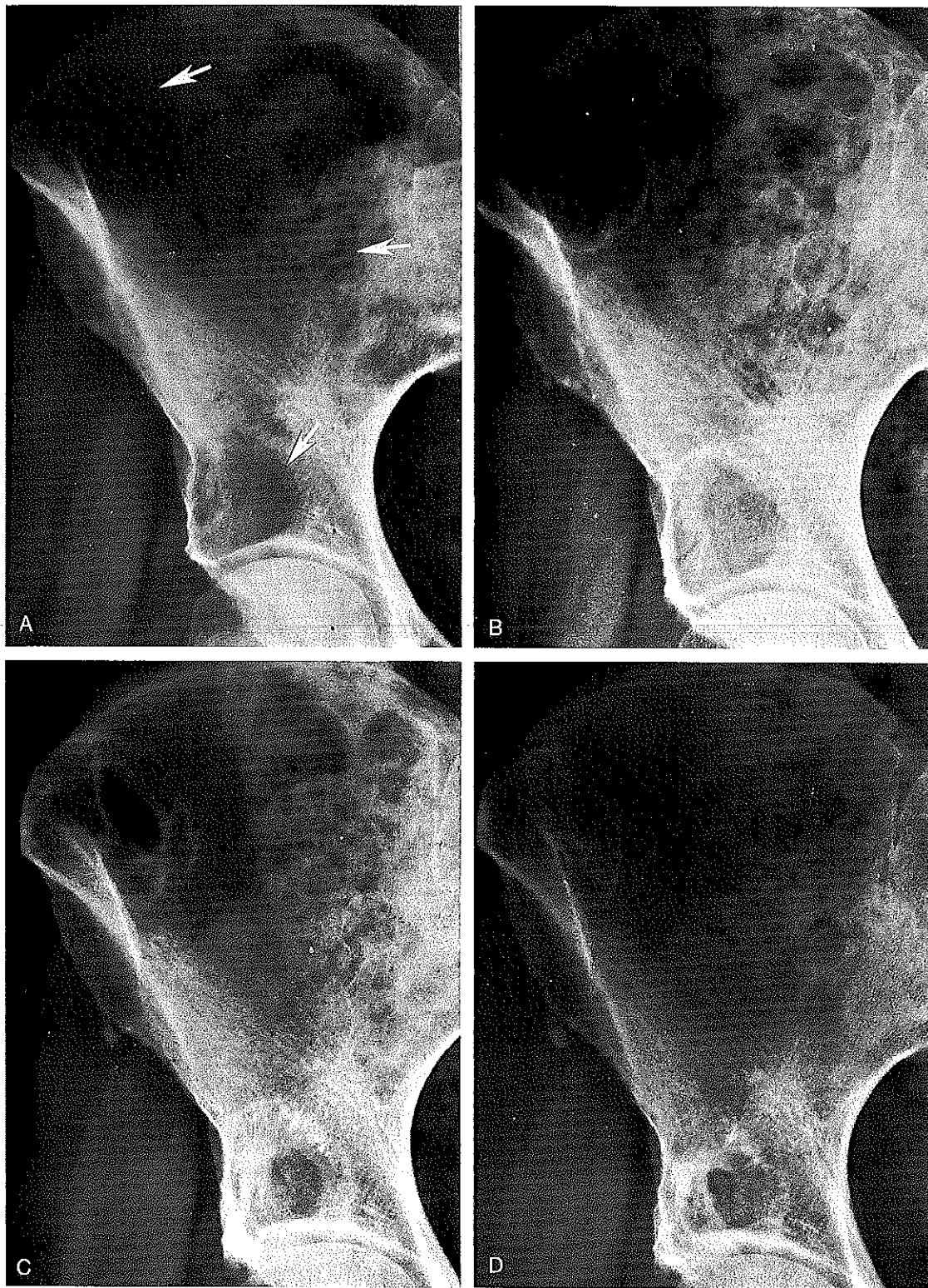
Figure 5. Progressive healing of osteolytic metastases from breast carcinoma, in response to hormonal therapy. *A,* Osteolytic lesions (*arrows*) in the ilium of a 43-year-old woman. *B,* Six months after start of therapy, sclerotic rims have formed around lesions. *C,* Two years later, healing has progressed, with further filling-in of lesions. *D,* After 2 more years, further improvement has occurred.

Figure 6. False-negative bone scan. An osteolytic metastasis in the inferior ramus of the left pubic bone is obscured by activity in the urinary bladder. *A*, Radiograph. *B*, Bone scan. (*From* Gold RH, Bassett LW: Radionuclide evaluation of skeletal metastases: Practical considerations. Skeletal Radiol 15:1–9, 1986; with permission.)

appearance of any radiographic change. Another alternative is to follow the abnormal scan findings with radiographs alone; radiographic changes of metastases may be delayed for as long as 18 months from the time of the earliest scan abnormality.[8] Another means of determining the origin of the scan abnormality is to perform a percutaneous needle biopsy, a relatively innocuous and productive procedure that is especially useful when an immediate therapeutic decision must be made. In the evaluation of patients with suspected or proved skeletal metastases, computed tomography (CT) or magnetic resonance (MR) imaging is useful for further evaluation of an abnormal focus of increased radionuclide activity that cannot be explained radiographically by a metastatic focus or benign abnormality.[10] Information provided by CT or MR imaging may influence the decision regarding the need for a biopsy, and CT can also be used to monitor the needle biopsy procedure.[11]

False-negative scan results arise from numerous causes. Accumulation of isotope in the urinary bladder may obscure abnormal isotope activity in the ischia, pubic bones, and sacrum. Rarely, at sites of extremely aggressive metastases with no accompanying new bone, the scan, instead of manifesting increased activity, shows normal or even diminished isotope accumulation. "Cold" or photopenic metastases are found most often in association with the lesions of highly aggressive anaplastic carcinomas and with leukemia (Fig. 7). Multiple myeloma, although not a metastatic process, is notorious for its association with negative and photopenic bone scan findings. Barium in the gut may absorb gamma rays emanating from the underlying spine on an anteroposterior view and thereby simulate an aggressive photopenic metastasis. Acute ischemic necrosis, joint protheses, and the changes that result from radiotherapy may also produce "cold spots." In diffuse metastatic disease the isotope accumulation in all the bones occasionally may be so uniform as to give a false-negative impression. One clue to the true state of affairs is the presence of a greater than normal intensity of isotope uptake in the skeleton, producing a so-called superscan (Fig. 8). Another clue is scant

or absent radionuclide activity in the kidneys, bladder, and soft tissues. In patients with metastatic carcinoma of the prostate, a disproportionately mild involvement of the skull compared with the remainder of the skeleton, combined with decreased imaging time because of the great intensity of skeletal activity, may produce a headless bone scan.[19] In infants and children, the normal increased activity in unfused epiphyses may mask adjacent metastases such as those of neuroblastoma.[15]

Follow-up bone scans are valuable for monitoring the progression or regression of metastatic disease. In the early stages of healing, metastatic lesions may occasionally undergo a paradoxic increase in activity. This "flare" phenomenon results from an increase in regional blood flow, an accentuation of bone turnover, or both. A more typical response of healing bony metastases is a progressive decrease in radionuclide activity on serial scans; this is a useful finding in the evaluation of patients with carcinomas of the prostate or breast in whom an increase in the radiographic density of healing metastases may sometimes be misinterpreted as evidence of tumor progression (Fig. 9).[12]

Although it is not yet universally available, single-photon-emission computed tomography (SPECT) has the potential for increasing the sensitivity and specificity of radionuclide bone scans for metastatic disease.

MAGNETIC RESONANCE IMAGING OF BONE

Although whole body radionuclide bone scanning with correlative radiography remains the most appropriate tool to screen for skeletal metastases and to follow their response to treatment, there are several circumstances in which MR imaging may have a significant impact on the management of the patient with suspected osseous metastatic disease[26]: in the detection of metastases in symptomatic patients in whom radiographs and radionuclide bone scans are equivocal or negative; in the asymptomatic patient for whom there exists a high suspicion of
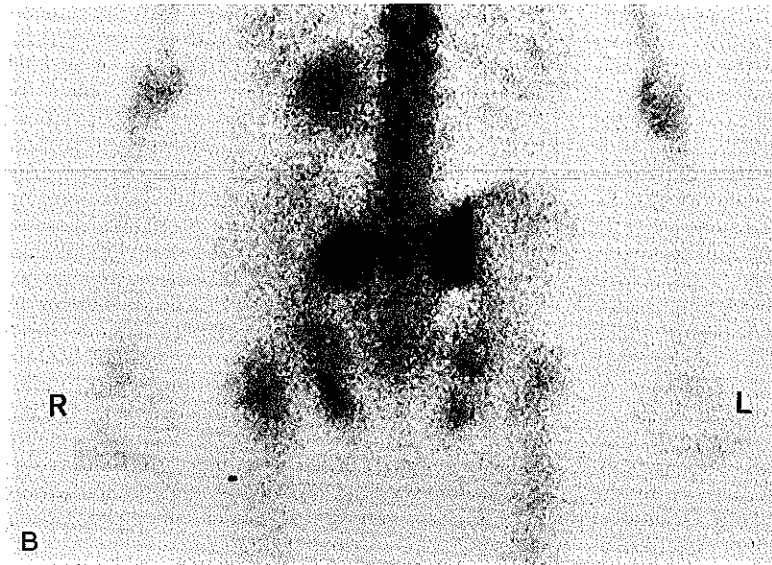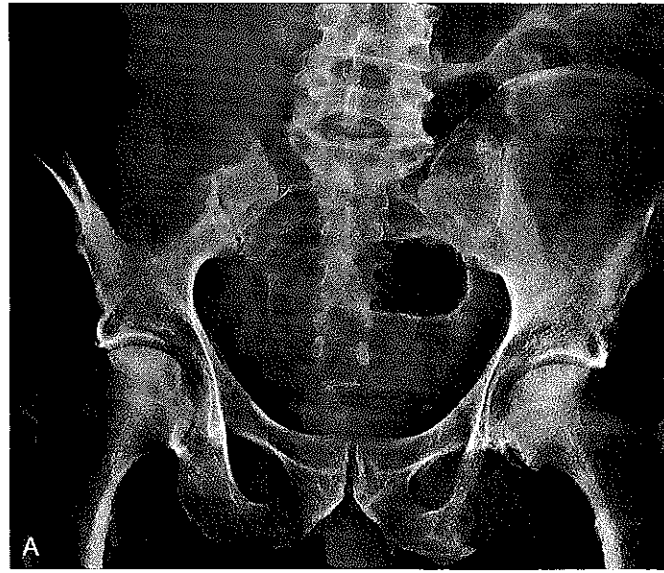
Figure 7. False-negative bone scan. Highly aggressive metastases of renal cell carcinoma in a 45-year-old man. *A*, Radiograph reveals huge osteolytic metastasis in right ilium, and a second metastasis in left ischium. *B*, Bone scan (posterior "cut" of tomographic scan) fails to reveal increased activity in right ilium, although the bone appears to be enlarged. Similarly, left ischial metastasis is less active than normal right ischium. A metastatic lesion in right femur is depicted in the scan, but not in the radiograph. (*From* Gold RH, Bassett LW: Radionuclide evaluation of skeletal metastases: Practical considerations. Skeletal Radiol 15:1–9, 1986; with permission.)

metastatic disease and an equivocal radiographic or scintigraphic abnormality; in the detection of metastases at sites that are difficult to evaluate by conventional radiography or scintigraphy, such as the symphysis pubis, sacroiliac regions, and sternum; and in determining the extent of metastatic disease when planning palliative surgery or radiotherapy. MR imaging may also be useful in determining the cause of vertebral collapse in osteopenic patients with a known primary malignancy.

Conventional radiography, radionuclide bone scanning, and CT all rely heavily on destruction and turnover of bone for the depiction of metastatic disease. Because the majority of skeletal metastases seed the marrow through hematogenous spread and MR is the imaging modality that offers the best direct evaluation of bone marrow, it follows that MR is the most sensitive imaging modality for the detection of early metastases to bone and provides the most detailed information regarding their location and extent. However, unlike the global evaluation of the skeleton provided by radionuclide bone scans, MR imaging, like CT, allows only regional evaluation. Thus, MR imaging should be employed primarily for further evaluation of a lesion deemed suspicious on clinical grounds or on the basis of other imaging studies, rather than to screen the whole body for "silent" metastases. CT is more sensitive than MR imaging for the depiction of cortical involvement by metastatic disease, whereas MR imaging is more sensitive than CT for the depiction of marrow involvement. Because marrow is affected by metastases earlier than cortical bone, it stands to reason that MR imaging is more effective in depicting the pres-
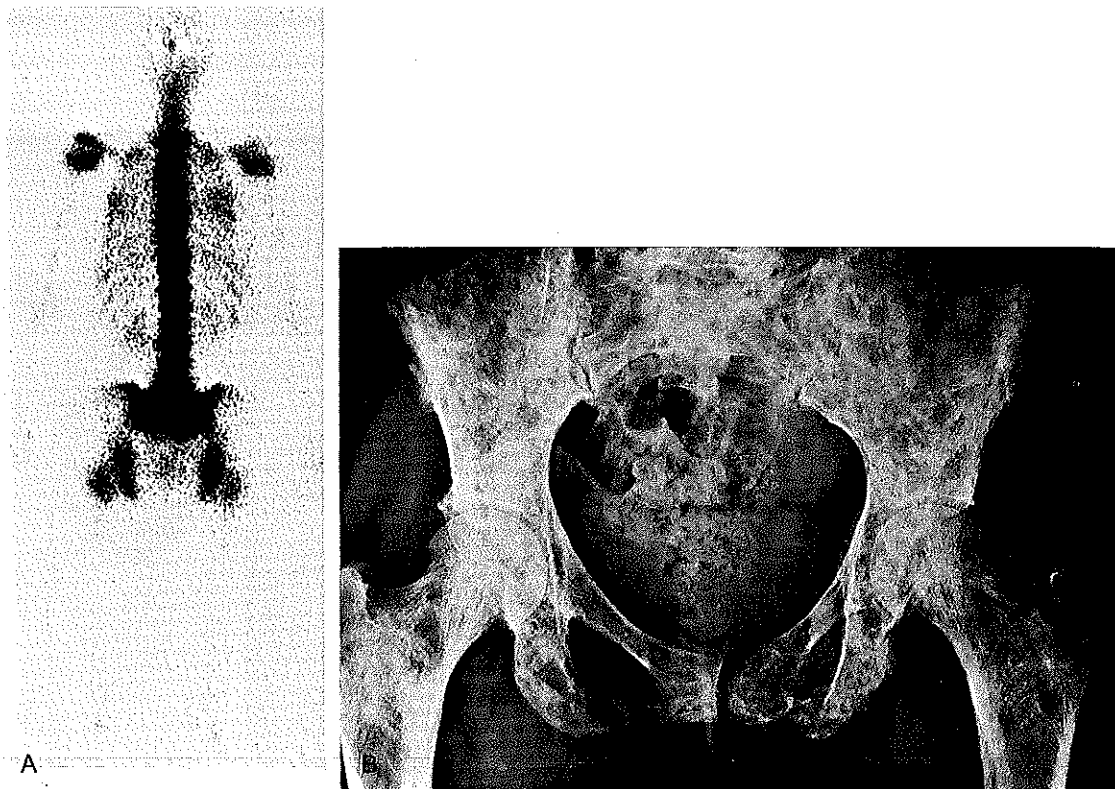
Figure 8. "Superscan" resulting from diffuse metastatic breast cancer. *A*, Bone scan discloses strikingly uniform skeletal uptake of radionuclide. Absent or scant uptake in kidneys, bladder, and soft tissue is key diagnostic clue to presence of diffuse skeletal metastases. *B*, Radiograph of pelvis reveals generalized mottled appearance of bone, indicating mixed osteolytic-osteosclerotic response. (*From* Gold RH, Bassett LW: Radionuclide evaluation of skeletal metastases: Practical considerations. Skeletal Radiol 15:1–9, 1986; with permission.)

ence and local extent of the metastatic process (Fig. 10). Nevertheless, the choice between CT and MR imaging in accessing a suspected osseous metastasis may depend most of all on their relative availability.

All osseous metastases demonstrate decreased signal intensity on T1-weighted images.[3] This fact makes metastastic foci conspicuous within the higher signal intensity of surrounding fatty marrow. Although the appearance of metastases on T2-weighted images varies considerably according to tissue type, cellularity, water content, and the presence of fibrosis, necrosis, hematoma, and inflammatory elements, metastases generally manifest increased signal intensity.[29] Thus, the most sensitive pulse sequence for depicting metastases is the T1-weighted sequence, where the metastases appear typically as foci of low signal intensity, well delineated from the surrounding high intensity normal marrow. Indeed, metastases are not as easily identified and may actually be obscured on T2-weighted images, where their increased signal intensity may be equal to or higher than that of the surrounding marrow.

COMPUTED TOMOGRAPHY AND THE EVALUATION OF SKELETAL METASTASES

CT has replaced conventional tomography for the evaluation of focal abnormalities identified on screen-ing radionuclide bone scans after conventional radiography has failed to confirm or elucidate them. CT is also effective in evaluating radiographically negative areas that are symptomatic and clinically suspicious for metastases. The contrast resolution of CT is approximately ten times greater than that of conventional radiography, and may disclose trabecular- and cortical-bone destruction, replacement of marrow fat by neoplastic tissue, extension into the surrounding soft tissues, and involvement of adjacent neurovascular structures.

PERCUTANEOUS NEEDLE-BIOPSY ASPIRATION

In 3 to 15 per cent of cases of patients presenting with metastatic carcinoma, the site of the primary tumor is unknown, and osseous metastases may be present in as many as 20 per cent of these cases.[27] Percutaneous needle biopsy provides a rapid, accurate, and relatively safe means of obtaining proof that a lesion detected on conventional radiography, radionuclide bone scan, CT, or MR imaging is a metastasis. Although the histologic features of the biopsy specimen may not identify the specific site of origin of the primary tumor, they often provide sufficient
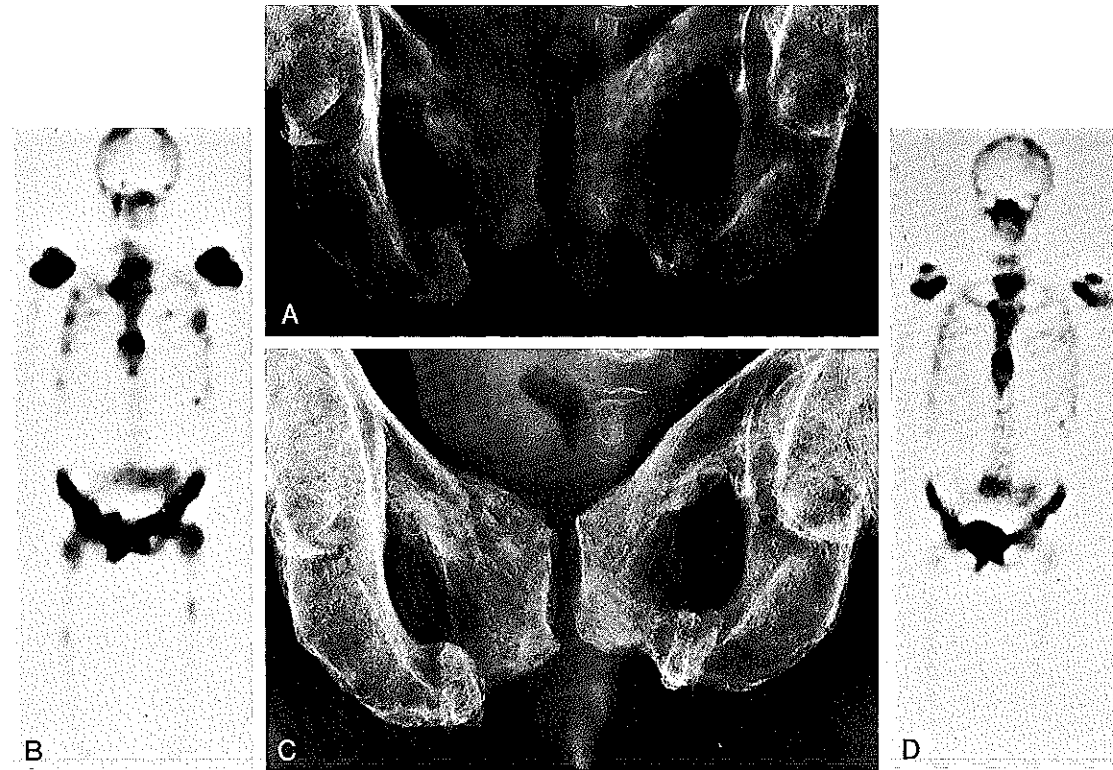
Figure 9. Healing of metastases from breast cancer in a 59-year-old woman. *A,* Radiograph of pubic bones reveals diffuse osteolytic metastatic disease and pathologic fractures. *B,* Bone scan accompanying *A* shows numerous foci of abnormally increased radionuclide activity. *C,* Radiograph taken 4 months later discloses remineralization of bones and healing of fractures. *D,* Bone scan accompanying *C* reveals substantial decrease in abnormal radionuclide activity.

information to determine whether there is a need for further diagnostic studies. For example, a biopsy diagnosis of undifferentiated carcinoma might imply that a further diagnostic workup to locate the site of origin would yield little or nothing of value, possibly creating a financial burden for a patient who can expect only a short survival time. All too often, dogged diagnostic persistence in the face of such strong odds does not improve the length or quality of life.[28] However, a biopsy specimen of a metastasis that yields a more specific histologic diagnosis such as squamous-cell carcinoma (probably from the lung or upper respiratory tract), or clear-cell carcinoma (probably from the kidney or thyroid gland) can be helpful in directing the search for the primary tumor to the most likely sites.[27]

Osteolytic lesions or those with an adjacent soft-tissue component usually can be evaluated by percutaneous biopsy with a fine or "skinny" needle. However, osteosclerotic lesions or those surrounded by intact cortex require core biopsy with a large cutting needle. The biopsy procedure is usually performed under local anesthesia and with fluoroscopic or CT guidance (Fig. 11).

Although the use of a "blind" needle biopsy of a radionuclide scan abnormality with negative radiographs has previously been frowned upon,[18] it may be highly productive with current high-resolution scan techniques (including SPECT) augmented by CT guidance.[21]

In one study of fine-needle aspiration biopsy of osteolytic lesions, the predictive value of a positive result (unequivocally malignant cells found in the aspirate) was 100 per cent.[5] Therefore, a positive needle-biopsy diagnosis precluded the need for open biopsy. However, in the same series of cases a negative result was *not* highly predictive; this necessitated repeat aspiration biopsy which, if still negative, necessitated open surgical biopsy. On the other hand, some investigators[22] have reported that a negative needle biopsy result has a predictive value as high as 92 per cent.

SUMMARY

The radionuclide bone scan is the most effective whole body screening test for bone metastases. Conventional radiography, although relatively insensitive to the presence of bone metastases, is the best modality for characterizing them once they are detected in radionuclide scans. When the radionuclide bone scan and appropriate correlative radiographs are analyzed and reported together, false-positive scan findings are reduced, and scan specificity is increased. Valuable information on response to treat-
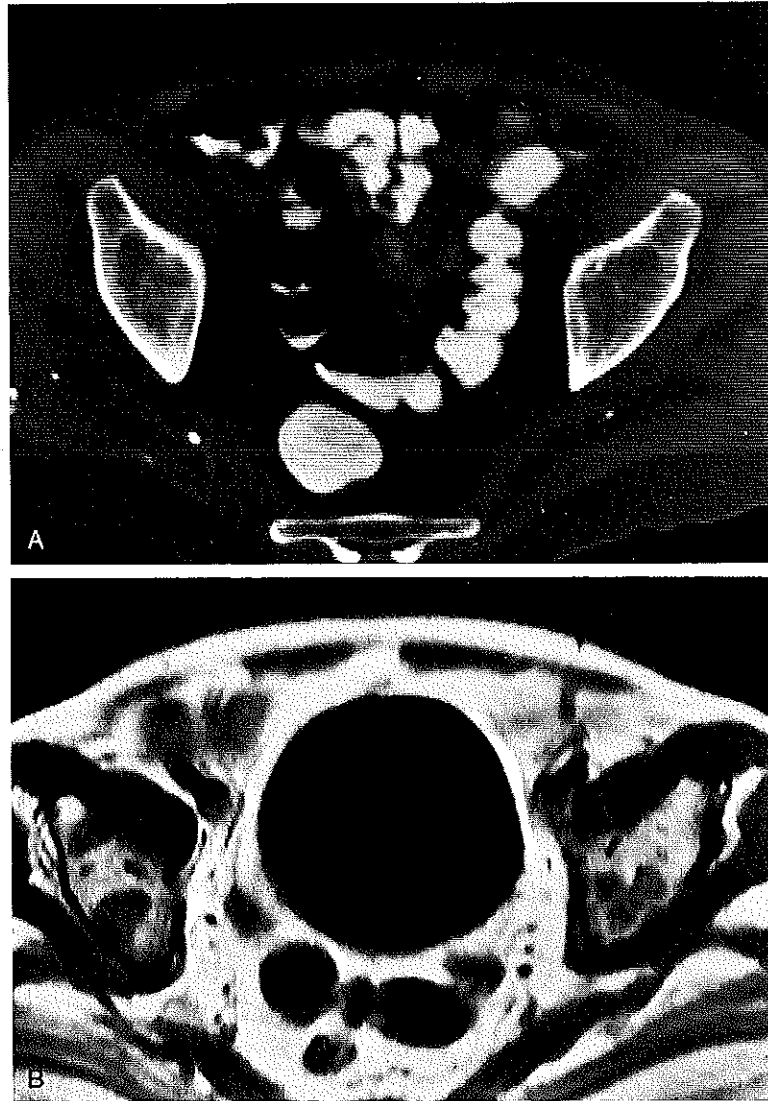
Figure 10. Comparison of CT scan and MR image in depicting metastases in ischia of a 61-year-old man with lung carcinoma. *A,* CT scan (performed without intravenous contrast infusion) fails to reveal metastases. *B,* Corresponding Tl-weighted MR axial image (spin-echo, TE = 28, TR = 500) discloses numerous metastases of intermediate signal intensity surrounded by high-intensity signal of normal marrow.
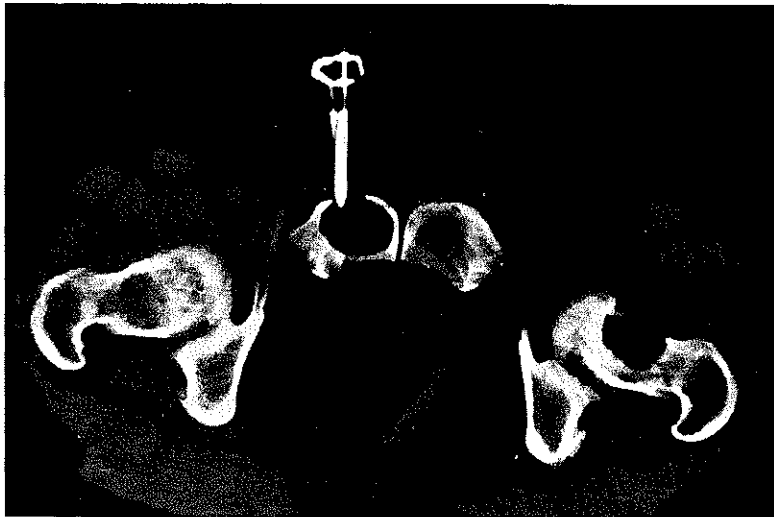
Figure 11. CT-guided percutaneous needle biopsy of a well-delimited osteolytic lesion in the right pubic bone. Another lesion is present in the left femoral neck. Pathologic diagnosis: metastatic adenocarcinoma, probably from gastrointestinal or ovarian primary tumor.
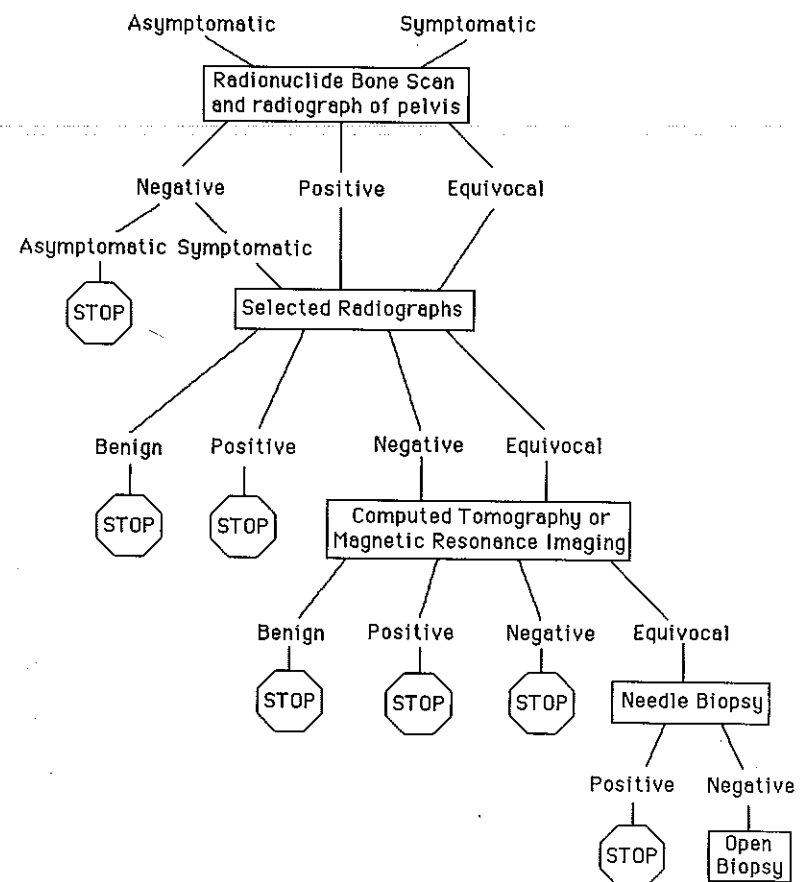

Figure 12. Algorithmic approach to work-up of possible skeletal metastasis.

ment may be obtained by correlating the changes seen in radiographs and radionuclide bone scans.

CT or MR imaging may be useful for evaluating suspicious radionuclide bone scan findings that cannot be explained radiographically, and may influence the decision regarding the need for biopsy. CT can also be used to monitor needle-biopsy procedures. The use of CT or MR imaging is helpful in determining the local extent of metastatic disease when planning palliative surgery or radiotherapy. Although a positive diagnosis by needle biopsy is considered definitive, a negative result must be suspect and may eventually necessitate open surgical biopsy. An algorithmic approach to the workup of a possible skeletal metastasis is illustrated in Figure 12.

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