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REVIEW ARTICLE

Bone Imaging in Metastatic Breast Cancer

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ABSTRACT

Bone is the most common site to which breast cancer metastasizes. Imaging—by skeletal scintigraphy, plain radiography, computed tomography, or magnetic resonance imaging—is an essential part, and positron emission tomography or single-photon emission computed tomography have a potential of evaluating bone metastases, but no consensus exists as to the best modality for diagnosing the lesion and for assessing its response to treatment. Imaging bone metastases is problematic because the lesions can be osteolytic, osteoblastic, or mixed, and imaging modalities are based on either direct anatomic visualization of the bone or tumor or indirect measurements of bone or tumor metabolism. Although bone metastases can be treated, their response to treatment is considered "unmeasurable" according to existing response criteria. Therefore, the process by which oncologists and radiologists diagnose and monitor the response of bone metastases needs revision, and the current inability to assess the response of bone metastases excludes patients with breast cancer and bone disease from participating in clinical trials of new treatments for breast cancer. In this review of the MEDLINE literature, we discuss the pros and cons of each modality for diagnosing bone metastases and for assessing their response to treatment and we present a practical approach for diagnosis and assessment of bone metastasis.

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INTRODUCTION

Bone is the most common site to which breast cancer metastasizes. Between 30% and 85% of patients with metastatic breast cancer will develop bone metastases during the course of the disease.[1-10] Bone also represents the first site of metastasis for 26% to 50% of patients with metastatic breast cancer.[6-9,11-14] Complications of bone metastasis include bone pain, pathologic fractures (the incidence of which ranges from 16% to 60%), hypercalcemia, and spinal cord compression, any of which can profoundly impair quality of life.[15-17] Conversely, elimination of skeletal complications can improve quality of life.[6,16,18-21] Imaging is an essential part of the management of bone metastasis in breast cancer; however, no consensus has been reached as to the optimal imaging modality for this purpose. Assessment of bone tumor response using criteria developed by the International Union Against Cancer (UICC),[22,23] the WHO,[24] or the Response Evaluation Criteria in Solid Tumors (RECIST)[25] group does not meet the needs of oncologists in clinical practice (Table 1). Most oncologists do not even use the WHO and UICC criteria, which define bone tumor response by plain radiography (XR) and skeletal scintigraphy (SS), and the RECIST system considers bone disease to be "nonmeasurable." In clinical practice, this situation results in heterogeneity in assessments of bone metastasis by oncologists. An integrated consensus regarding how best to evaluate bone tumor response is needed. Our goal here is to review the current evidence, from the peer-reviewed literature and from our own experience over the past decades, to evaluate the imaging modalities used to assess bone metastasis in breast cancer. In a structured search of English-language peer-reviewed journals, we searched the MEDLINE database for the period 1966 to 2003, with the combinations of search terms shown in Figure 1. We further evaluated the level of the evidence presented in each reported study in terms of the statistical strength of the study design and the scientific strength of the treatment outcomes (ie, end points) measured, based on guidelines

Table 1. UICC and WHO Criteria for Assessment of Disease Response in Bone

Response Type	International Union Against Cancer*	WHO†
Complete response	Disappearance of all known disease Lytic lesions should have radiologic evidence of calcification	Complete disappearance of all lesions on x-ray or scan for at least 4 weeks
Partial response	At least 50% decrease in size of measurable lesions Objective improvement in evaluable or nonmeasurable lesions No new lesions or progressive lesions	Partial decrease in size of lytic lesions, recalcification of lytic lesions, or decreased density of blastic lesions for at least 4 weeks
No change (stable disease)	Unchanged, or between 25% increase and 50% decrease in size of measurable lesions‡	Because of the slow response of bone lesions, the classification of "no change" should not be applied until at least 8 weeks have passed from start of therapy
Progressive disease	Mixed; some lesions persist while others progress, or new lesions appear Failure; some or all lesions progress and/or new lesions appear No lesions regress	Increase in size of existent lesions or appearance of new lesions

Abbreviation: UICC, International Union Against Cancer.
*Criteria are based on plain radiography; the duration of response is to be dated from the start of therapy until either new lesions appear or any one existing lesion increases by 25% or more above its smallest recorded size.
†Occurrence of bone compression or fracture and its healing should not be used as the sole indicator for evaluation of therapy.
‡If lesions that cannot be measured but are otherwise evaluable represent the bulk of disease and these lesions clearly do not respond even though measurable lesions have improved, then the response is considered no change, rather than an objective regression.

from the National Cancer Institute.[26] The evidence-level scale is as follows: Level I, randomized controlled clinical trials; Level II, nonrandomized controlled clinical trials; Level III, Case series; and Level IV, Best Case Series. The deficiencies in study design of much of the published literature result primarily from the lack of a reliable "gold standard" with which to compare results from the various imaging modalities. Most of the papers reported a single, integrated result that combined findings from several imaging modalities or from assessments of clinical symptoms or biochemical markers. Thus we did not attempt any meta analysis of quantitative data.

In this review, we discuss the pros and cons of six imaging modalities—SS, XR, computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and single photon emission computed tomography (SPECT)—with regard to how well they detect bone metastases and the response of such metastases to treatments such as chemotherapy or endocrine therapy. We conclude with a discussion of how these imaging modalities should be used in the context of daily oncology practice and propose a revised set of response criteria for bone metastases.

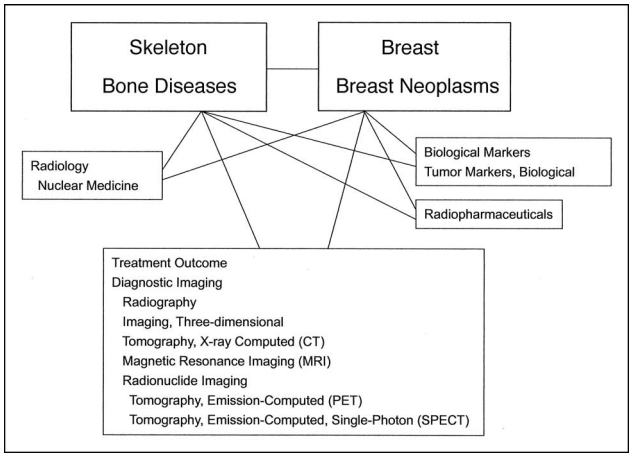

Fig 1. Structure of the MEDLINE search. MEDLINE's Medical Subject Headings (MeSH) were chosen as search terms whenever possible.

TYPES OF BONE METASTASES IN BREAST CANCER

Bone consists of cortical, trabecular, and marrow components (Fig 2). Cortical bone, which represents 80% of skel-

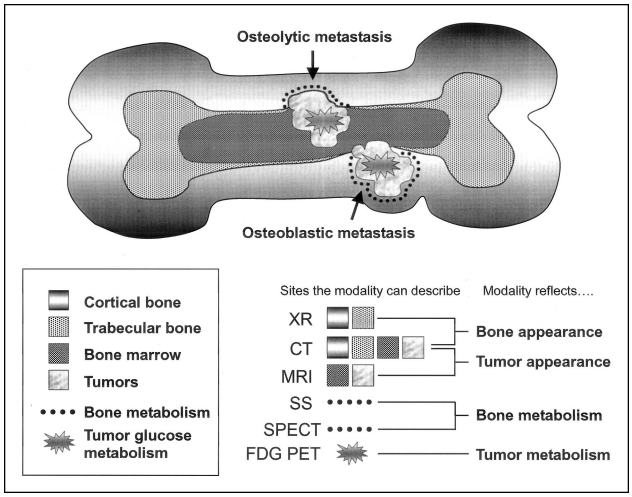

Fig 2. Schematic of bone structure, and types of metastases visualized by the various imaging modalities. Each modality visualizes different aspects of tissues; plain radiography (XR) and computed tomography (CT) visualize bone structure, CT and magnetic resonance imaging (MRI) visualize tumors and bone marrow, skeletal scintigraphy (SS) and single photon emission computed tomography (SPECT) reveal bone osteoblastic metabolism, and positron emission tomography (FDG-PET) visualize tumor metabolism. CT, MRI, and FDG-PET can potentially detect small bone marrow metastases early, before any structural changes in cortical bone are visible.

etal volume, is compact and has canals containing vessels. A thin layer of compact bone surrounds trabecular bone, also known as cancellous or spongy bone, which encompasses the bone marrow.[27] Most of the red marrow is located in axial bones (eg, vertebrae, pelvis, proximal femora), whereas fat marrow is found in appendicular bones (eg, long bones). Bone undergoes constant remodeling, which involves maintaining a dynamic balance between osteoclast and osteoblast activity. The fact that both cell types can be active at the same time explains how bone metastases can present on images as osteolytic (bone resorption), osteoblastic (bone formation), or mixed lesions (Fig 2). In many cases, osteolytic and osteoblastic changes occur simultaneously.[28] Up to half of all bone metastases from breast cancer tend to show osteolytic changes.[5,7,29-31] However, because all types of bone metastases show constant activation of osteoclasts, bisphosphonates and other osteoclast inhibitors are effective against all types of bone metastases.[32] Breast cancer preferentially metastasizes to vertebrae and the pelvis, followed by ribs, skull, and femur,[1,33-37] probably because the vertebrae are highly vascularized and contain 75% of the body's red marrow.[38-42]

Because each of the imaging modalities to be discussed here visualizes different aspects of tissues (bone or bone marrow) or visualizes tumors from different perspectives (eg, in terms of density, metabolism, vascularity, or water content), the appearance of osteolytic, osteoblastic, or mixed lesions can differ considerably depending on the imaging modality used (Fig 2).

IMAGING MODALITIES

SS

SS is the most commonly used means of detecting bone metastasis[7,43-48]; it visualizes increases in osteoblastic activity and skeletal vascularity.[46,49-53] Many radiopharmaceuticals (radionuclides) have been used in SS,[29,54-57] including technetium-99m bound to methylene diphosphonate, hydroxymethylene diphosphonate, or dicarboxypropane diphosphonate.[30,44,55-61] Published sensitivity and specificity rates of SS for diagnosis have varied, with sensitivity ranging from 62% to 100% and specificity from 78% to 100% (evidence level II-III).[46,55,59,61-71] However, SS is generally considered sensitive for detecting osteolytic or osteoblastic bone metastases on whole-body images,[44,45,51,55] which can be obtained at reasonable cost ($212.00 according to the Medicare fee schedule for Harris County, Texas). Although SS is more sensitive than XR,[30,53,55,56,72-74] SS reportedly has lower specificity and higher false-positive rates than does XR because the findings of SS reflect the metabolic reaction of bone to several disease processes, including neoplasia, trauma, or inflammation.[30,34,37,48,53,56,59,73,75-78] False-negative findings can occasionally result when pure osteolytic metastases are growing rapidly, when bone turnover is slow, or when the site is avascular (photon-deficient lesions; "cold spots").[52,75,79,80] Therefore, despite the usefulness of SS in diagnosing widespread, multifocal lesions, it should never be considered diagnostic when it produces equivocal findings (eg, "suspicious" lesions or a single "hot spot"). Other imaging modalities such as XR, CT, or MRI should be used to characterize such lesions, including any soft tissue components, and to assess the risk of fracture. SS should also be supplemented with images obtained with other modalities to provide a valid baseline for the assessment of bone tumor response.[65] Histologic confirmation may also be needed for the final diagnosis of suspicious lesions. The advantage of SS is not for diagnosis but rather for screening, as it is widely available and can produce rapid whole-body images at a reasonable cost.

The appropriate intervals between screening for bone metastases, and the frequency with which such screenings should take place, have not been defined.[81-83] Level II evidence[84-86] indicates that the rate at which bone metastasis was detected by SS among patients with node-positive breast cancer was 2.4%. In the same studies, the rates at which findings on SS changed from negative on the initial scans to positive during the next 2 years were 1.1% for patients with T1 breast cancer and 1.2% for those with N0 disease. A combination of level II and level III findings suggest that the bone-metastasis detection rates by SS are 0.82% for patients with stage I disease, 2.55% for those with stage II disease, 16.75% for stage III, and 40.52% for those with stage IV breast cancer.[43,77,87-92] However, results from a large randomized study of patients with breast cancer immediately after initial treatment showed that semiannual screening by SS detected more bone metastases than did clinical follow-up alone (84 *v* 53 patients at 5 years, *P* value not given for bone metastases) but did not improve 5-year survival rates.[93] Level I evidence from this and another randomized controlled trial revealed no difference in survival between patients followed up with physical examinations and those followed up with physical examinations and XR and SS.[83,93] Two retrospective studies suggest that initial detection of an abnormality or asymptomatic bone metastasis by SS produced a 14% improvement in overall survival rate at 4 years and a 10% improvement at 5 years (level III evidence).[94,95] However, other level III evidence suggests that early detection of asymptomatic breast cancer recurrence at any site (ie, not limited to bone) does not affect overall survival rates.[96,97] Further, the American Society of Clinical Oncology guidelines do not recommend using SS for post-treatment surveillance of asymptomatic disease.[98] On the basis of these results and the fact that most abnormal findings have benign causes (eg, trauma or inflammation), routine SS screening of patients with early (stage I or II) breast cancer is not recommended.

A bone tumor response usually appears on SS as a decrease in the intensity of radionuclide uptake by meta-

static foci. Progressive disease, conversely, is visualized as increased uptake or the appearance of new lesions.[45] A limited retrospective study of 101 patients with breast cancer with bone metastasis showed that regression of bone lesions on SS was associated with a survival benefit, and failure to develop a radiographically and scintigraphically stable pattern after treatment was associated with shorter survival (mean, 2.1 ± 1.3 years) relative to those who showed evidence of improvement (mean 4.3 ± 2.3 years; $P < .001$).[99] However, false-positive and false-negative findings characteristic of SS can impede the assessment of bone tumor response. Three issues must be borne in mind when considering SS for assessing response of bone metastases. The first is its relative lack of specificity, as increases in bone metabolic rates can be caused by conditions other than tumor (eg, fracture, arthritis, or infection, among others).[34,37,48,53,56,59,75-78] The second issue is the so-called "flare" phenomenon.[7,27,29,50,82,100-112] In one prospective report (evidence level II), 75% of patients who showed a partial response of bone metastases from breast cancer showed escalation of activity or new lesions on SS during the first 3 months after treatment because of increased tracer uptake by new bone that had formed in the repair process. Such a situation could well be interpreted as progressive disease; however, after 6 months, the activity associated with the flares gradually decreased.[107] The third issue is that SS sometimes—albeit rarely—depicts a reduction in isotope uptake in rapidly progressive disease, when overwhelming destruction allows little chance for new bone to form (photon-deficient lesions; "cold spots").[52,75,79,80] Some patients who have "stable" disease (according to SS) can experience clinical improvement, prolonged survival, or both,[113] suggesting that such subgroups may include patients with partial response that is not evident on SS. We conclude that determining the final response of bone metastases solely on the basis of changes in SS signal level over time is not appropriate.[12]

XR

On XR, bone lesions can appear as areas of faint or absent density (osteolytic), as disrupted or absent trabecular structure, or as sclerotic lesions or rims (osteoblastic). Because XR depicts the net results of bone resorption and repair, this modality is useful as a complement to SS for clarifying nonspecific or atypical findings or for following up cases in which clinical findings indicate bone pain but SS findings are negative. However, because 30% to 75% of normal bone mineral content must be lost before osteolytic lesions in the lumbar vertebrae become apparent on XR, metastatic lesions may not appear on XR for several months.[1,27,114] Lesions in trabecular bone (medullary lesions) are more difficult to detect by XR than are lesions in cortical bone because of the limited contrast in trabecular bone.[53] Therefore, XR is less sensitive (44% to 50%, according to level II-III evidence) than SS for detecting initial bone metastasis.[1,30,53,55,56,115] A whole-body roentgenographic bone survey requires multiple exposures to x-rays, as each radiograph covers only a limited anatomic field; nevertheless, at $84.32 for a whole-body survey (based on the Medicare fee schedule for Harris County, Texas), XR is relatively inexpensive.[44] We thus recommend XR for evaluating "suspicious" lesions on SS or symptomatic lesions but not for screening because of its limited sensitivity.

In terms of assessing bone tumor response, XR can detect the response of osteolytic lesions by depicting active bone formation (osteoblastic or osteosclerotic change) and the reappearance and normalization of trabecular structure.[12,22,30,116-118] In several studies, indicators of bone metastasis response on XR correlated with other response indicators (eg, clinical symptoms or confirmation at long follow-up) 24% to 34% better than SS did.[1,7,28,49] However, as noted in the previous paragraph, changes in XR often do not become apparent for 3 to 6 months after the initiation of treatment.[27,45,49,106,107,119-121] In one prospective study (evidence level II), clinical improvement was associated with evidence of improvement on XR in only 50% of the patients evaluated.[122] This shortcoming may lead to underestimates of tumor response rates.[6,45,121,123] According to the UICC criteria, which were published in the 1970s, a response requires a 50% reduction in tumor dimensions on XR.[22,23] However, tumor dimensions are not easy to measure on plain radiographs, and most radiologists rely instead on the dimensions of the bone destruction, at best an indirect assessment of tumor extent.[6] Thus, response to therapy cannot be reflected by decreases in the radius or diameter of the radiographic lesion, but rather by the reappearance of new bone or sclerotic changes. Such changes are very difficult to quantify. For osteoblastic lesions, increases in density are seen in both responding and progressing disease, which makes evaluating response of osteosclerotic metastases difficult as well.[27]

CT

Computed tomography (using the bone window setting) offers superior skeletal detail, including bone marrow, because of its ability to distinguish among materials of different densities.[27,45,50,109,115,124,125] The sensitivity of CT for the diagnosis of bone metastases ranges from 71% to 100% (evidence level II-III).[63,72,115] Despite the limited data that are available, CT is generally thought to be highly sensitive. At its earliest stages, bone metastasis starts in the bone marrow, having arrived there via vascular or lymphatic pathways; CT can detect metastases in the marrow, before bone destruction becomes evident.[53] As the marrow cavity becomes replaced by tumor, the abnormal area appears more highly attenuated than does marrow that is not replaced.[53,126,127] CT is also better than XR and SS for depicting lesions in the spine[51,128] and calvarium,[72] as such

lesions are difficult to visualize in sufficient anatomic detail on XR or SS.

The disadvantage of CT is that in its most widely available form, only limited anatomic areas can be scanned at a time. Thus, at present CT is not the most useful means of detecting abnormalities on whole-body screening. Expanded CT applications such as multislice and volumetric scan modes can be used to scan the torso and proximal long bones in a short time, thereby allowing the entire axial skeleton to be scanned in a single session. However, these applications are not yet suitable for screening purposes.

Sclerosis of a lytic component on CT, like XR, generally suggests a response to treatment.[122] However, progressive lysis or new areas of lysis appearing within a sclerotic or mixed region[109] or an increase in the size of an originally blastic lesion may represent disease progression. In one prospective study (evidence level II), CT was used to assess the response of lytic metastatic bone lesions in 20 patients. Improvement on CT was associated with improvement in symptoms for 67% of all patients; this percentage improved to 86% when only those who responded were considered.[122] Because CT can contribute to the accuracy of assessment of bone tumor response, it holds great promise for both detecting bone metastases and assessing their response to treatment.[1,33-37] Unfortunately, bone-window CT scanning is currently underutilized by radiologists and oncologists.

MRI

MRI can provide detailed images of the bone and bone marrow; the diagnostic sensitivity of skeletal MRI ranges from 82% to 100%, and its specificity ranges from 73% to 100% (evidence level II-III), and hence MRI is at least as sensitive as CT, SS, or XR for detecting bone marrow metastases.[47,61,63,65-68,71,129-142] Marrow lesions are not visible on XR or SS. On MRI, normal bone marrow shows a high-intensity signal on T_1 imaging, whereas metastases appear as areas of reduced signal, reflecting the replacement of fat in the marrow by the tumor.[51,53,143-145] CT also can visualize bone marrow lesions, but the resolution is better in MRI.[129] MRI also has better contrast resolution than CT for visualizing soft tissue and spinal cord, and thus it aids in distinguishing benign from malignant causes of vertebral compression fracture and in detecting spinal cord compression.[47,50,63,109,131,146-151] However, MRI is less desirable than XR or CT for detecting destruction of bone structure, because cortical bone does not produce a signal and thus appears black on T_1 and T_2-weighted sequences.[48,50,51,109,129,143,152]

MRI's capability to obtain wide sagittal views allows large sections of the skeleton (such as the entire spine) to be assessed in one imaging session, thereby providing more accurate information than SS for patients with spinal symptoms.[51] Use of newer techniques for obtaining whole-body skeletal studies such as contiguous, coronal, or "Turbo STIR" [short tau inversion–recovery] imaging requires further study.[68,140,153] Although MRI can be valuable for follow-up after detection of bone lesions, and it has the additional advantage of not involving exposure to ionizing radiation, its high cost (C Spine without contrast, $521.33; T Spine without contrast $568.86; L Spine without contrast, $562.87, according to the Medicare fee schedule for Harris County, TX) makes MRI a poor choice for initial bone metastasis screening.[44]

Evidence to support the use of MRI for assessing bone tumor response is limited. Its high-quality images of the spinal cord can be beneficial for monitoring the response of osseous metastases, especially when symptoms of spinal cord compression are evident.[44,51] Bone marrow lesions may be more accurately assessed by MRI than by other imaging modalities. In one prospective study of 18 patients, MRI revealed tumor response in 4 patients for whom biochemical-marker findings were equivocal and SS suggested progressive disease.[154] A retrospective study of 41 patients revealed that MRI could accurately predict disease progression or stability of vertebral metastases in 75% to 79% of cases as confirmed by clinical, biochemical, radiographic, and scintigraphic variables.[155] Use of gadolinium with MRI may allow viable tumor to be distinguished from necrotic tissue, offering another dimension to assessments of response.[156,157]

PET

PET, which visualizes the uptake of positron-emitting radiopharmaceuticals by tissues, can be used for whole-body scanning to detect metastases in either soft tissue or bone. Breast carcinomas often display moderate increases in glucose metabolism, less than that of other types of tumors (eg, lung cancer).[158,159] However, level II-III evidence indicates that the sensitivity of PET is fairly high for identifying occult primary breast lesions (67% to 100%), for detecting axillary lymph node involvement (50% to 100%), and for detecting metastases in bone and at other sites (84% to 100%).[158-166] The disadvantages of PET are its high cost ($2,097.22, according to the Medicare fee schedule for Harris County, TX), its relative lack of availability, and the additional time required for scanning over that of other imaging modalities.[44,166] For skeletal metastases, one of two radiopharmaceuticals is typically used: ^{18}F-fluoride, a nonspecific bone tracer, or 2-deoxy-2-[^{18}F] fluoro-D-glucose (^{18}FDG), a tumor tracer.[167] The mechanism of ^{18}F-fluoride uptake is similar to that of ^{99m}Tc-methylene diphosphonate, the tracer used in SS; its accumulation depends on osteoblastic activity and local blood flow.[167,168] ^{18}F-fluoride PET, which showed superior results over SS in the detection of benign and malignant lesions of bone in a prospective study of 44 patients,[169,170] could potentially replace SS or SPECT for bone imaging, but its high cost

remains a concern. ^{18}FDG PET has been used to measure glucose metabolism in many types of cancer[171] and can be useful for distinguishing benign from malignant bone lesions.[172-174] Estimates of the sensitivity of ^{18}FDG PET for detecting bone metastasis range from 62% to 100%, and specificity from 96% to 100% (evidence level II-III).[71,74,142,162,166,175-177] In one prospective study of 57 patients with metastatic breast cancer, ^{18}FDG PET produced more false-negative findings for skeletal metastases than for nonosseous metastases because of the low uptake of ^{18}FDG by bone. False-positive findings, on the other hand, were a result of the much higher uptake of ^{18}FDG by muscle, inflamed tissue, blood pooled in large vessels, and bowel.[52,162,164] In another study of 23 patients with breast cancer, ^{18}FDG PET was more sensitive for detecting osteolytic metastases but less sensitive for detecting osteoblastic metastases.[52,121,171] For detecting purely osteolytic or marrow metastases, ^{18}FDG PET may be more sensitive than SS because those lesions involve little to no osteoblastic activity.[52,174] At present, SS is more advantageous than PET as a whole-body screening modality for detecting bone metastases from breast cancer because of its low cost.

PET has shown promise for monitoring the response of primary breast tumors and other nonosseous tumors to treatment.[161,178,179] "Flares" observed on PET after hormonal therapy for osseous and nonosseous lesions has been considered an early indicator of response in some prospective reports.[180,181] However, a clinical role for PET in monitoring the response of bone metastases remains undefined at this time.[52] Chemotherapy in conjunction with cytokines (eg, granulocyte colony-stimulating factor) can lead to increased FDG uptake by hyperplastic bone marrow, which can be difficult to distinguish from diffuse marrow involvement by tumor.[182,183] The fusion of PET and CT technologies (PET-CT)[184] has the potential for sensitive detection; however, no data are available as yet for bone metastases.

SPECT

SPECT uses the same radionuclide markers as does SS[185]; its sensitivity for the diagnosis of bone metastases is 87% to 92%, and its specificity is 91% to 93% (evidence level II–III).[42,67,69,186] SPECT is useful in evaluations of complex areas that are extensively surrounded by soft tissue such as the thoracolumbar spine and pelvis; it can also clarify "hot spots" obtained with other imaging modalities by virtue of its improved contrast resolution.[187,188] For imaging the spine, use of SPECT to study "hot spots" found by SS had a negative predictive value of 98%,[42] which makes SPECT useful for distinguishing benign from malignant lesions.[42,69,189] Although very little information is available on the use of SPECT in routine screening, it has been used for diagnosis in cases already screened with SS.

For the assessment of bone tumor response, SPECT can be used to augment SS by virtue of its more sensitive tomographic imaging. Although SPECT has some potential for evaluating therapeutic response,[188] few studies have been done on its utility for monitoring bone tumor response.

SUMMARY: IMAGING FOR DETECTING BONE METASTASES

Our literature review disclosed substantial variations in estimates of the sensitivity and specificity of each imaging modality (Table 2), in large part because the basis for measuring sensitivity and specificity differed from study to study. Most studies used findings from multiple imaging modalities (eg, typical XR finding, positive SS finding), with clinical and imaging follow-up, to confirm the presence of tumors.[67,72,115,132] Studies involving histologic confirmation of bone metastasis were rare.[162,166]

Despite the many descriptive studies indicating its limited accuracy, the first choice for screening should be SS. However, SS often needs to be followed by other modalities (XR, CT, or MRI) for an accurate diagnosis because SS reflects only bone metabolism. If focal symptoms are present, then XR can be used to visualize the painful area. CT and MRI can depict anatomic changes in more detail. CT is preferable for assessing axial bone metastasis, regardless of whether the main tumor involves the bone marrow or cortex. MRI, on the other hand, is better for detecting bone marrow disease or spinal cord compression. Although routine use of PET or PET-CT for screening is not supported by the literature, the future may bring improvements in sensitivity and specificity and reductions in the cost of these technologies; lower-cost whole-body MRI or CT may also become available in the near future. At present, use of combinations of imaging modalities, in an appropriate sequence, for detecting bone metastasis remains the most effective management strategy.[190,191]

SUMMARY: IMAGING FOR ASSESSING TREATMENT RESPONSE

Bone tumor response can be assessed on the basis of changes in symptoms, changes in levels of biochemical markers, or changes in the appearance of lesions on imaging studies. Recommendations regarding the use of SS, XR, CT, MRI, PET, and SPECT for monitoring response vary considerably among studies. No consensus has been reached on the validity of any of these assessments. In particular, the processes by which oncologists and radiologists classify the response of bone metastases from imaging modalities need to be revised because of the inadequacy of the response criteria, for the following reasons. First, the imaging modalities visualize fundamentally different characteristics; XR, CT, and MRI reveal the structure of bones and lesions and SS, PET, and SPECT reveal the metabolism of bones and lesions (Fig 2). Second, the different appearances of the

Table 2. Comparison of Imaging Modalities for the Detection of Bone Metastases

Imaging Modality	Anatomic Detail	Extent of Image*	Appearance of Bone Disease	Causes of False-Negative Findings	Causes of False-Positive Findings	Diagnostic Sensitivity	Diagnostic Specificity	Approximate Global Charge†
SS	No	Whole body	Hot spots	Rapid/pure osteolytic progression	Trauma Inflammation Benign tumor Healing	Varies (62-100%)‡[46,55,59,61-66,68-71,74]	Varies (78-100%)‡[46,59,61,62,64,66,68-70]	Low ($212.00)
XR	Yes	Local/regional Whole body	Lytic, sclerotic, mixed	Bone marrow only Lysis/sclerosis not at threshold for detection Osteopenia	Trauma Inflammation Benign tumor Healing	Low (44-50%)[1,55,115]	Numerical specificity values not addressed	Low ($84.32)
CT	Yes	Local/regional§	Lytic, sclerotic, mixed for bone, higher attenuation for marrow	Lysis/sclerosis not at threshold for detection	Trauma Inflammation Benign tumor Healing	High (71-100%)[63,72,115]	Numerical specificity values not addressed	Moderate (thoracic $291.02; abdominal $282.76 without contrast)
MRI	Yes	Regional§	Lower or higher intensity signal on T_1/T_2 scans	Lesion only in cortex	Edema	High (82-100%)[61,63,66-68,71,131,132,136,140,142]	High (73-100%)[61,63,66,68,131,136,140,142]	Moderate (cervical spine $521.33; thoracic spine $568.86; lumbar spine $562.87 without contrast)
PET	No	Whole body	Hot spots	Lesion only in cortex	After chemotherapy	Varies (62-100%)[71,74,142,162,166,175-177]	High (96-100%)[70,142,162,176,177]	High ($2,097.22)
SPECT	No	Local	Hot spots	Same as SS	Same as SS	High (87-92%)[42,67,69,186]	High (91-93%)[42,69,186]	Moderate ($285.29)

Abbreviations: SS, skeletal scintigraphy; XR, plain radiography; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography.

*Terms are defined as follows: whole body, the entire body is studied at one time with one image; regional, large anatomic area studied at one time with one image; and local, focal or small anatomic area studied at one time with one image.

†Estimates are based on Medicare fee schedules for Harris County, TX. Low, less than $250; moderate, $250 to $999.99; high, more than $1,000. (Values are given in U.S. dollars.)

‡Although the ranges of sensitivity and specificity values for SS vary, in most reports SS is regarded as a highly sensitive but poorly specific modality.

§Newer applications of CT or MRI may be useful for obtaining whole-body images in a reasonable time, but the cost of central axial skeletal imaging remains high.

three types of bone metastases (osteolytic, osteoblastic, or mixed) complicate assessments of treatment outcome; an example is the osteoblastic flare activity after successful response of osteolytic metastases (Fig 2).[28] Third, the existing standardized criteria (those of the UICC[22,23] or WHO[24];Table 1) were based on information obtained with 1970s-era imaging technology (XR or SS). Further, the widely used RECIST[25] system considers bone metastases a "nontarget" (ie, nonmeasurable) lesion. The UICC and WHO criteria rely on XR or SS, which cannot show evidence of lesion response for at least 6 months after treatment.[27,45,49,51,106,107,119-121] Indeed, documentation of a complete or partial response in bone (according to the UICC criteria) often cannot be achieved because of the limitations in imaging bone tumor response by XR, which can result in underestimates of overall response rates.[6,45,121,123] Survival rates among patients whose bone disease remains "stable" (according to the UICC criteria) for more than 6 months are similar to those among patients who show a partial response to treatment,[27,192] most likely because of the insensitivity of radiographic assessment methods. Although these criteria can be used for the evaluation of osteolytic lesions, evaluations of osteoblastic lesions are problematic because XR or SS cannot accurately describe a response (no tendency toward uniformly blastic appearance or fading of lesions on XR, no tendency to show increased or decreased activity on SS).[12,30] Fourth, most oncologists do not use these criteria but instead use CT or MRI in addition to XR or SS to evaluate treatment response. This means that assessments of bone treatment response are based on oncologists' own experience and decisions, not on accepted, published criteria. Finally, the unreliability of the published criteria excludes patients with bone-only metastases from participating in clinical trials in which assessment of treatment response is the sole end point, because bone disease is considered unmeasurable. That unmeasurability, in turn, reflects the ill-defined nature of "response" according to SS and XR. SS suffers from ambiguities in radionuclide uptake and accumulation after treatment, resulting in flare phenomena and reduced isotope uptake in rapidly progressive disease. XR is still the most cost-effective and convenient way of assessing the response of bone metastases to treatment; however, evidence of a response takes considerable time to appear on XR. CT and

Table 3. Comparison of Imaging Modalities for Assessing Response of Bone Metastases

Modality	Time Course Appearance of Tumor Response	Advantages	Disadvantages	Preferred Sites
SS	Hyperactive areas ⇒ clear	Detects new lesions	Low specificity Flare phenomenon	Appendicular bone
XR	Lytic ⇒ sclerotic	Demonstrates structural changes of bone Assesses risk of pathologic fracture No need for contrast injection Less expensive	Low sensitivity Local images Delayed appearance of response	Appendicular bone
CT	Lytic ⇒ sclerotic or Regression of tumor	Higher specificity than SS and XR Evaluates cortical and cancellous bone and calcifications more accurately than MRI	Local images Expensive	Axial skeleton
MRI	Regression of tumor	Higher specificity than SS and XR Evaluates spinal cord compression and soft tissue more accurately than CT No ionizing radiation	Poor cortical bone detail Expensive	Bone marrow Spinal cord
PET	Hyperactive areas ⇒ clear	Detects new marrow lesions	Not specific to bone False-positives after chemotherapy Expensive	Bone marrow
SPECT	Hyperactive areas ⇒ clear	Improved contrast resolution and detection in complex anatomy compared with SS planar imaging	Local images Expensive	Axial skeleton

Abbreviations: SS, skeletal scintigraphy; XR, plain radiography; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single photon emission computed tomography.

MRI provide more anatomic details by virtue of their higher-contrast and higher-resolution capabilities. The roles of PET, PET-CT, and SPECT in the management of bone metastasis in breast cancer remain unknown at this time because of the limited data collected with these modalities to date (Table 3).

DISCUSSION

The remainder of this section constitutes a review of the literature that has shaped current practice, with the goal of providing a practical way of assessing the effects of therapy on bone metastases from breast cancer. Clinically, metastases can manifest as symptoms such as bone pain or changes in circulating levels of biochemical markers. Many oncologists acknowledge that a change in symptoms or in biochemical marker levels can herald clinical tumor response or progression, and such changes may precede evidence of change on radiography.[119] Although biochemical markers that reflect the rates of bone formation (eg, carboxyl-terminal propeptide of type I procollagen, alkaline phosphatase or alkaline phosphatase specific to bone, and osteocalcin) and resorption (eg, pyridinoline [Pyr; hydroxy-lysyl pyridinoline] and deoxypyridinoline [Dpd; lysyl-pyridinoline], serum bone sialoprotein, C-telopeptide cross-links, free pyridinoline [F-Pyr] and free deoxypyridinoline [F-Dpd], the free portions of cross-linking molecules[193]) could serve as early indicators of response to treatment,[194] such markers are not sufficiently sensitive to detect early bone metastases, and their use has yet to be validated.[28,109,195] Other markers being studied include NTx/Crosslaps (a protein-bound molecule that cross-links at either the *N*-terminal or C-terminal part of type I collagen), a possible predictor of response to bisphosphonates.[51] Although we routinely measure carcinoembryonic antigen and CA 27.29 to monitor tumor response, the specificity of these markers for bone tumor response is controversial.[51,109,194-197]

On the basis of our literature review, current estimates of cost-effectiveness, and our experience at M.D. Anderson Cancer Center, we propose two imaging algorithms: one for use in diagnosing bone metastases from breast cancer (Fig 3) and the other for use in assessing the response of such metastases to treatment (Fig 4). It should be noted that these algorithms would be effective only when the participating radiologists are experienced in musculoskeletal imaging and committed to describing the details of changes in bone lesions. Technical quality, quality control, and the experience of the radiologist with bone imaging are all crucial, especially for XR. Validation of technical quality and quality-control measures, and studies of the possible influence of these factors on prognosis, would be useful. Whether to incorporate symptoms and biomarkers in these algorithms is at the discretion of the clinician.

Algorithm for Diagnosis of Bone Metastasis

Screening for bone metastases is generally thought to be unnecessary if the primary tumor is at an early stage. Once a clinical justification (eg, pain, biomarker elevation) is made for screening (Fig 3), we favor using SS as the first

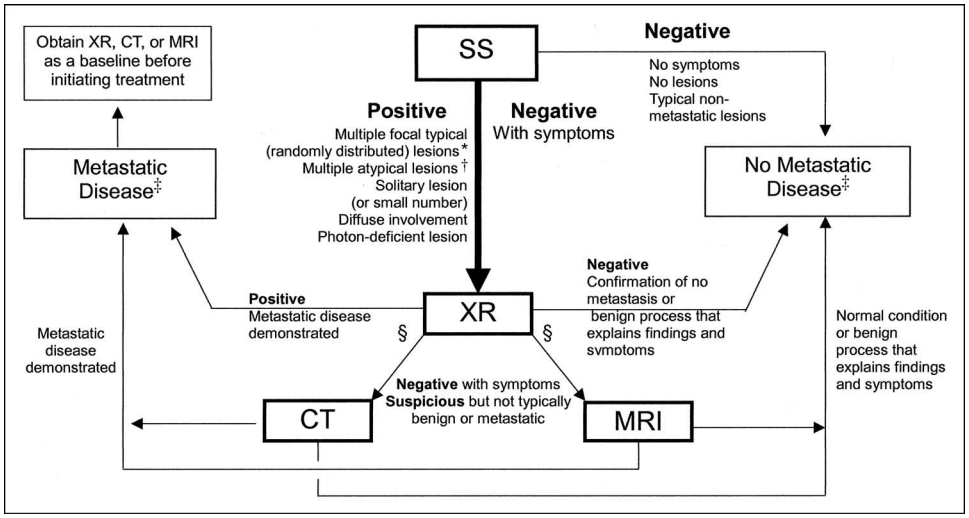

Fig 3. Algorithm for detection of bone metastases. *, These lesions can be diagnosed as "metastatic disease." However, XR images are needed as a baseline for future assessment of bone tumor response. †, Can be caused by metabolic disease (osteoporosis, Cushing's syndrome, osteomalacia), trauma, arthritis inflammatory disease (osteomyelitis), Paget's disease, or infarction.[199] ‡, Bone biopsy may be required for confirmation. §, Indications for CT *v* MRI are not well defined. Both CT and MRI have pros and cons (Table 4). In general, CT is indicated for lesions in weight-bearing or chest-wall bones, and MRI is indicated for spinal lesions. XR, plain radiography; CT, computed tomorgraphy; MRI, magnetic resonance imaging; SS, skeletal scintigraphy.

imaging modality because of its high sensitivity for detection with whole-body scanning and its low cost; this approach is favored by others as well.[28,29,65,198] If SS findings are abnormal, XR can be added to assess the degree of bone loss and risk of pathologic fracture and to establish a baseline for comparison with future treatment assessments. Given the low specificity of SS with regard to multiple atypical lesions,[199] solitary lesions, diffuse involvement, and photon-deficient lesions, findings on SS suggestive of such lesions should be examined further by XR and, in the case of solitary lesions, by biopsy.

Any patient with breast cancer and clinical symptoms or a change in biochemical marker levels suggestive of skeletal metastasis should undergo XR regardless of the findings on SS. This strategy will allow confirmation of the presence of a bone metastasis in the event of negative or equivocal findings on SS and will provide a baseline image in the event of positive findings on SS. However, because bone-tumor response on XR and SS cannot be defined precisely, if the need for such a definition exists, use of CT or MRI as a baseline imaging modality is justified. XR findings typical of a benign bone lesion such as osteoarthritis, chondroma, or cyst should stop further work-up of these areas with CT or MRI. CT or MRI is highly recommended when the lesion is thought to be in the bone marrow. The indications for CT as opposed to those for MRI have not been well established. However, CT is more useful for detecting disease in cortical or trabecular bone, and MRI is more useful for early bone marrow metastasis and detecting spinal cord compression. If a bone lesion cannot be confirmed as being a metastasis, a bone biopsy should be done before treatment is begun. Because FDG-PET can be used for whole-body scanning and has the potential to be highly sensitive for detecting bone lesions, it may eventually take the place of SS as a first-line imaging modality for diagnosing bone metastasis from breast cancer, if issues regarding its cost and ways of distributing the equipment can be resolved.

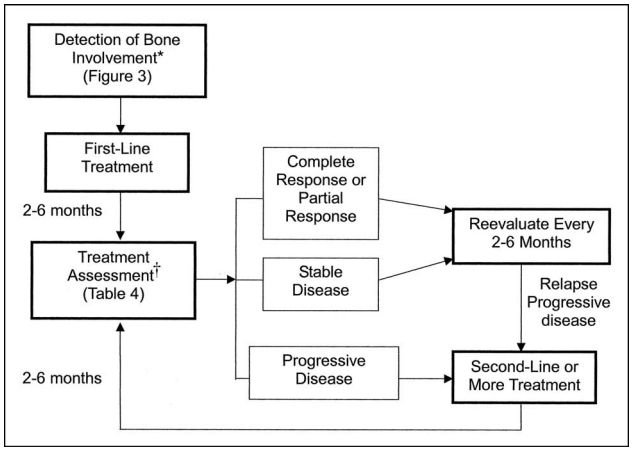

Fig 4. Algorithm for assessment of bone metastasies response to treatment. *, Annual screening is recommended. If clinical symptoms are present, the evaluation should be done as soon as possible. After relapse, skeletal scintigraphy and plain radiography are recommended for every assessment. †, Treatment assessments should be done with the modality that best visualized the metastatic bone lesion.

Algorithm for Tumor Response Assessment

The imaging modalities used to follow-up tumor response should be compared against the baseline images that most clearly define the bone metastases and the lesions to be monitored. Those baseline images can be obtained by XR, CT, MRI, or by some other modality. SS should be used only to support other imaging modalities for assessing tumor response. In the proposed algorithm (Fig 4), we recommend that images be obtained every 2-6 months.[12,106] CT or MRI may visualize a response as soon as 2 months after the treatment is begun as compared with 3 to 6 months before responses become evident on SS and XR.[27,29,45,49,50,82,100-112,119-121] However, it is important to recognize that early detection of

response has not translated into improved survival. If symptoms of new lesions, worsening of existing lesions, or biochemical changes indicating progressive disease are suspected clinically, we recommend use of SS; its high sensitivity and low cost support its use over that of any other imaging modality for this purpose—with the notable exception of during the first 3 to 6 months after treatment, when SS is quite unreliable. XR can visualize response in terms of a known lytic lesion becoming sclerotic or a sclerotic lesion becoming smaller or fading.[12,22,30,116-118] However, XR alone may not be an accurate measure of tumor response because of its tendency to underestimate response.[6,45,121,123] Despite the limited information available on the use of CT or MRI in these circumstances, we recommend that the modality that gave the most definitive image of the bone metastases at diagnosis (SS, XR, CT, or MRI) be used again to assess the response of those metastases to treatment.

New Bone Response Criteria

We propose that the response criteria for the practical management of osseous metastases be updated to include results from CT and MRI (Table 4). Findings from PET or SPECT are not included in these proposed criteria because the evidence to support their use in bone tumor assessment is limited and because both modalities are very expensive at the present time. However, the fusion of PET and CT technologies (PET-CT)[184] has the potential to become useful in response criteria in the near future. In our revised criteria, a complete response, no change (stable disease), and progressive disease are defined in the same way as in the UICC and WHO criteria, except for the inclusion of CT and MRI findings. In the partial response category, we propose that rapid regression of lesions as indicated by SS should not be included in the definition of partial response because this finding can also result from rapid osteolytic progression.[45,104] Furthermore, we propose eliminating the percentage change in lesion size used in the UICC system and instead using the appearance of a sclerotic rim around an initially lytic lesion; sclerosis of a previously undetected lesion; or partial fill-in or sclerosis of a lytic lesion on XR or CT, in addition to regression of measurable lesions on SS, XR, CT, or MRI or regression of blastic lesions on XR or CT. The measurement of percent change in tumor size is not practical for either SS or XR, and the literature does not support quantification of size as an accurate reflection of overall response. Therefore, the best way to distinguish a partial response from stable disease is to acknowledge the response rather than quantifying the response. Finally, these criteria should be rigorously tested in clinical trials to validate these measures and to improve the accuracy of the entire process by which bone lesions are diagnosed and followed during treatment.

Table 4. Revised Criteria Proposed for Assessment of Bone Response

Response Type	Criteria
Complete response	Complete fill-in or sclerosis of lytic lesion on XR and CT Disappearance of hot spots or tumor signal on SS, CT, or MRI Normalization of osteoblastic lesion on XR and CT
Partial response*	Sclerotic rim about initially lytic lesion or sclerosis of previously undetected lesion on XR or CT Partial fill-in or sclerosis of lytic lesion on XR or CT Regression of measurable lesion on XR, CT, or MRI Regression of lesion on SS (exclude rapid regression†) Decrease in blastic lesion on XR or CT
No change (stable disease)	No change in measurable lesion on XR, CT, or MRI No change in blastic/lytic lesion on XR, CT, or MRI No new lesion on XR, SS, CT, or MRI
Progressive disease	Increase in size of any existing measurable lesions on XR, CT, or MRI New lesion on XR, SS (exclude flares), CT, or MRI Increase in activity on SS (exclude flares) or blastic/lytic lesion on XR or CT

Abbreviations: XR, plain radiography; CT, computed tomography; SS, skeletal scintigraphy; MRI, magnetic resonance imaging.

*Every lesion need not have regressed to qualify for response, but no lesion should have progressed. Occasionally, findings on the first plain radiograph after treatment are normal but a new sclerotic rim or mixed lesion appears on later films; this does not indicate progressive disease, but rather response to treatment.

†Rapid osteolytic progression may show decreased osteoblastic activity, resulting in apparent regression of "hot spots" on SS. XR or CT may be helpful in detecting progressive osteolysis and thus helping to identify progressive disease in this situation.

After the recognition of response, the largest question that remains is whether these responses reflect improved overall survival and quality of life. Proving this point may allow bone disease to be considered measurable rather than unmeasurable disease. We further recommend that all imaging modalities be subjected to appropriately powered studies to define their sensitivity and specificity. Such studies should include the more common imaging modalities (XR, CT, SS, MRI) as well as newer modalities such as PET or PET-CT. The next step is to evaluate in clinical trials whether use of these modalities improves survival through early detection, treatment, and accurate assessment of response in a cost-effective way. Such improvements will open the way for development of new bone metastasis–specific drugs.

In conclusion, documenting a true response of bone metastases is not easy even now. We hope that this review will stimulate debate that will ultimately lead to better management strategies for metastatic breast cancer.

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Authors' Disclosures of Potential Conflicts of Interest

The authors indicated no potential conflicts of interest.

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References 101-199 are included in the full-text version of this article, available on-line at www.jco.org. They are not included in the PDF (via Adobe® Acrobat Reader®) version.